

PHARMACOPOEIA

OF THE PEOPLE'S REPUBLIC OF CHINA

(2005)

Volume II

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Chinese Pharmacopoeia Commission

People's Medical Publishing House

PHARMACOPOEIA OF THE PEOPLE'S REPUBLIC OF CHINA

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Preface

This edition of the Pharmacopoeia of the People's Republic of China (known as *the Chinese Pharmacopoeia 2005* or in abbreviation as Ch. P 2005) has been prepared in accordance with the principles and designed plan decided by the Eighth Chinese Pharmacopoeia Commission and accomplished with the effort made by Commission members and its Secretariat over more than two years. *The Chinese Pharmacopoeia 2005* adopted by the Executive Commission of the Chinese Pharmacopoeia Commission is approved for implementation by the State Food and Drug Administration of China. This is the eighth edition of Chinese Pharmacopoeia since the founding of the People's Republic of China.

The Chinese Pharmacopoeia 2005 has been considerably revised and improved in General Notices, Requirements of Monographs, General Requirements for Preparations in Appendices and new testing methods, etc. Based on the introduction of advanced technology and experimental methods widely adopted in China and abroad, the contents of Appendices are revised by and large in consistence with those nowadays applied internationally for drug quality control. On the premise that every effort should be made to follow the principle of "safety for use, reliability of therapeutic effect, feasibility of processes, controllability of manufacturing quality and perfection of specification", the monographs admitted in the Pharmacopoeia on the whole reflect the actual clinical use of drugs in China. Furthermore, stylistic rules and layout, wording, units, and symbols, etc. have also been standardized.

The Chinese Pharmacopoeia 2005 is published in three volumes. Volume I contains monographs of Chinese materia medica and prepared slice, vegetable oil/fat and its extract, Chinese traditional patent medicines, single ingredient of Chinese crude drug preparations etc.; Volume II deals with monographs of chemical drugs, antibiotics, biochemical preparations, radiopharmaceuticals and excipients for pharmaceutical use; Volume III contains biological products. *The Requirements for Biologics of the People's Republic of China* is now incorporated into the Chinese Pharmacopoeia for the first time. Based on the characteristics and the needs of improvement of Chinese traditional medicines, chemical drugs and biological products, the research work and the studies are carried out in an active way on drug standards and methodology. At the same time, great efforts are made to unify the national drug standards and to bring them in line with the international standards progressively. In addition, emphasis have been put to harmonization in Appendices of different volumes of Pharmacopoeia, to a sound connection between individual monographs and the relevant appendices, and to the standardization of text wording so as to make this edition more precise and better structured.

The increase of the number of monographs in *the Chinese Pharmacopoeia 2005* is obvious which contains up to 3214 monographs of drugs, with 525 new admissions in total. Volume I contains 1146 monographs, with 154 new admissions and 453 revised; Volume II deals with 1967 monographs, with 327 new admissions and 522 revised; Volume III contains 101 monographs, with 44 new admissions and 57 revised. 9 monographs adopted in *the Chinese Pharmacopoeia 2000* are not admitted in this edition and

123 monographs adopted in *the Requirements for Biologics of the People's Republic of China 2000* and in its *Supplement 2000* are not admitted in this edition.

The number of monographs in Appendices of this edition is much expanded. There are 98 monographs admitted in Appendices of Volume I with 12 new admissions, 31 revised and 1 deleted. There are 137 monographs in Appendices of Volume II with 13 new admissions, 65 revised and 1 deleted. There are 140 monographs in Appendices of Volume III with 62 new admissions, 78 revised and 1 deleted. The monographs in Appendices common to all the three volumes are presented in each volume respectively in a harmonized and unified form.

Extensive applications of contemporary techniques of analysis are shown in this edition. In Volume I, the number of monographs adopting thin layer chromatography in the test for identification reaches 1523 and 45 monographs for content determination; the number of monographs adopting high performance liquid chromatography (HPLC) reaches 479 and 518 items are involved; and the number of monographs adopting gas chromatography in the tests for identification and content reaches 47. In Volume II, the number of monographs, including testing items, adopting HPLC reaches 848 with an increase of 566 in comparison with that in 2000 edition, and this method is mostly used for the analysis of complex formulation and those drugs containing much more interfering factors such as impurities or excipients, and used for content determination in 223 newly admitted monographs. The number of monographs required for identification by infrared analysis reaches 70; the tests for dissolution and test of content uniformity are added in test items in 93 and 37 monographs, respectively, and the test for related substances is added in 226 monographs, and the requirements for systematic suitability testing are more reasonable. Based on the validation of methodology, the test for bacterial endotoxins instead of pyrogen test in rabbits is introduced to 73 monographs; on the premise that the drug purity is ensured, the test for undue toxicity for 42 monographs is deleted.

Significant revisions and expansion are made in the Appendices of this edition leading a great improvement in the monographs of Appendices. In order to adapt the need of drug administration, new preparations such as implants, rinsing agents, enemas, paint, and smeared films, etc. are admitted in the General Requirement for Preparations. Many subtypes of dosage form are also admitted in General Requirement for Preparations, such as soluble tablets and vaginal effervescent tablets admitted into General Requirement for tablets; sustained release capsules and controlled release capsules admitted into General Requirement for capsules, etc. Test for sterility is added in test items in some of preparations of General Requirement for Preparations. New general testing methods have been admitted, such as Determination of Total Organic Carbon in the Water for Pharmaceutical Use, Test for Visible Particles in Injections, Mass Spectrometry, Determination of Cataplasms Adhesion, Test for Allergen, Biological Assay of Calcitonin and Growth Hormone, etc. Furthermore, considerable revisions are made for a number of Appendices according to modern techniques and practical situation, for example, the tests on 12 pesticides containing organic phosphorous and 3 pesticides containing pyrethroid are added for determination of pesticide residues; the test for small volume of injection is included in the Test for Particulate Matter in Injections; the test for system suitability is admitted for Thin-layer Chromatography; Microbial Limit Tests is revised according to the requirements of drug administration route and tests for validation are added; the time of incubation in sterility test has been changed from 7 to 14 days.

In the section of guidelines, such guidelines have been revised to keep pace with the development of

research and production of drugs as the Guidelines the Stability Testing of Drug Substances and Preparations and the Guidelines for Sustained, Controlled and Delayed Release Preparations, and new guidelines are admitted such as the Guidelines for Hygroscopicity and Guidelines for Near-infrared (NIR) Spectrophotometry, etc. Although those guidelines do not serve as legal requirements, they play an important role in assessment of drug quality, in establishing, standardizing and implementing uniform pharmaceutical specification of drugs and medicines.

The safety of pharmaceuticals is another important issue of *the Chinese Pharmacopoeia 2005*. In Appendices of Volume I, for example, atomic absorption spectrophotometry or inductively coupled plasma mass spectrometry is introduced to determine 6 kinds of heavy metals and deleterious elements, and the limits for lead, cadmium, mercury, arsenic and copper are stipulated for the first time; the harmful solvents, such as benzene etc. used in pharmaceuticals should be substituted by other solvents as far as possible. The Guidelines for Application of Safety Tests for Injection of Traditional Chinese Medicine is also admitted in this edition; In Volume II, the Test for Particulate Matter in Injections is applied to 126 Injections intended for intravenous injection; the number of monographs adopting the Test for Bacterial Endotoxin reaches 112; the Determination of Residual Solvent includes the requirements of the International Conference on Harmonization (ICH) for residual solvents, and the test is required for 24 drug substances; the Guidelines for the Analysis of Impurities in Drugs; Guidance for the Quality Control of Positron Emission Tomographic and Technetium [^{99m}Tc] Radiopharmaceutical Preparations are also admitted. In Volume III, new methods, such as Determination of Reverse Transcriptase Activity and Test for Residual Aluminum Content in Human Albumin etc. are admitted, and some test methods are improved such as the test for residual bovine serum albumin and test for residual CHO cell protein, etc. On consideration of the status quo of medical industry and practical situation of drugs for clinical use, the requirements set forth in Detailed Regulations for Clarity Test and Criteria formerly issued by the Ministry of Health are replaced by the method for Determination of Visible Particles in this edition so as to enhance the safety of pharmaceuticals including injections.

According to the theory of traditional Chinese medicine—diagnosis and treatment based on an overall analysis of the illness and the patient's condition, the *Indications* under the Chinese patent preparations have been scientifically standardized, so as to avoid the phenomenon of easy misleading usage of drugs and to give prominence to features of the above theory. At the same time, the attention should be paid to the fact that a phenomenon of “different diseases having same syndrome” and “same disease having different syndromes” exists between “Syndrome” in traditional Chinese medicine and “Disease” in Western medicine. The close combination of “Syndrome” in traditional Chinese medicine and corresponding “Disease” in Western medicine embodies the scientificity and accuracy of the expression of *Indications*, so as to ensure clinicians to understand the *Indications* precisely and make use of drugs rationally, thus facilitating the sound development of traditional Chinese medicine in the new era.

The working procedures for preparation of this edition also has been improved. In addition to the traditional way of requesting for comments, the contents of revised appendices and monographs should be publicized on the website of the Chinese Pharmacopoeia Commission for three months, aiming at collecting comments widely from various institutions and organizations. All the feedbacks and inputs should be reviewed by the relevant subcommittee to ensure the feasibility and practicability of the standards and methods revised in this edition of Pharmacopoeia, and ensure that the principle of “openness, justice and fairness” is kept in the process of compiling and editing.

In order to make it easy for reading, *the Chinese Pharmacopoeia 2005* adopts the half-measure in its layout for the first time, and the improvement of quality in printing and binding makes this edition look more elegant.

Thanks to the well-organized work by the Secretariat of the Chinese Pharmacopoeia Commission, the joint efforts made by all the participants and the support from institutions and organizations concerned, the compilation of *the Chinese Pharmacopoeia 2005* proceeded smoothly and the goal is reached as designed despite the heavy work schedule and high requirements for the task. Now *the Chinese Pharmacopoeia 2005* is presenting its new style in front of the world and will play a greater role both in initiating new prospect of national drug administrative work and in the development of the medical industry in China.

郑筱萸

Chairman, the eighth Chinese Pharmacopoeia
Commission of the People's Republic of China

(December 2004)

History of the Pharmacopoeia of the People's Republic of China

The Chinese Communist Party and the Chinese Government have attached great importance to medical and health care of the Chinese people. The People's Republic of China was founded on October 1, 1949 and right in November of that year the Ministry of Health convened a meeting of medical and pharmaceutical experts in Beijing on the compilation of a pharmacopoeia. In January 1950, the Ministry of Health invited Professor Meng Mudi, a well-known pharmacist from Shanghai, to take up the responsibility for the establishment of the Editorial Commission of Pharmacopoeia of China and its secretariat to deal with daily work concerning the compilation of such a compendium for new China.

In April 1950, a working seminar was held in Shanghai, at which the principles and guidelines on the selection of monographs were discussed and the monographs to be included in the Pharmacopoeia were decided. It was recommended under the direction of the Ministry of Health that the new Pharmacopoeia should be compiled in such a way that it is in conformity with the Chinese situations and that it should be nationalistic, scientific and popular in nature. Thereafter, The Ministry of Health invited 49 experts as members and 35 as correspondent members of the Commission who were appointed to 8 panels (nomenclature, chemicals, pharmaceutical preparations, medicaments of plant origins, biological products, medicaments of animal origins, pharmacology, and dosage) respectively. Health Minister Li Dequan served as the chairperson of the Commission. The first Editorial Commission of Pharmacopoeia of the People's Republic of China was thus formally established.

The first Editorial Commission meeting composed of all members was held in Beijing April 24-28, 1951, where resolutions were made on the title of the Pharmacopoeia, list of selected monographs, the nomenclatures, units of measurement and weights, format, the order of arrangement etc. Based on recommendations from the Commission meeting, the draft of the pharmacopoeia was then revised by the Secretariat and submitted to the Ministry of Health for review and the Culture and Education Commission of the State Council for approval at the end of 1952. The Ministry of Health published the first *Chinese Pharmacopoeia* in 1953.

The Chinese Pharmacopoeia 1953 edition contained 531 monographs of substances and articles, including 215 chemicals, 65 medicaments from plant origins, oils and fats, 13 medicaments from animal origins, 2 antibiotics, 25 biological products, and 211 pharmaceutical preparations. After the publication of the Pharmacopoeia the first addendum of the 1953 edition was published in 1957.

The Ministry of Health set up the second Chinese Pharmacopoeia Commission in 1955, with 49 members and 68 correspondent members. Due to various reasons, this Commission failed to fulfill its mission. The third Commission was established in 1957, with 80 members (no correspondent members appointed) and

Professor Tang Tengan, a well-known pharmaceutical chemist, as its chairman. The first meeting of the third Commission was convened from July 28 to August 5 of the same year. Health Minister Li Dequan pointed out at the meeting that it was a big flaw that the first Pharmacopoeia did not cover Chinese traditional medicines that the Chinese people were so used to. At the meeting principles in compiling a Pharmacopoeia were made and nature and purpose of such a compendium were discussed and constitution of the Commission was revised. It was agreed unanimously to admit well-defined Chinese traditional medicines to the Pharmacopoeia. On August 27, six expert committees and a panel under the Commission were approved and set up by the Ministry of Health, namely, the committees of medicines, chemicals, pharmaceutical preparations, biochemicals, pharmacognosy and biological products, and a panel of nomenclature. Under the Commission a Standing Committee was organized, however, routine work in general was dealt with by its Secretariat.

In 1958, it was recommended by the Standing Committee and approved by the Ministry of Health to invite 8 doctors of Chinese traditional medicine and 3 experts of Chinese traditional medicaments as members of an expert committee dealing with the quality specifications of crude drugs used as Chinese traditional medicaments and Chinese patent preparations. Collaborative efforts were made by experts in this field in many parts of this country to incorporate the theory and practical experience of Chinese traditional medicine into the monographs concerned.

The second meeting of this Commission was held in Beijing from June 25 to July 5, 1959. A list of monographs being admitted to the new Pharmacopoeia was proposed and the draft texts reviewed in detail by the expert committees concerned. The work was accomplished in 1962. The State Council approved the publication of the Pharmacopoeia of the People's Republic of China 1963 edition. On January 26, 1965, the Ministry of Health issued a document for *the Chinese Pharmacopoeia 1963* edition and the relevant provisions for its implementation.

The Chinese Pharmacopoeia 1963 edition contained 1310 monographs in its two volumes, each with separated General Notices and relevant appendices. 446 monographs of commonly used Chinese traditional medicaments and 197 monographs of Chinese traditional patent preparations were admitted to Volume I, and 667 monographs of chemical drugs were admitted to Volume II. Additionally, "therapeutic function and chief indication" were stated in the monographs admitted to Volume I and "action and use" of those admitted to Volume II.

The Chinese Pharmacopoeia Commission stopped functioning in 1966 due to the turmoil caused by the "Cultural Revolution". On April 28, 1972, the State Council agreed to the suggestion in the report of the Ministry of Health that "the Commission should be re-established with the participation of Ministries of Health, Petroleum and Chemical industry, Commerce and the PLA's Ministry of Health, headed by the Ministry of Health". A working meeting of the Chinese Pharmacopoeia Commission was convened under the above direction from May 31 to June 10 of the same year in Beijing. 88 representatives of various competent authorities and organizations, including all Provincial (Autonomous regional or Municipal) Departments of Drug Policy and Management, Institutes for Drug Control and others attended the meeting. The focus of the meeting was on the guiding principle, working process, requirements and objects of the editing of the national Pharmacopoeia. The revision plan was recommended after exchange of past experiences in various aspects. Arrangements were made for the drafting of individual monographs by the organizations concerned. The second meeting of the Chinese Pharmacopoeia Commission was held

in Beijing in April 1973. Some guidelines, basic requirements of the Pharmacopoeia and sample monographs for Chinese traditional medicaments and modern medicinal substance as well as the respective explanatory notes had been well discussed and appropriate recommendations were made. The drafting of individual monographs was rearranged according to the place of origin of Chinese medicines and the conditions of pharmaceutical production. On October 4, 1979 the Ministry of Health promulgated that *the Chinese Pharmacopoeia 1977* edition would come into use on January 1, 1980. The total of monographs contained in the 1977 edition is 1925. In Volume I, 1152 monographs were admitted, including 882 monographs of Chinese herbal drugs in general used and in the region of national minorities, extracts of Chinese herbal medicines, oils and fats and some preparation made of single medicinal ingredient. 270 monographs of Chinese traditional patent preparations (including those preparations used in the region of national minorities) were also admitted in the Volume I. 773 monographs of chemicals and biological products etc. were admitted in Volume II.

In 1979 the Ministry of Health invited 112 experts as members to form the fourth Chinese Pharmacopoeia Commission, and Health Minister Qian Xinzong was its Chairman. The first plenary meeting of that Commission was held from Nov. 22 to Nov. 28 in the same year in Beijing. Discussion and amendment were made on the constitution of the commission, provisions for the management of specifications for pharmaceutical preparations and its working plan in the meeting. Ten specialized advisory groups were appointed in the fields of Chinese traditional medicine, Chinese traditional medicaments, medicine and pharmacology, chemicals, biochemicals, pharmaceutical preparations, antibiotics, biological products, radiopharmaceuticals and nomenclature respectively. Monographs being admitted to the new Pharmacopoeia were recommended by the advisory groups concerned. The advisory group on Chinese traditional medicine had the responsibility to review and select the range of monographs to be included in Volume I and the advisory group on medicine and pharmacology had the same responsibility for Volume II. The institutes for drug control and competent authorities or organizations in the locality (provinces, autonomous regions and municipalities), where the drug substance concerned was produced provided draft text of individual monograph with prominent experience and excellent quality. Coordinated review and technical validation were organized by the Secretariat. Some monographs were drafted only after the completion of objective collaborative studies as required. Finally, members of respective advisory groups and representatives of institutes for drug control and drug manufacturers concerned reviewed the draft text, and then sent to the Ministry of Health for approval. *The Chinese Pharmacopoeia 1985* edition was published in September 1985 as planned. The effective date was set on April 1, 1986 as approved by the Ministry of Health. In this edition of Pharmacopoeia, 1489 monographs of drugs were admitted. 506 monographs of Chinese traditional medicaments, crude drugs, vegetable oils and fats and preparations of single ingredient, 207 monographs of Chinese traditional patent preparations, totally amount to 713 monographs were admitted to Volume I. 776 monographs of chemicals, biological products etc. were admitted to Volume II.

The "Drug Administration Law of the People's Republic of China" came into effect on July 1, 1985. It stipulated that "the quality of drugs and medicines must comply with a national, provincial, autonomous regional or municipal standard", and that "the Pharmacopoeia of People's Republic of China and standards for drugs and medicines published and promulgated by Ministry of Health of the State Council are national standards for drugs and medicines". It further stated, "The Chinese Pharmacopoeia Commission subordinate to the Ministry of Health of the State Council is responsible for the stipulation and revision of national standards for drugs and medicines". It defines clearly the official nature of standards for drugs

and medicines and responsibilities of the Commission.

In 1986 the Ministry of Health reorganized the Chinese Pharmacopoeia Commission in accordance with its constitution and invited 150 experts as members of the fifth Commission with Health Minister Cui Yueli as Chairman. The office dealing with routine work was changed to a system with the Secretary General as its chief executive officer. The first meeting of this Commission was convened May 5-8 of the same year. The constitution of the Commission was revised. Comments were made on the task of drug standardization during the seventh Five-year Plan for National Reconstruction. The guidelines and principles of the 1990 edition of the pharmacopoeia were discussed and agreed at the meeting. Panel meetings on Chinese traditional medicaments, Chinese patent preparations, chemicals, antibiotics, biochemicals and pharmacology were held respectively for the tasks of drafting different parts of the next edition and necessary research projects to be carried out. The addendum to *the Chinese Pharmacopoeia 1985* edition was published in November 1987 with 23 new admissions and 172 specific monographs and 21 general monographs were revised or amended. Based on *the Chinese Pharmacopoeia 1985* edition, its first English version was formally published in October 1988. Also published in that year were the selected notes in Volume II. By March 1989, the draft text of the new pharmacopoeia was basically ready for comments through the efforts made by various organizations and associations. The Secretariat of the Chinese Pharmacopoeia Commission was authorized to organize reviewing and editing. In December 1989, an extended meeting attended by the chairman, vice-chairmen of the Commission and the chairmen of all advisory groups was held in Beijing. It was recommended to send the draft text to the Ministry of Health for comments and approval. The Ministry of Health then publishes it as *the Chinese Pharmacopoeia 1990* edition, on December 3, 1990 with effective date on July 1, 1991.

This new edition of the pharmacopoeia is still published in two volumes containing 1751 monographs of substances and articles. 784 monographs including 509 monographs of Chinese traditional medicaments and 275 monographs of Chinese traditional patent preparations and single ingredient preparations are admitted to Volume I, while 967 monographs on chemicals, antibiotics, biological products and pharmaceutical preparations are admitted to Volume II. In comparison with the preceding edition, 80 new monographs are admitted and 3 monographs deleted from Volume I; 213 new monographs are admitted (including 5 monographs transferred from Volume I to Volume II) and 25 monographs deleted (3 from Volume I and 22 from Volume II). Appropriate changes have been made on titles of certain drug substances and articles as required. The headings "Action and use" and "Administration and dose" are changed to "Category" and "Dosage" respectively. "A Guide to Clinical Use of Drugs" was published as a companion volume to *the Chinese Pharmacopoeia* to serve as a guiding reference for medical and pharmaceutical practices. The infrared reference spectra are deleted from the Appendix with the publication of a separate volume—the Atlas of Infrared Spectra of Drugs.

The sixth Chinese Pharmacopoeia Commission was organized in 1991 with 168 members invited by the Ministry of Health, and Health Minister Chen Minzhang as its chairman. The first meeting of that Commission took place May 16-18 of the same year, attended by all members. In this meeting, the constitution of the Commission was further revised and the working plan for compilation and editing of *the Chinese Pharmacopoeia 1995* edition were discussed and substantial recommendations were made. A Standing Committee composed of the chairman, vice chairman and 11 other experts were set up with 13 subcommittees in respective specialized fields, namely, Chinese traditional medicine, Chinese traditional medicaments, Chinese traditional patent medicines, Modern medicine, Pharmacology, Chemicals I, II

and Ⅲ, Antibiotics, Biochemicals, Biological products, Radiopharmaceuticals and Nomenclature. The subcommittees then convened extended meetings in their specific fields, respectively, to work out the programs for revision of the Pharmacopoeia.

Drafts of the appendices of the 1995 edition were sent out in 1993 to relevant local organizations as a reference for the compilation and revision of the new edition. By July 1994 almost all local drafting had been finished and the subcommittees started organizing reviews. On Nov. 29, 1994 the drafts were discussed and further reviewed at an extended meeting of the Standing Committee, and then submitted to the Ministry of Health for approval. *The Chinese Pharmacopoeia 1995* edition came into use as of April 1, 1996 as promulgated by the Ministry of Health.

There are 2375 monographs in that edition. 920 monographs, including 522 monographs of Chinese traditional crude drugs and of oils and fats, 398 monographs of Chinese traditional patent medicines and of preparations of single ingredient were admitted to Volume I. In Volume II, it was composed of 1455 monographs of chemicals, antibiotics, biochemicals, radiopharmaceuticals, biological products and some excipients. In comparison with the previous edition, 142 and 499 new admissions were admitted in Volume I, II respectively. English titles of drugs and preparation were adopted in Volume II and the Latin titles were deleted, while Chinese titles only use their official common names and no alternate names. The first Volume (1995 edition) of "Atlas of Infrared Spectra of Drugs and Medicines" was also compiled. "A Guide of Clinical Use of Drugs" was revised, and published together with the 1995 edition of *the Chinese Pharmacopoeia*. Ministry of Health approved that the "Indication" and "Dosage" in the later should be adopted as the basis for promotion of drug administration and management by competent authorities of drug management and drug manufacturing.

The sixth Chinese Pharmacopoeia Commission published the first and second addenda in 1992 and 1993, respectively. It also published "Commentary to Volume II of *the Chinese Pharmacopoeia 1990* edition". "Selected Commentary to Volume I of *the Chinese Pharmacopoeia 1990* edition", "Atlas of Traditional Chinese Medicines", "Atlas of Thin Layer Chromatography of Chinese Traditional Medicines" and "Adopted names of Chinese pharmaceutical products" as references in series relevant to pharmacopoeia. English version of *the Chinese Pharmacopoeia 1990* edition was published in July 1993.

To strengthen standardization of drugs and medicines, the Ministry of Health decided, on May 21, 1993, that the Secretariat of the Chinese Pharmacopoeia Commission separated from the National Institute for the Control of Pharmaceutical and Biological Products and subordinated directly to the Ministry of Health. That was an important reform measure in the restructuring of the Commission.

Approved by the Ministry of Health, the seventh Chinese Pharmacopoeia Commission was set up in May 1996. The Ministry invited 204 members, including 18 honorary members, to form the Commission. Health Minister Chen Minzhang served as its Chairman. In September 1998 as approved by Document No. 32 (1998) of Central Office of Organization, the name of Pharmacopoeia Commission of the Ministry of Health was changed to the Chinese Pharmacopoeia Commission, and the administration of the Commission was transferred to the State Drug Administration (SDA). After change of the management system and passing away of Health Minister Chen Minzhang, the Standing Committee of the seventh Pharmacopoeia Commission decided to appoint chairman and vice chairmen of the Commission, as so stipulated in its Constitution in December 1999. Under that Commission there were 16 specialty

subcommittees: Chinese traditional medicine, Chinese traditional medicaments I, II, III, and IV, modern medicine, nomenclature, appendices, pharmaceutical preparations, pharmacology, chemicals I and II, antibiotics, biochemicals, radiopharmaceuticals and biological products.

The first meeting of the seventh Commission was held in 1996, at which the design plans for the 2000 edition of *the Chinese Pharmacopoeia* were endorsed. The guiding principles decided were that the Volume I should have special features in content and its quality should be largely improved, and the Volume II should reflect the combination of improvement and suitability to specific situations in China as well as a combination of advancement and characteristics. As scheduled in the plans, all subcommittees convened their own meetings and carried out their tasks starting from October 1996. By the end of 1997, all revision of the appendixes and general rules for drug and medicine preparations had been finished and sent to local drafting organizations for comments. A first draft was finalized at the end of 1998, and after reviews by related organizations in different parts of China; the 16 subcommittees further reviewed it by the end of October 1999. *The Chinese Pharmacopoeia 2000* edition was finally reviewed and passed by the seventh Chinese Pharmacopoeia Commission in December 1999, and submitted to the State Drug Administration for approval of publication. This edition was published in January 2000 and come into effect from July 1, 2000.

The 2000 edition contains a total of 2691 monographs, with 992 ones in Volume I and 1699 in Volume II. There are 399 new monographs and 562 revised ones in this edition. Appendixes have been considerably improved. There are 10 new and 31 revised appendixes in Volume I, and 27 new and 32 revised ones in Volume II. The Volume II has, for the first time, included 6 guidelines for Validation of Analytical Method Adopted in Pharmaceutical Quality Specification etc., which will play a role in the standardization and regulation of testing methods. Application of modern analytical techniques is further enhanced and stressed in this edition.

The seventh Chinese Pharmacopoeia Commission has also compiled the 1997 and the 1998 addendum of *the Chinese Pharmacopoeia 1995* edition, the “Adopted Names of Chinese Pharmaceutical Products (1998 Addendum)”, “Atlas of Infrared Spectra of Drugs and Medicines” (Volume II) and the third edition of “A Guide to Clinical Use of Drugs”. The English edition of *the Chinese Pharmacopoeia 1995* was published in 1997. To strengthen exchanges and cooperation, this Commission has decided to publish concurrently both Chinese and English versions of *the Chinese Pharmacopoeia 2000* edition.

“Dosage” and “Precaution” in preceding editions are too simple to reflect accurately the actual clinical use of drugs therefore deleted from this edition (Volume II) as so proposed in the design plans for the relevant contents of those two headings have been included in “A Guide to Clinical Use of Drugs”.

Approved by the State Drug Administration (redesigned to be State Food and Drug Administration in September 2003), the eighth Chinese Pharmacopoeia Commission was set up in October 2002. The State Drug Administration invited 312 experts as members of the Commission and did not appoint any honorary member. The Commissioner of the State Drug Administration, Mr. Zheng Xiaoyu served as its Chairman. The Standing Committee of the Commission was assigned as Executive Committee. The plenary session of the Chinese Pharmacopoeia Commission was authorized to examine and approve *the Chinese Pharmacopoeia* and the important items of the national specifications for pharmaceutical preparations. 24 subcommittees of specific duty and/or appointment are set up under the Commission. On the basis of previous Commission, 3 new subcommittees were established; namely ethnic medicines, microorganism, and packing materials and excipients; former subcommittee of biological products was expanded to 6 ones,

namely: blood products, viral vaccines, bacterial vaccines, somatic cell therapy and gene therapy, recombinant DNA products and diagnostic reagents for *in vivo test*.

The first meeting of the eighth Chinese Pharmacopoeia Commission and its Executive Committee took place in October 2002, approved “the design plans for the 2005 edition of *the Chinese Pharmacopoeia*”. The design plans clearly indicated that the *Pharmacopoeia* should adhere to guiding principles of “succession and development” and “theory combined with practice”; and editing principles of pharmacopoeia should be adhered to scientific, practical and specific basis. The meeting decided that *Requirements for Biologics of the People’s Republic of China*, known as the *Chinese Requirements for Biologics* (CBR), would be integrated into the pharmacopoeia as its Volume III; “A Guide to Clinical Use of Traditional Chinese Patent Preparations” is to be compiled for the first time.

All designated subcommittee meetings have been convened since November 2002, to deal with the assigned duty recommended on the meeting in various aspects. By July 2003, the draft of appendices was accomplished at first and sent to relevant authorities and institutions for comments. Early in 2004, the first draft of appendices and text of pharmaceutical and biological products was basically ready and consecutively published on the website of the Chinese Pharmacopoeia Commission for 3 months, so as to get the feedbacks from various organizations and associations. Subcommittees, one after the other, convened meetings to review and revise the drafts from June to August, the Executive Committee of eighth Chinese Pharmacopoeia Commission endorsed *the Chinese Pharmacopoeia 2005* in September of the same year. In December 2004, the draft text was sent to the State Food and Drug Administration for approval and promulgation. *The Chinese Pharmacopoeia 2005* was published on January 2005 with effective date on July 1, 2005. The number of monographs in *the Chinese Pharmacopoeia 2005* is considerably increased. It contains up to 3214 monographs of drugs and other articles with 525 new admissions. Volume I contains 1146 monographs, with 154 new admissions and 453 revised; Volume II deals with 1967 monographs, with 328 new admissions and 522 revised; Volume III contains 101 monographs, with 44 new admissions and 57 revised. 9 monographs adopted in *the Chinese Pharmacopoeia 2000* are deleted in this edition. 123 monographs adopted in the *Requirements for Biologics of the People’s Republic of China 2000* and in its *Supplement 2002* are not admitted in this edition.

The numbers of appendices in this edition are as follows: 98 monographs admitted in Volume I with 12 new admissions, 31 revised and 1 deleted; 137 monographs in Volume II with 13 new admissions, 65 revised and 1 deleted; 140 monographs in Volume III with 62 new admissions, 78 revised and 1 deleted. Appropriate monographs common to all three volumes are presented in each volume respectively in a harmonized and unified form.

Under the active leadership of the Chairman of the Chinese Pharmacopoeia Commission, the issue of pharmaceutical safety is emphasized particularly. In Volume I, atomic absorption spectrophotometry and inductively coupled plasma mass spectrometry are applied to determine the deleterious elements (lead, cadmium, mercury, arsenic and cuppers) and the limits of these elements have been stipulated; the guidelines of the safety test for the injections of traditional Chinese medicines is also added to the Volume I. In Volume II, the Test for Particulate Matter in Injections is applied to 126 injections intended for intravenous injections; the number of monographs adopting the Test for Bacterial Endotoxin reaches 112; the Determination of Residual Solvents includes the requirements of International Conference on

Harmonization (ICH) for residual solvents, and the test is required for 24 drug substances; In Volume II, the Guidelines for Analysis of Impurities in Drugs, Guidance for the Quality Control of Positron and Technetium [^{99m}Tc] Radiopharmaceutical Preparations are also admitted. In Volume III, new methods such as Determination of Reverse Transcriptase Activity and Test for Residual Aluminum Content in Human Albumin etc. are admitted, and some test methods are improved such as the test for residual bovine serum albumin and test for residual CHO cell protein, etc. On consideration of the status quo of medical industry and practical situation of drugs for clinical use, the requirements set forth in Detailed Regulations for Clarity Test and Criteria formerly issued by the Ministry of Health are replaced by the method for Determination of Visible Particles in this edition so as to enhance the safety of pharmaceuticals including injections.

The Chinese Pharmacopoeia 2005 attaches great importance to the consistent principle of environmental protection, therefore the harmful solvents, such as benzene etc. used in pharmaceuticals should be substituted by other solvents as far as possible.

According to theory of Traditional Chinese Medicine—diagnosis and treatment based on an overall analysis of the illness and the patient's condition, the *Indications* under the Chinese patent preparations have been scientifically standardized so as to provide the assurance of understanding the *Indications* precisely and making use of drugs rationally, and to facilitate the healthy development of traditional Chinese medicine.

Volume III of this edition is originated from *CBR*. Six editions of the *CBR* have been promulgated for implementation since 1951, i. e. the edition 1951 and its addendum 1952, and the edition 1959, 1979, 1990 and 1993 (for diagnostic products), 1995 and 2000 and its supplement were published respectively. The English version of *CBR 2000* was published for the first time in 2002.

The eighth Chinese Pharmacopoeia Commission also has completed the Addendum 2002 and Addendum 2004 of *the Chinese Pharmacopoeia 2000*, the Adopted Names of Chinese Pharmaceutical Products (2005 edition), Atlas of Infrared Spectra of Drugs and Medicines (third volume) and “Guide to Clinical Use of Drugs” (the first edition for Chinese traditional patent preparations and the fourth edition for chemicals).

The English version of *the Chinese Pharmacopoeia 2005* was completed in 2005. In order to enhance the international cooperation and communication, the Chinese Pharmacopoeia Commission has organized the first “China-USA joint forum on Pharmacopoeia”.

Aiming at the strengthening and improving the efficiency and level of national standard work, the Secretariat of the Chinese Pharmacopoeia Commission has completed the construction of office automation and realized standards enacted the Chinese for computer network retrieval and statistical analysis.

New Admissions

Aciclovir Capsule	Bulleyaconitine A
Aciclovir Chewable Tablets	Calcitonin (Salmon) Injection
Aciclovir Cream	Calcium Carbonate Chewable Tablets
Aciclovir Eye Drops	Calcium Carbonate Granules
Aciclovir for Injection	Calcium Folate Capsules
Aciclovir Granules	Calcium Folate Tablets
Aciclovir Tablets	Carbachol Injection
Adenosine Disodium Triphosphate	Carbachol
Adenosine Disodium Triphosphate for Injection	Carbocisteine Granules
Adenosine Disodium Triphosphate Injection	Carmofur Tablets
Alarelin Acetate for Injection	Carmofur
Alarelin Acetate	Cefathiamidine for Injection
Alfacalcidol Tablets	Cefathiamidine
Alfacalcidol	Cefdinir Capsules
Almitrine Bismesylate	Cefdinir
Alprostadil for Injection	Ceftezole Sodium for Injection
Alprostadil	Ceftezole Sodium
Amantadine Hydrochloride Granules	Cimetidine and Sodium Chloride Injection
Amantadine Hydrochloride Syrup	Ciprofloxacin
Ambroxol Hydrochloride Capsules	Citicoline Sodium for Injection
Ambroxol Hydrochloride Oral Solution	Citicoline Sodium Injection
Ambroxol Hydrochloride Sustained-release Capsules	Citicoline Sodium
Ambroxol Hydrochloride Tablets	Clarithromycin Granules
Ambroxol Hydrochloride	Clobetasol Propionate Cream
Amrinone for Injection	Clomipramine Hydrochloride Injection
Amrinone	Codeine Phosphate and Platycodon Tablets
Arginine Hydrochloride Tablets	Coenzyme Q ₁₀ Soft Capsules
Arginine	Compound Almitrine Tablets
Asparagine Tablets	Compound Aspartate, Vitamin B ₆ and Dipotassium Glycyrhetate Eye Drops
Asparagine	Compound Bismuth Aluminate Capsules
Aspirin Effervescent Tablets	Compound Camphor Tincture
Aspirin Enteric Capsules	Compound Dexamethasone Acetate Cream
Aspirin, Heavy Magnesium Carbonate and Dihydroxyaluminium Aminoacetate Tablets	Compound Furosemide Tablets
Azithromycin Dispersible Tablets	Compound Glycyrrhiza Oral Solution
Azithromycin Granules	Compound Ketoconazole Cream
Bendazac Lysine Eye Drops	Compound Miconazole Nitrate Cream
Bendazac Lysine	Compound Sodium Chloride Eye Drops
Benorilate, Pseudoephedrine Hydrochloride and Chlorphenamine Maleate Tablets	Compound Sulfamethoxazole Oral Suspension
Benproperine Phosphate Granules	Compound Zedoary Turmeric Oil Suppositories
Benproperine Phosphate Oral Solution	Cydiodine Buccal Tablets
Benzathine Benzylpenicillin	Daunorubicin Hydrochloride for Injection
Bifonazole Suppositories	Daunorubicin Hydrochloride
Bisacodyl Suppositories	Dexamethasone Tablets
Black Ferric Oxide	Diclofenac Sodium and Codeine Phosphate Tablets
Black Ferric Oxide	Diffunisal Capsules
Brown Ferric Oxide	Diffunisal
Brown Ferric Oxide	Dipivefrin Hydrochloride Eye Drops
Bulleyaconitine A Oral Solution	Dipivefrin Hydrochloride
Bulleyaconitine A Tablets	

Doxorubicin Hydrochloride for Injection	Ibuprofen Syrup
Doxorubicin Hydrochloride	Indocyanine Green for Injection
Enalapril Maleate Capsules	Indocyanine Green
Enalapril Maleate Tablets	Inosine Capsules
Enalapril Maleate	Inosine Injection
Enoxacin Eye Drops	Inosine Oral Solution
Erythromycin Ethylsuccinate Capsules	Inosine Tablets
Erythromycin Ethylsuccinate Dispersible Tablets	Inosine
Estradiol Sustained-release Patches	Isosorbide Dinitrate Spray
Ethacriding Lactate Solution	Ketotifen Fumarate Eye Drops
Etimicin Sulfate for Injection	Kitasamycin Tablets
Etimicin Sulfate Injection	Kitasamycin
Etimicin Sulfate	Levodopa and Benserazide Hydrochloride Capsules
Etoposide Injection	Levodopa and Benserazide Hydrochloride Tablets
Etoposide	Lidocaine Carbonate Injection
Famciclovir Capsules	Ligustrazine Phosphate Capsules
Famciclovir Tablets	Ligustrazine Phosphate Injection
Famciclovir	Ligustrazine Phosphate Tablets
Felodipine Tablets	Ligustrazine Phosphate
Felodipine	Lofexidine Hydrochloride Tablets
Ferrous Fumarate Chewable Tablets	Lofexidine Hydrochloride
Ferrous Fumarate Granules	Meleumycin Tablets
Fleroxacin Capsules	Meleumycin
Fleroxacin Tablets	Meloxicam
Fleroxacin	Meropenem for Injection
Fluconazole Tablets	Meropenem
Fosfomycin Calcium Capsules	Metamizole Sodium Nasal Drops
Fosfomycin Calcium Granules	Methacrylic Acid Copolymer I
Fosfomycin Calcium Tablets	Methacrylic Acid Copolymer II
Fosfomycin Calcium	Metoprolol Tartrate Sustained-release Tablets
Fosfomycin Trometamol Powder	Miconazole Nitrate Liniment
Fosfomycin Trometamol	Micronomicin sulfate Injection
Gadopentetate Dimeglumine Injection	Micronomicin sulfate Oral Solution
Ganciclovir and Sodium Chloride Injection	Micronomicin sulfate Tablets
Ganciclovir for Injection	Micronomicin sulfate
Ganciclovir	Mifepristone Tablets
Glipizide Capsules	Mifepristone
Gliquidone Tablets	Minocycline Hydrochloride Capsules
Gliquidone	Minocycline Hydrochloride Tablets
Glycerol and Fructose Injection	Minocycline Hydrochloride
Glycerol for Injection	Moclobemide Capsules
Glycine Irrigation Solution	Moclobemide Tablets
Glycopyrrolate Tablets	Moclobemide
Glycopyrrolate	Moracizine Hydrochloride Tablets
Granisetron Hydrochloride Injection	Moracizine Hydrochloride
Granisetron Hydrochloride Tablets	Naphazoline Hydrochloride Eye Drops
Granisetron Hydrochloride	Naphazoline Hydrochloride, Chlorphenamine Maleate and Vitamin B ₁₂ Eye Drops
Halcinonide Film	Naproxen and Codeine Phosphate Tablets
Heparin Sodium Cream	Nicardipine Hydrochloride and Glucose Injection
Huperzine A Capsules	Nicardipine Hydrochloride Injection
Huperzine A Injection	Nimodipine Capsules
Huperzine A Tablets	Nimodipine Dispersible Tablets
Huperzine A	Nimodipine Injection
Hydrocortisone Sodium Succinate for Injection	Nimodipine Tablets
Hydrocortisone Sodium Succinate	Nimodipine
Ibuprofen and Pseudoephedrine Hydrochloride Tablets	Nitroglycerin Aerosol
Ibuprofen Capsules	Norfloxacin Cream
Ibuprofen Drops	Ofloxacin Capsules
Ibuprofen Oral Solution	

Ofloxacin Ear Drops	Rifampicin and Isoniazid Capsules
Ofloxacin Eye Drops	Rifampicin and Isoniazid Tablets
Ofloxacin Eye Ointment	Rifampicin for Eye Use
Omeprazole Enteric-coated Capsules	Rifampicin Isoniazid and Pyrazinamide Capsules
Omeprazole Enteric-coated Tablets	Rifampicin Isoniazid and Pyrazinamide Tablets
Omeprazole	Roxithromycin Dispersible Tablets
Ondansetron Hydrochloride Injection	Roxithromycin for Suspension
Ondansetron Hydrochloride Tablets	Salbutamol Sulfate Sustained-release Capsules
Ondansetron Hydrochloride	Salbutamol Sulfate Sustained-release Tablets
Opium Tablets	Sodium Ferulate for Injection
Oxaprozin Enteric-coated Capsules	Sodium Ferulate Tablets
Oxaprozin Enteric-coated Tablets	Sodium Ferulate
Pantoprazole Sodium	Sodium Glycerophosphate Injection
Paracetamol and Caffeine Tablets	Sparfloxacin Capsules
Paracetamol Chewable Tablets	Sparfloxacin Tablets
Paracetamol Drops	Sparfloxacin
Paracetamol Effervescent Tablets	Sucralfate Dispersible Tablets
Paracetamol Gel	Sucralfate Oral Solution
Paracetamol Granules	Sultamicillin Tosilate Capsules
Paroxetine Hydrochloride Tablets	Sultamicillin Tosilate Granules
Pefloxacin Mesylate Capsules	Taurine Capsules
Pefloxacin Mesylate for Injection	Taurine Eye Drops
Pefloxacin Mesylate Injection	Tegafur Capsules
Pefloxacin Mesylate Tablets	Testosterone Undecanoate Soft Capsules
Pefloxacin Mesylate	Ticlopidine Hydrochloride Capsules
Pentoxifylline Sustained-release Tablets	Ticlopidine Hydrochloride Tablets
Phenoxymethylpenicillin Potassium Capsules	Ticlopidine Hydrochloride
Piperazine Ferulate Tablets	Timolol Maleate Tablets
Piperazine Ferulate	Tinidazole and Glucose Injection
Piracetam and Sodium Chloride Injection	Tinidazole Capsules
Piracetam Capsules	Tinidazole Suppositories
Piracetam Injection	Tramadol Hydrochloride Capsules
Piracetam Oral Solution	Tramadol Hydrochloride Suppositories
Piracetam Tablets	Tramadol Hydrochloride Sustained-release Capsules
Piracetam	Tramadol Hydrochloride Sustained-release Tablets
Piroxicam Gel	Tretinoin Cream
Polymycin B Sulfate for Injection	Triamcinolone Acetonide and Econazole Nitrate Cream
Polymycin B Sulfate	Ubenimex Capsules
Polyvinyl Alcohol Resin	Ubenimex
Poppy Capsule Extractive	Valacyclovir Hydrochloride Capsules
Potassium Dehydroandrographolide Succinate for Injection	Valacyclovir Hydrochloride Tablets
Potassium Dehydroandrographolide Succinate	Valacyclovir Hydrochloride
Powdered Poppy Capsule Extractive	Vindesine Sulfate for Injection
Probuco Tablets	Vindesine Sulfate
Probuco	Vinorelbine Tartrate Injection
Puerarin and Glucose Injection	Vinorelbine Tartrate
Puerarin and Sodium Chloride Injection	Vitamin C Effervescent Granules
Puerarin Injection	Xanthinol Nicotinate Injection
Puerarin	Xanthinol Nicotinate
Purple Ferric Oxide	Xylitol Granules
Raubasine	Xylitol
Refined Corn Oil	Yellow Ferric Oxide
Ribavirin and Glucose Injection	Zedoary Turmeric Oil Injection
Ribavirin and Sodium Chloride Injection	Zein
Ribavirin Buccal Tablets	Zinc Acexamate Capsules
Ribavirin Capsules	Zinc Acexamate
Ribavirin for Injection	Zinc Citrate Tablets
Ribavirin Granules	Zinc Citrate
Ribavirin Oral Solution	

Appendices

I J	Implants	XX G	Guidance for the Quality Control of Positron Emission Tomographic Radiopharmaceutical Preparation
VIII R	Total Organic Carbon in Water for Pharmaceutical Use	XX H	Guidance for the Quality Control of Technetium [^{99m}Tc] Radiopharmaceutical Preparations
IX H	Test for Visible Particles in Injection	XX J	Guidelines for Hygroscopicity
IX J	Mass Spectrometry	XX K	Guideline for Near-infrared (NIR) Spectrophotometry
X J	Determination of Patches Adhesion		
XI K	Test for Allergen		
XII O	Biological Assay of Calcitonin		
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XX F	Guidelines for the Analysis of Impurities in Drugs		

Omissions or Adjustments included in Volume II (2000 Edition)

Ciprofloxacin Lactate
Enterosoluble Capsules

Kanamycin Monosulfate
Vacant Capsules

Appendices

II General Requirements for Biological Products
(moved into Volume III of the Pharmacopoeia)
IV B Colourimetry (incorporated into IV A Ultraviolet-Visible Spectrophotometry)

XX F Guideline for Application of Bacterial Endotoxin
Tests (incorporated into XI E Test for Bacterial
Endotoxin)

General Notices

The Pharmacopoeia of the People's Republic of China known as Chinese Pharmacopoeia in abbreviation, is the official general scientific and technical provisions for drug quality control and administration.

Where the Pharmacopoeia is issued for enforcement by the drug regulatory authority of the State Council, the same drug standard of the previous Pharmacopoeia or the original national standard shall not be used. When the Chinese Pharmacopoeia is quoted in this compendium, it denotes the current edition of the Pharmacopoeia of the People's Republic of China, except where a specific edition is indicated.

General Notices serve as the basic guidelines for the proper interpretation and application of the Chinese Pharmacopoeia in quality control. It applies to any articles, appendices and general statements related to quality control of drugs so as to obviate replication in this compendium. The related requirements in General Notices are official in the Pharmacopoeia.

The wording "unless specified otherwise" adopted in General Notices and Appendices indicates that appropriate requirement is admitted in the related monograph wherever the requirement is not conform to that specified in General Notices or Appendices.

The drugs cited in the Pharmacopoeia should be those admitted in this edition of Pharmacopoeia and comply with the requirements of corresponding monographs.

The Guidelines stated in Appendices are not considered as official requirements but used as statements in principles applied to the implementation of Pharmacopoeia, monitoring of drug quality, and revising or verifying of drug standards.

Titles and Arrangements

1. The Chinese titles of drugs admitted in the monographs are recommended according to the guideline for the nomenclature of "Chinese Approved Drug Names". The Chinese title of a drug is adopted as official designation. Unless specified otherwise, the "International Nonproprietary Name" for pharmaceutical substances (INN) is adopted as the English title.

Titles of organic chemical drugs are adopted on the basis of "Guideline for the Nomenclature of Organic Chemistry" published by the Chinese Chemical Society. The selection of main part of its chemical structure is in line with the rules of the International Union of Pure and Applied Chemistry (IUPAC).

2. The chemical structure of the drugs are portrayed according to "Guidelines for Graphic Representation of Chemical Formulae" recommended by the World Health Organization.
3. The monographs are arranged alphabetically on the English titles of drugs. Monographs for formulated preparations are followed that of drug substance on title in the Pharmacopoeia. Monographs of excipients are listed in separate section. Appendices are arranged into sections including general requirements of formulated preparations, general testing methods and guidelines.
4. The monograph of each drug substance or different dosage forms is stated with respect to following

items; (1) Title of drug substance or dosage forms; (2) Structural formula of organic chemicals; (3) Molecular formula and molecular weight; (4) Sources or chemical name of organic drugs; (5) Content or potency; (6) Formulary of the dosage form; (7) Processing; (8) Description; (9) Identification; (10) Test; (11) Assay of content or potency; (12) Category; (13) Strength or specification; (14) Storage; (15) Preparation.

Specifications

5. *Description* refers to the appearance, odour, taste, solubility and other physical constants of the drug.

(1) Appearance of a drug is the requirements of colour and external appearance.

(2) *Solubility* refers to the physical property of a drug substance. Solvents described under the monograph and the relevant solubility behaviors are stated for reference for purification or preparation of solution of a drug substance. Requirement should be stated under the item of test of the drug, if specific quality control is needed for the solubility behavior of the solvent accordingly.

Approximate solubilities of drugs are indicated by the following descriptive phrases:

Very soluble refers to that 1 g (ml) of solute is soluble in less than 1 ml of solvent;

Freely soluble refers to that 1 g (ml) of solute is soluble in 1 ml to less than 10 ml of solvent;

Soluble refers to that 1 g (ml) of solute is soluble in 10 ml to less than 30 ml of solvent;

Sparingly soluble refers to that 1 g (ml) of solute is soluble in 30 ml to less than 100 ml of solvent;

Slightly soluble refers to that 1 g (ml) of solute is soluble in 100 ml to less than 1000 ml of solvent;

Very slightly soluble refers to that 1 g (ml) of solute is soluble in 1000 ml to less than 10000 ml of solvent;

Practical insoluble refers to that 1 g (ml) of solute is not soluble completely in 10000 ml of solvent.

Testing method: Unless specified otherwise, weigh out finely powdered sample or measure an amount of liquid sample, place the sample in a certain volume of the solvent at a temperature of $25^{\circ}\text{C} \pm 2^{\circ}\text{C}$, shake strongly for 30 seconds at an interval of 5 minutes. Observe the solubility behavior for 30 minutes. It is considered to be completely soluble, if none of the particles or droplet of the solute is observed.

(3) Physical constants or parameters including relative density, distilling range, melting point or melting range, congealing point, specific rotation, refractive index, viscosity, specific absorbance, iodine value, saponification value and acid value etc., are useful for tests for identification and give some indication of the drug purity. It is one of the chief criteria for appraisal and assessment of drug quality.

6. Testing methods given in the identification section are intended to give some of the physical and chemical characteristics of the drug, they are not designed to give a full confirmation of the chemical structure of the drug.

7. Test section under the monograph includes the testing methods and acceptance criteria, uniformity and purity requirements for manufacturing process, which are related to the safety and efficacy of the drug. The specified testing items for impurities are framed from those possibly existed and produced in the drug, which is manufactured according to the approved manufacturing process and stored under normal condition, and those impurities are needed to be controlled, such as residual solvents and related substances, etc. Revising to the relevant items may be necessary for where the manufacturing process is changed.

The drug substance intended for direct use in the preparation of sterile powders for injection should be

tested according to the corresponding requirements of the injection and conform with the requirements. Preparations, unless specified otherwise, must comply with the requirements stated under the general requirements for preparations of the Pharmacopoeia.

8. The testing methods specified under the item of Assay are designed to determine the content of active ingredient of drug substance and preparations, Chemical, instrumental or biological methods can usually be adopted.
9. *Category* refers to main action and use of the drugs or its classified scientific designation. A drug is not framed from using in other category on the basis of experiences in clinical practices.
10. *Strength* of preparations or dosage forms refers to the amount (units of potency), labelled amount (%) or content of active ingredient or ingredients in each ampoule, tablet or other unit container, or preparation. For injections, the expression "1 ml; 10 mg" indicates that the injection contains 10 mg of active ingredient in 1 ml. Specification of weight or content may also be specified for the monographs of the preparation in which the formula is listed or the concentration is indicated.
11. *Storage* refers to the basic conditions for storage and preservation of a drug. It is stated by the following terms:
 - Protected from light* refers to that a drug should be kept in light resistant container such as amber coloured container, or a colourless transparent or semitransparent container wrapped with black paper.
 - Well closed* refers to that the container is able to protect the content from extraneous matters or lose of contents on normal handling condition.
 - Tightly closed* refers to that the container should be able to protect the contents from efflorescence, deliquescence, volatilization or interference of extraneous matters.
 - Hermetically sealed or Tightly sealed* refers to that the container is sealed on fusion or sealed tightly with suitable material to protect against contamination and from permeability of air and moisture.
 - Cool place* refers to that the storage temperature is not exceeding 20°C.
 - Cool and dark place* refers to that the container is kept in the dark place, protected from light and the ambient temperature is not exceeding 20°C.
 - Cold place* refers to that the container is kept at ambient temperature of 2-10°C.
 - Normal temperature* refers to that the container is kept at ambient temperature of 10-30°C
12. The drug substances and excipients used in preparations or dosage forms should comply with the requirements stated in the individual monographs of this edition of Pharmacopoeia; for those not admitted in this edition of Pharmacopoeia their specifications should be established, which should comply with requirements for pharmaceutical use and be approved by the drug regulatory authority of the State Council. Where the same drug substance is used for different preparations, especially for preparations with different administration routes, it is necessary to establish corresponding testing items for quality control according to the clinical usage of the drug.

Testing Methods and Limits

13. The drug substances and preparations should be tested with official methods stated in the Pharmacopoeia. It is not precluded from the application of alternative methods, if they have been proved to be satisfactory in comparison with official methods accordingly. In case of doubt or

dispute, the methods of the Pharmacopoeia are authoritative for judgement.

14. Purity requirements and limits of purity of a drug substance as well as the weight (or content) variation of a preparation or dosage form stated in the monograph concerned include the values of upper and lower limits and the medium value. Whether these values are expressed in percentage or in absolute numerical value, the last decimal is a significant value.

In calculating of testing result, the last effective figure is measured in one decimal place more than the significant decimal place indicated in the requirement and round up or down to the specified decimal place by the rule of commensuration, the value obtained is compared with the limits of the standard to determine the conformity with the specified limits.

15. The percentage content of the drug substance is calculated by weight, unless specified otherwise. If an upper limit of the content of a drug is stated as over 100% it refers to a value possibly obtained by the assigned assay method in the monograph, representing the limit or permissible deviation stated in the Pharmacopoeia. In case of no upper limit is stated, the upper limit is considered to be not more than the equivalent amount of 101.0%.

The limit range of content of a preparation or dosage form is assigned on the basis of contents of active ingredient or ingredients, assay method being applied and possible change occurred in the process of manufacturing and/or storage. A 100% labelled amount of active ingredient or ingredients should be used in manufacturing process. If a certain active ingredient is known to be lowering its content in manufacturing process or in the storage period, sufficient amount of active ingredient concerned may be used to ensure that the content of the drug produced or being used in its shelf life complies with the requirements of the Pharmacopoeia.

Reference Standards, Chemical Reference Substances

16. Reference standards and chemical reference substances refer to the standard materials used in testing of identification, test and assay. Those, excluding from internal standard materials used in chromatographic methods, are established, standardized, and distributed by the institution designated by the drug regulatory authority of the State Council. Reference standards are used for bioassay in assay of potency (content) of antibiotics or biochemical drugs. The potency is expressed in units (or μg), standardized against International Reference Standard. Chemical reference substances, unless specified otherwise, are used by calculation on the basis of dried or anhydrous materials.

The establishment or alteration in unit of potency or content of reference standards and chemical reference substances should be conducted in comparison with the original reference standard, chemical reference substances or International Reference Standard by collaborative standardization, and the protocol and testing results should be reviewed and approved by audit process.

Reference standards and chemical reference substances are distributed with appropriate instruction insert to state the method of usage, quality specification (including water content etc), expiry date and amount or content of the standard material concerned.

Units of Measurement

17. The measuring apparatus used for tests and assays should comply with the relevant requirements promulgated by the technical supervision authority of the State Council.
18. The units of measurement in this edition of Pharmacopoeia:

(1) The official names and symbols of units of measurement are listed as follows: Units of length; meter m; decimeter dm; centimeter cm; millimeter mm; micrometer μm ; nanometer nm

Units of volume: liter (L); milliliter (ml); microliter (μl)

Units of mass (weight): kilogram (kg); gram (g); milligram (mg); microgram (μg)

Units of pressure: pascal (Pa); kilopascal (kPa); megapascal (MPa)

Units of kinetic viscosity : pascal seconds ($\text{Pa} \cdot \text{s}$)

Units of kinematic viscosity: square millimeter per second (mm^2/s) Units of wave number; reciprocal of centimeter (cm^{-1})

Units of density: kilogram per cubic meter (kg/m^3); gram per cubic centimeter (g/cm^3)

Units of radioactivity: becquerel (Bq); kilobecquerel (kBq); megabecquerel (MBq)

(2) Where the strengths or concentrations of the volumetric solutions and test solutions are expressed in terms of mol/L in this edition of Pharmacopoeia, the expression of “XXX volumetric solution (YYY mol/L)” is adopted for the volumetric solution which should be accurately standardized. The expression of “YYY mol/L XXX solution ” is adopted for solutions of other purpose without specific accuracy of their concentration.

(3) Temperature is expressed in $^{\circ}\text{C}$ (degree Celsius).

The temperature of a *Water bath* is $98\text{--}100^{\circ}\text{C}$, unless specified otherwise;

Hot water refers to that at a temperature of $70\text{--}80^{\circ}\text{C}$;

Slightly warm or Warm water refers to that at a temperature of $40\text{--}50^{\circ}\text{C}$;

Room temperature refers to that at a temperature of $10\text{--}30^{\circ}\text{C}$;

Cold water refers to that at a temperature of $2\text{--}10^{\circ}\text{C}$;

Ice bath refers to the bath temperature is kept at about 0°C ;

Allow to cool refers to that the object is cooled to room temperature;

(4) The symbol used for the expression of percentage is %, usually by weight, but the percentage of solutions, unless specified otherwise, refers to the number of grams of solute in 100 ml of the solution. The percentage of ethanol refers to percentage by volume at 20°C .

The following symbols may be used when needed:

% (g/g) expresses the number of grams of a solute in 100 g of solution;

% (ml/ml) expresses the number of milliliters of a solute in 100 ml of solution;

% (ml/g) expresses the number of milliliters of a solute in 100 g of solution;

% (g/ml) expresses the number of grams of a solute in 100 ml of solution.

(5) The Drop of a liquid refers to that 1.0 ml of water is equivalent to 20 drops at the temperature of 20°C .

(6) The expression “ (1 \rightarrow 10)” stated under the solution refers to a solution of 10 ml produced by adding sufficient quantity of solvent to dissolve 1.0 g or 1.0 ml of a solute. It is understood to be aqueous solution, if the solvent is not specified. In case of two or more solvents are used as a mixture, a hyphen is inserted between different solvents indicated by names, the parenthesis followed expresses the proportion of each solvent by volume in the mixture.

(7) Sieves of Chinese National Standard R40/3 series are adopted in the Pharmacopoeia and the numbers are assigned as follows:

Sieve No.	Average internal diameter of aperture (μm)	Mesh No.
1	2000 ± 70	10
2	850 ± 29	24
3	355 ± 13	50
4	250 ± 9.9	65

5	180±7.6	80
6	150±6.6	100
7	125±5.8	120
8	90±4.6	150
9	75±4.1	200

Powders are graded as follows:

Very coarse All particles pass through No. 1 sieve, not more than 20% pass through No. 3 sieve;

Coarse All particles pass through No. 2 sieve, not more than 40% pass through No. 4 sieve;

Medium All particles pass through No. 4 sieve, not more than 60% pass through No. 5 sieve;

Fine All particles pass through No. 5 sieve, not less than 95% pass through No. 6 sieve;

Very fine All particles pass through No. 6 sieve, not less than 95% pass through No. 7 sieve;

Ultra fine All particles pass through No. 8 sieve, not less than 95% pass through No. 9 sieve.

(8) Ethanol refers to that of 95% (ml/ml) in strength, unless specified otherwise.

19. The atomic weights adopted for calculating the molecular weights and the conversion factors are the values recently published by the International Union of Pure and Applied Chemistry.

Precision and Accuracy

20. The accuracy of sampling quantity and precision of testing are defined in this edition of Pharmacopoeia.

(1) The quantity obtained by weighing or measuring the substance being examined and reagent being used is expressed in Arabic figures. The required precision is expressed by the significant numerical place. For example, the measurement of "0.1 g" by weight, refers to that 0.06-0.14 g of the substance may be weighed; for "2 g", 1.5-2.5 g of the substance may be weighed; for "2.0 g", it refers to 1.95-2.05 g of the substance may be weighed; for "2.00 g", it refers to that 1.995-2.005 g of the substance may be weighed.

Weigh accurately indicates that the precision of measurement should be made to an accuracy of 0.1%; *weigh* indicates that an accuracy being made to 1%. *Measure accurately* indicates the accuracy of the volume being measured complies with the national standard of pipet being used for the measurement of required volume;

Measure indicates that the measuring cylinder or other measuring apparatus being used complies with requirements for the measurement of volume to the significant numerical place. The word *about* states that the measuring quantity should not exceed $\pm 10\%$ of the specified quantity.

(2) *Constant weight*, unless specified otherwise, refers to that the drying or ignition of a substance or material in two consecutive weighings do not differ by more than 0.3 mg. The second and subsequent weighing are made after an additional hour of drying each time under the similar condition. The second weighing of the substance or material made to constant weight by ignition is made after 30 minutes under similar condition.

(3) The expression of *calculated on the dried (anhydrous or solvent free) basis* indicates that, unless specified otherwise, the undried substance or solvent containing substance is used for the required testing. The result of "Loss on drying (moisture or solvent)" should be subtracted from the amount of substance

(4) *Blank test* refers to a test carried out in the similar manner without the substance being examined or using same amount of solvent instead of the solution being tested. The statement of *to make any necessary correction of the result with a blank test* refers to that the result is calculated by subtracting number of milliliters of titrant used in blank test from that consumed in assay of the substance being examined.

(5) The temperature for a test is at room temperature whenever the temperature is not stated. In case of that the temperature variation influences significantly to the testing result, the test should be carried out at a temperature of $25^{\circ}\text{C} \pm 2^{\circ}\text{C}$, unless specified otherwise.

Reagents, Test solutions and Indicators

21. Reagents used in tests and assays, unless specified otherwise, should comply with the requirements stated in the Appendix of the Pharmacopoeia. Different grades of reagents conform to national standards or those issued by the competent authorities may be used of choice. Test solutions, buffer solutions, indicator solutions, volumetric solutions and so on should comply with the statements or be prepared as directed in the Appendix of the Pharmacopoeia.
22. Water being used in tests and assays refer to purified water. Water being used for the test of acidity or alkalinity is of the water freshly boiled and cooled to room temperature.
23. Test for acidity or alkalinity of a solution without the statement of indicator being used refers to that Litmus paper is used.

Animal Test

24. Laboratory animals used and managed in animal tests should comply with the requirements stipulated and promulgated by competent authorities of the State Council.
The strain, age, sex etc., should comply with the requirements for quality control of drugs and biological products.
The animal tests should be adopted only in necessary condition and become less popular, as for the purity of drugs raise to higher level and more precise chemical, physical or cellular method should be applied to replace the animal test as much as possible for the quality control of drugs and biological products.

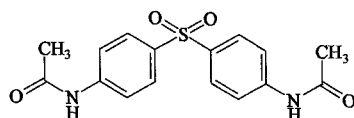
Insert sheet, Package and Labelling

25. The insert sheet of drugs should be in conformity with the requirements of “The Drug Administration Law of the People’s Republic of China”, and provisions for insert sheet promulgated by the drug regulatory authority of the State Council.
26. The immediate packaging materials and containers should be in conformity with the relevant provisions promulgated by the drug regulatory authority of the State Council. The immediate packaging materials and containers must be innocuous, clean, not interact with the drugs being packed, and do not affect the drug quality in the containers.
27. Labelling of drugs must comply with the requirements of “The Drug Administration Law of The People’s Republic of China”, and the provisions for the package and labeling promulgated by the drug regulatory authority of the State Council. The content of the labeling for different packaging should be printed in accord with the above requirement, in which the drug information should be provided as more as possible.
28. A stated mark should be printed on the insert sheet and the labelling of package for narcotics, psychological drugs, toxic drugs for medical use, radioactive drugs, drugs for external use and nonprescription drugs.

MONOGRAPHS

PART I

Acedapsone



$C_{16}H_{16}N_2O_4S$ 332.38

[77-46-3]

Acedapsone is 4,4'-sulfonylbis (acetanilide). It contains not less than 99.0% of $C_{16}H_{16}N_2O_4S$, calculated on the dried basis.

Description A white to slightly yellow crystalline powder; odourless; tasteless. Very slightly soluble in ethanol; practically insoluble in water, ether, dilute hydrochloric acid or sodium hydroxide TS.

Identification (1) To 0.1 g add 5 ml of ethanol and 1 ml of sulfuric acid, mix well, heat, the characteristic odour of ethylacetate is perceptible.

(2) The light absorption of a solution of 5 μ g per ml in dehydrated ethanol exhibits maxima at 256 nm and 284 nm (Appendix IV A).

(3) The infrared absorption spectrum (Appendix IV C) is concordant with the reference spectrum of acedapsone (Appendix XVI).

(4) Dissolve 0.1 g in 5 ml of sulfuric acid solution (2→5) by heating, allow it to cool, add 5 ml of water, the solution yields the reaction characteristic of primary aromatic amines (Appendix III).

Dapsone Carry out the method for thin layer chromatography (Appendix V B), using silica gel G as the coating substance and a mixture of toluene-acetone (2 : 1) as the mobile phase. Apply separately to the plate 20 μ l of solution (1) containing 1 mg per ml of the substance being examined in methanol, 5 μ l of solution (2) containing 50 μ g per ml and (3) 200 μ g per ml of dapsone CRS respectively in methanol. After developing and removal of the plate, dry it in air and spray with a 0.5% solution of sodium nitrite in hydrochloric acid solution (0.1 mol/L). Allow it to stand for a few minutes, spray with a 0.1% solution of *n*-(1-naphthyl) ethylenediamine dihydrochloride. Any spot other than the principal spot in the chromatogram obtained with solution (1) is not more intense than the principal spot obtained with solution (2), and not more than two of secondary spots are intense than the principal spot obtained with solution (3).

Loss on drying When dried to constant weight at 105°C, loses not more than 1.0% of its weight (Appendix VIII L).

Residue on ignition Not more than 0.1% (Appendix VIII N), using 1.0 g.

Heavy metals Carry out the limit test for heavy metals (Appendix VIII H, method 2), using the residue obtained in the test for Residue on ignition; not more than 0.001%.

Assay Dissolve about 0.5 g, accurately weighed, in 75 ml of hydrochloric acid solution (1→2) in a conical flask, place a small funnel on the conical flask, heat to boiling and keep boil gently for about 30 minutes, cool. Transfer the solution to a beaker, wash the conical flask with 25 ml of water in portions and add the washings to the beaker. Carry out the method for dead-stop titration (Appendix VII A), titrate with sodium nitrite (0.1 mol/L) VS. Each ml of sodium nitrite (0.1 mol/L) VS is equivalent to 16.62 mg of

$C_{16}H_{16}N_2O_4S$.

Category Teprostatic.

Storage Preserve in tightly closed containers.

Preparation Acedapsone Injection

Acedapsone Injection

Acedapsone Injection is a sterile suspension of acedapsone in oil for Injection. It contains not less than 90.0% and not more than 110.0% of the labelled amount of acedapsone ($C_{16}H_{16}N_2O_4S$).

Description A fine granular oily suspension. Allow it to stand, a fine sediment may be produced, which is readily dispersible on shaking.

Identification Shake about 2 ml with 10 ml of chloroform and filter with filter paper moistened with chloroform, wash the residue with 15 ml of chloroform in 3 portions. Dry the residue at 105°C, it complies with tests (1) and (4) for Identification described under Acedapsone.

Particular matter Shake vigorously a quantity of acedapsone injection. Place immediately 1 drop of the suspension on a microscope slide and cover it with a cover glass. Examine the object under a microscope equipped with eyepiece micrometer, shift the slide to examine the uniformity of the particles in the visual fields, no particles larger than 100 μ m in diameter are observed; then examine the object for 4-5 visual fields and count the number of the particles, not less than 90% of the particles are smaller than 15 μ m in diameter and not more than 10% of the particles of 15-20 μ m in diameter (20-100 μ m may be occasionally observed).

Other requirements Complies with the general requirements for injections (Appendix I B).

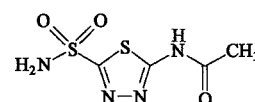
Assay Mix well the suspension and measure accurately a quantity equivalent to about 0.3 g of acedapsone, carry out the Assay described under Acedapsone.

Category As described under Acedapsone.

Strength (1) 1.5 ml : 0.225 g (2) 3 ml : 0.45 g
(3) 6 ml : 0.9 g

Storage Preserve in tightly closed containers, protected from light.

Acetazolamide



$C_4H_6N_4O_3S_2$ 222.25

[59-66-5]

Acetazolamide is *N*-[5-(aminosulfonyl)-1,3,4-thiadiazol-2-yl]-acetamide. It contains not less than 98.0% and not more than 102.0% of $C_4H_6N_4O_3S_2$.

Description White needle crystals or a white crystalline powder; odourless; taste, slightly bitter. Sparingly soluble in boiling water; very slightly soluble in water or ethanol; practically insoluble in chloroform or ether; freely soluble in ammonia solution.

Identification (1) Dissolve about 0.1 g by adding sodium hydroxide TS dropwise, add 10 ml of water and 1 drop of phenolphthalein IS. Add dilute hydrochloric acid dropwise until the pink colour disappears and add a few drops of mercuric nitrate TS; a white precipitate is formed.

(2) To 0.2 g in a test tube add 1 ml each of ethanol and sulfuric acid, the odour of ethyl acetate is perceptible on heating.

(3) The infrared absorption spectrum (Appendix IV C) is concordant with the reference spectrum of acetazolamide (Appendix XVI).

Acidity Shake 1.0 g with 50 ml of hot water and cool, pH 4.0-6.0 (Appendix VI H).

Clarity of alkaline solution A solution of 1.0 g in 5 ml of 10% sodium hydroxide solution is clear.

Chloride Dissolve 2.0 g in 100 ml of water by heating, cool quickly and filter. Carry out the limit test for chlorides (Appendix VIII A), using 25 ml of the filtrate. Any opalescence produced is not more pronounced than that of a reference using 2.0 ml of sodium chloride standard solution (0.014%).

Sulfate Carry out the limit test for sulfates (Appendix VIII B), using 25 ml of the filtrate obtained in the test of Chloride. Any opalescence produced is not more pronounced than that of a reference using 2.0 ml of potassium sulfate standard solution (0.04%).

Related Substance Carry out the method for thin-layer chromatography (Appendix V B), using silica gel GF₂₅₄ as the coating substance and a freshly prepared mixture of isopropanol-ethyl acetate-13.5 mol/L ammonia solution (50 : 30 : 20) as the mobile phase. Apply separately to the plate 20 µl of each of two solutions of the substance being examined containing (1) 50 mg and (2) 0.05 mg per ml in a mixture of 96% ethanol-ethyl acetate (1 : 1). After developing and removal of the plate, dry it in the air, and examine under ultra violet light (254 nm). Any spot other than principal spot in the chromatogram obtained with solution (1) is not more intense than the principal spot obtained with solution (2).

Reducing substances Impregnate 5.0 g with 5 ml of dehydrated ethanol, add 125 ml of water, 10 ml of nitric acid and 5.0 ml of silver nitrate (0.1 mol/L) VS, shake thoroughly and allow to stand in the dark for 30 minutes. Filter through a sintered glass filter and wash with 10 ml of water. Combine the filtrate and washings, add 5 ml of ferric ammonium sulfate IS, titrate with ammonium thiocyanate (0.1 mol/L) VS, not less than 4.8 ml of ammonium thiocyanate (0.1 mol/L) VS is required.

Loss on drying When dried to constant weight at 105°C, loses not more than 0.5% of its weight (Appendix VIII L).

Residue on ignition Not more than 0.1% (Appendix VIII N).

Heavy metals Carry out the limit test for heavy metals (Appendix VIII H, method 3), using 0.50 g; not more than 0.002%.

Assay Dissolve 0.2 g, accurately weighed, in 400 ml of boiling water, cool, transfer to a 1000 ml volumetric flask, dilute with water to volume, and mix well. Measure accurately 5 ml to a 100 ml volumetric flask, add 10 ml of 1 mol/L hydrochloric acid solution, dilute with water to volume and mix well. Measure the absorbance at 265 nm (Appendix IV A), calculate the content of C₄H₆N₄O₃S₂, taking 474 as the value of A (1%, 1 cm).

Category Carbonic anhydrase inhibitor.

Storage Preserve in tightly closed containers, protected

from light.

Preparation Acetazolamide Tablets

Acetazolamide Tablets

Acetazolamide Tablets contain not less than 95.0% and not more than 105.0% of the labelled amount of acetazolamide (C₄H₆N₄O₃S₂).

Description White tablets.

Identification (1) To a quantity of the powdered tablets, equivalent to about 0.2 g of acetazolamide, add 3 ml of water and 1 ml of sodium hydroxide TS, stir and filter. To 2 ml of the filtrate add 8 ml of water and mix well. The solution complies with test (1) for Identification described under Acetazolamide.

(2) A quantity of the powdered tablets equivalent to about 50 mg of acetazolamide complies with test (2) for Identification described under Acetazolamide.

Dissolution Carry out the dissolution test (Appendix X C, method 2), using 150 ml of acetic acid-sodium acetate BS (pH 4.5) diluted with water to 900 ml as the dissolution medium, adjust the rotational speed of the paddle to 100 rpm. Withdraw 5 ml of the solution after exactly 45 minutes and filter. Transfer 2 ml of the successive filtrate, accurately measured, to a 50 ml volumetric flask, dilute with the dissolution medium to volume and mix well. Measure the absorbance at 265 nm (Appendix IV A). Calculate the dissolution of C₄H₆N₄O₃S₂ from each tablet, taking 474 as value of A (1%, 1 cm), not less than 75% of the labelled amount is dissolved.

Other requirements Comply with the general requirements for tablets (Appendix I A).

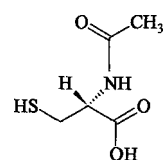
Assay Weigh accurately and powder 10 tablets. To a quantity of the powder equivalent to about 0.2 g, accurately weighed, of acetazolamide add 400 ml of boiling water, stir for 15 minutes and cool. Transfer to a 1000 ml volumetric flask, add water to volume, mix well and filter. Measure accurately 5 ml of the successive filtrate to a 100 ml volumetric flask, add 10 ml of 1 mol/L hydrochloric acid solution, dilute with water to volume and mix well. Measure the absorbance at 265 nm (Appendix IV A). Calculate the content of C₄H₆N₄O₃S₂, taking 474 as the value of A (1%, 1 cm).

Category As described under Acetazolamide.

Strength 0.25 g

Storage Preserve in tightly closed containers, protected from light.

Acetylcysteine



C₅H₉NO₃S 163.20

[616-91-1]

Acetylcysteine is *N*-acetyl-*L*-cysteine. It contains not less than 98.0% and not more than 102.0% of

$C_5H_9NO_3S$, calculated on the dried basis.

Description A white crystalline powder; odour, characteristic, resembling that of garlic; taste, sour; hygroscopic. Freely soluble in water or ethanol.

Melting range 101-107°C (Appendix VI C).

Identification (1) Dissolve about 0.1 g in 2 ml of 10% sodium hydroxide solution, add 1 ml of lead acetate TS, boil, a yellowish-brown colour is produced gradually and then a black precipitate is formed.

(2) Dissolve about 10 mg in 1 ml of sodium hydroxide TS, add a few drops of sodium nitroprusside TS, mix well, a deep red colour is produced, which turns to yellow with a red ring on standing, and then to red again on shaking.

(3) The infrared absorption spectrum (Appendix IV C) is concordant with the reference spectrum of acetylcysteine (Appendix XVI).

Acidity Dissolve 1.0 g in 20 ml of water, pH 1.5-2.5 (Appendix VI H).

Clarity of solution A solution of 1.0 g in 10 ml of water is clear.

Loss on drying When dried under reduced pressure over phosphorous pentoxide for 24 hours, loses not more than 3.0% of its weight (Appendix VIII L).

Residue on ignition Not more than 0.1% (Appendix VIII N), using 1.0 g.

Heavy metals Carry out the limit test for heavy metals (Appendix VIII H, method 2), using the residue obtained in the test for Residue on ignition; not more than 0.001%.

Assay Dissolve about 0.3 g, accurately weighed, in 30 ml of water, titrate with iodine (0.05 mol/L) VS rapidly at 20-25°C until the solution turns yellow and persists for not less than 30 seconds. Each ml of iodine (0.05 mol/L) VS is equivalent to 16.32 mg of $C_5H_9NO_3S$.

Category Mucolytic agent.

Storage Preserve on tightly closed containers, stored in a dark and cool place.

Preparation Acetylcysteine for inhalation

Acetylcysteine for inhalation

Acetylcysteine for Inhalation contains not less than 95.0% and not more than 105.0% of the labelled amount of acetylcysteine ($C_5H_9NO_3S$), calculated on the basis of average content.

Description A white crystalline powder.

Identification Complies with tests for Identification (1), (2) described under Acetylcysteine.

Acidity, Clarity of solution, Loss on drying Complies with the corresponding requirements described under Acetylcysteine.

Weight variation Complies with the test described under powders for injections (Appendix I B).

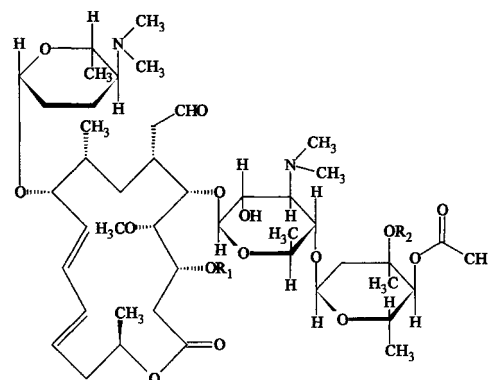
Assay Mix the contents obtained from the test for weight variation of contents, carry out the Assay described under Acetylcysteine. Each ml of iodine (0.05 mol/L) VS is equivalent to 16.32 mg of $C_5H_9NO_3S$.

Category As described under Acetylcysteine.

Strength (1) 0.5 g (2) 1 g

Storage Preserve in hermetically sealed containers, stored in a dark and cool place.

Acetylspiramycin



Monoacetylspiramycin II: $R_1 = COCH_3$ $R_2 = H$

Monoacetylspiramycin III: $R_1 = COCH_2CH_3$ $R_2 = H$

Diacetylspiramycin II: $R_1 = COCH_3$ $R_2 = COCH_3$

Diacetylspiramycin III: $R_1 = COCH_2CH_3$ $R_2 = COCH_3$

Acetylspiramycin is a mixture mainly containing monoacetylspiramycin II, monoacetylspiramycin III, diacetylspiramycin II and diacetylspiramycin III. It has a potency of not less than 1200 Acetylspiramycin Units per mg, calculated on the dried basis.

Description A white or slightly yellow powder; taste, bitter. Soluble in methanol, ethanol, acetone or ether; practically insoluble in water; insoluble in petroleum ether.

Identification (1) Carry out the method for thin-layer chromatography (Appendix V B), using 0.6 g of silica gel G mixed with 2.5 ml of sodium hydroxide (0.1 mol/L) as the coating substance and a mixture of toluene-methanol (9 : 1) as mobile phase, dry the coated glass plate (20 cm × 5 cm) in air and activate at 105°C for 30 minutes. Apply separately to the plate 10 μl each of two solutions in methanol containing (1) 5 mg per ml of the substance being examined and (2) 5 mg per ml of acetylspiramycin CRS respectively. After developing and removal of the plate, dry it in air, visualize with iodine vapor. The colour and position of the four principal spots in the chromatogram obtained with solution (1) correspond to that of the principal spots obtained with solution (2).

(2) The retention times of the four principal peaks of acetylspiramycin in the substance being examined in the chromatogram obtained in the test for Acetylspiramycin components are identical with those of the four principal peaks of acetylspiramycin CRS in the chromatogram of the reference solution correspondingly.

Test (1) or (2) may be used alternative.

Loss on drying When dried to constant weight at 105°C, loses not more than 3.0% of its weight (Appendix VIII L).

Acetylspiramycin components Carry out the method for high performance liquid chromatography (Appendix V D), using a column packed with octadecylsilane bonded silica gel and a mixture of acetonitrile-0.1 mol/L ammonium acetate (60 : 40) with a pH value adjusted to 7.2 ± 0.1 by acetic acid as the mobile phase. Detection wavelength is 232 nm. The number of the theoretical plates of the column is not less than

1000, calculated with reference to the peak of monoacetylspiramycin III. The resolution factor between the peaks of monoacetylspiramycin III and diacetylspiramycin II complies with the related requirements.

Procedure Dissolve an accurately weighed quantity in mobile phase to produce a solution of 1 mg per ml, mix well and filter. Inject 10 μ l of the successive filtrate into the column and record the chromatogram. The retention times of the four principal peaks are in this order: monoacetylspiramycin II, monoacetylspiramycin III, diacetylspiramycin II, and diacetylspiramycin III. Calculate the content of monoacetylspiramycin (II + III) and diacetylspiramycin (II + III) as follows. Either the content of monoacetylspiramycin (II + III) or that of diacetylspiramycin (II + III) is not less than 35%.

$$\begin{aligned} \text{Monoacetylspiramycin (II + III)} \\ &= \frac{A_{\text{mono II}} + A_{\text{mono III}}}{A_{\text{mono II}} + A_{\text{mono III}} + A_{\text{di II}} + A_{\text{di III}}} \times 100\% \\ \text{Diacetylspiramycin (II + III)} \\ &= \frac{A_{\text{di II}} + A_{\text{di III}}}{A_{\text{mono II}} + A_{\text{mono III}} + A_{\text{di II}} + A_{\text{di III}}} \times 100\% \end{aligned}$$

Where $A_{\text{mono II}}$ is the peak area of monoacetylspiramycin II; $A_{\text{mono III}}$ is the peak area of monoacetylspiramycin III; $A_{\text{di II}}$ is the peak area of diacetylspiramycin II; $A_{\text{di III}}$ is the peak area of diacetylspiramycin III.

Repeat the operation, using acetylspiramycin CRS instead of the substance being examined. Calculate the sum content of the four main contents by the external standard method, not less than 75%.

The sum content of the four main components

$$= \frac{A_T W_S P}{A_S W_T} \times 100\%$$

Where A_T is the sum area of the four peaks of the substance being examined; A_S is the sum area of the four peaks of acetylspiramycin CRS; W_S is the weight of the substance being examined; W_T is the weight of acetylspiramycin CRS; P is the sum area of the four peaks of acetylspiramycin CRS.

Assay Dissolve an accurately weighed quantity in ethanol (using 2 ml of ethanol for 5 mg), dilute with sterile water to produce a solution of 1000 Units per ml. Carry out the microbiological assay of antibiotics (Appendix XI A).

Category Macrolide antibiotic.

Storage Preserve in tightly closed containers, stored in a dry, cool and dark place.

Preparation (1) Acetylspiramycin Capsules
(2) Acetylspiramycin Tablets

Acetylspiramycin Capsules

Acetylspiramycin Capsules contain not less than 90.0% and not more than 110.0% of the labelled amount of acetylspiramycin.

Description Capsules containing almost white to slightly yellow powder or granules.

Identification A quantity of the content of the capsule complies with the tests for Identification described under Acetylspiramycin Tablets.

Loss on drying When dried to constant weight at 105°C, loses not more than 4.0% of its weight (Appendix VIII L).

Acetylspiramycin components Dissolve an accurately weighted quantity of the contents of the capsules in mobile phase to produce a solution of 1 mg per ml, mix well and filter, carry out the test for Acetylspiramycin components described under Acetylspiramycin. Either the content of monoacetylspiramycin (II + III) or that of diacetylspiramycin (II + III) is not less than 35%, the sum content of the four principal components is not less than 70%, calculated by the following formula.

The sum content of the four main contents

$$\begin{aligned} &A_T W_S \times \text{average weight} \times P \times \\ &= \frac{\text{Potency of Acetylspiramycin CRS}}{A_S W_T \times \text{labelled amount}} \times 100\% \end{aligned}$$

Where A_T is the sum area of the four peaks of the substance being examined;

A_S is the sum area of the four peaks of the acetylspiramycin CRS;

W_S is the weight of the substance being examined;

W_T is the weight of the acetylspiramycin CRS;

P is the sum area of the four peaks of the acetylspiramycin CRS.

Dissolution Carry out the dissolution test (Appendix X C, method 2), using hydrochloride acid solution (24 ml of dilute hydrochloride acid solution \rightarrow 1000 ml) as the dissolution medium, adjust the rotational speed of the paddle to 50 rpm. Withdraw the solution after exact 45 minutes and filter. Dilute an accurately measured quantity of the successive filtrate with the above hydrochloride acid solution to produce a solution of 20 μ g per ml. Dissolve an accurately weighted quantity of the mixed contents in the test for weight variation of contents equivalent to about the average weight of one capsule in ethanol, using 2 ml of ethanol for 5 mg and dilute with the above solvent to produce a solution of 100 μ g per ml and filter, dilute an accurately weighted quantity of the successive filtrate with hydrochloride acid solution to produce a solution of 20 μ g per ml. Measure the absorbance of the resulting solutions at 232 nm (Appendix IV A), calculate the dissolution of acetylspiramycin from each capsule. Not less than 75% of the labelled amount is dissolved.

Other requirements Comply with the general requirements for capsules (Appendix I E).

Assay Dissolve an accurately weighted quantity of the mixed contents in the test for weight variation of contents (equivalent to about 0.1 g of acetylspiramycin) in ethanol (using 2 ml of ethanol for 5 mg), dilute with sterile water to produce a solution of 1000 Units per ml, mix well and allow to stand. Measure accurately a quantity of the supernatant liquid and carry out the Assay described under Acetylspiramycin (Appendix VI A).

Category As described under Acetylspiramycin.

Strength (1) 0.1 g (100000 units)
(2) 0.2 g (200000 units)

Storage Preserve in tightly closed containers, stored in a dry, cool and dark place.

Acetylspiramycin Tablets

Acetylspiramycin Tablets contain not less than 90.0% and not more than 110.0% of the labelled amount of acetylspiramycin.

Description Sugar coated or film coated tablets with almost white or slightly yellow core.

Identification Carry out the following test, using a quantity of the powdered and coating-removed tablets.

(1) To a quantity equivalent to about 0.1 g of acetylspiramycin add 10 ml of methanol, shake thoroughly to dissolve acetylspiramycin and filter. Dilute 1 ml of the successive filtrate with methanol solution (1→5) to produce a solution of 20 µg per ml. The light absorption of the resulting solution exhibits a maximum at 232 nm (Appendix IV A).

(2) The retention times of the four principal peaks of acetylspiramycin in the substance being examined in the chromatogram obtained in the test for Acetylspiramycin components are identical with those of the four principal peaks of acetylspiramycin CRS in the chromatogram of the reference solution correspondingly.

(3) Dissolve a quantity in methanol to produce a solution of 5 mg of acetylspiramycin per ml and filter, using the successive filtrate as solution (1). Dissolve a quantity of acet is iram cin CRS in methanol to produce a solution of 5 mg per ml as solution (2). Measure the equal volume of the two solutions and mix well as solution (3). Apply separately to the plate 10 µl of each of the three solutions. Carry out the test (1) for identification described under Acetylspiramycin. There are four principal spots obtained with solution (3), and the colour and position of the spots correspond to the principal spots obtained with solution (2) or solution (3).

(2) or (3) may be used alternative.

Acetylspiramycin components Dissolve an accurately weighted quantity of the powdered tablets in mobile phase to produce a solution of 1 mg per ml, mix well and filter, carry out the test for Acetylspiramycin components described under Acetylspiramycin. Either the content of monoacetylspiramycin (II + III) or that of diacetylspiramycin (II + III) are not less than 35%, the sum content of the four main component is not less than 70%, calculated by the following formula.

$$\frac{A_T W_S \times \text{average weight} \times P \times \text{Potency of Acetylspiramycin CRS}}{A_S W_T \times \text{labelled amount}} \times 100\%$$

Where A_T is the sum area of the four peaks of the substance being examined;

A_S is the sum area of the four peaks of the acetylspiramycin CRS;

W_S is the weight of the substance being examined;

W_T is the weight of the acetylspiramycin CRS;

P is the sum area of the four peaks of the acetylspiramycin CRS.

Dissolution Carry out the dissolution test (Appendix X C, method 1), using 900 ml of hydrochloride acid solution (24 ml of dilute hydrochloride acid solution→1000 ml) as the dissolution medium, adjust the rotational speed of the paddle to 100 r/min. Withdraw the solution after exact 45 minutes and filter. Dilute an accurately measured quantity of the successive filtrate with the dissolution medium to produce a solution of 20 µg per ml. Dissolve an accurately weighed quantity of the mixed contents in the test for weight variation of contents equivalent to about the average weight of one tablet in ethanol using 2 ml of ethanol for 5 mg, dilute with the dissolution medium to produce a solution of 100 µg per ml and filter. Dilute an accurately measured quantity of the successive filtrate with the dissolution medium to produce a solution of 20 µg per ml. Measure the absorbance of the resulting solutions at 232 nm (Appendix IV A), calculate the dissolution of acetylspiramycin from each tablet. Not less than 75% of the labelled amount is dissolved.

Other requirements Comply with the general requirements for tablets (Appendix I A)

Assay Weigh accurately and triturate 10 tablets or 5 tablets for the sugar coated tablets, accurately weighed a quantity (equivalent to about 0.1 g of acetylspiramycin) in ethanol (using 2 ml of ethanol for 5 mg), dilute with sterile water to produce a solution of 1000 Units per ml, mix well and allow to stand. Measure accurately a quantity of the supernatant liquid and carry out the Assay described under Acetylspiramycin.

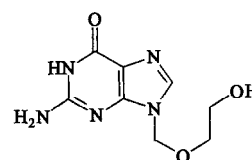
Category As described under Acetylspiramycin.

Strength (1) 0.1 g (10 000 units)

(2) 0.2 g (20 000 units)

Storage Preserve in tightly closed containers, stored in a dry, cool and dark place.

Aciclovir



$C_8H_{11}N_5O_3$ 225.21

[59277-89-3]

Aciclovir is 2-amino-9-[(2-hydroxyethoxy) methyl]-1,9-dihydro-6H-purin-6-one. It contains not less than 98.0% of $C_8H_{11}N_5O_3$, calculated on the dried basis.

Description A white crystalline powder; odourless; tasteless. Sparingly soluble in glacial acetic acid or hot water; very slightly soluble in water; practically insoluble in chloroform or ether; soluble in dilute sodium hydroxide solution.

Specific absorbance Measure the absorbance of a solution of 10 µg per ml in water at 252 nm (Appendix IV A), the value of A (1%, 1 cm) is 603-641.

Identification (1) The retention time of principal peak of aciclovir in the chromatogram obtained in the Assay is identical with the principal peak of aciclovir CRS in the chromatogram of the reference solution.

(2) The infrared absorption spectrum (Appendix IV C) is concordant with the reference spectrum of aciclovir (Appendix XVI).

Clarity and colour of solution Triturate and dissolve 0.5 g in 10 ml of 1% sodium hydroxide solution, the solution is clear and colourless; any opalescence produced is not more pronounced than that of reference suspension II (Appendix IX B); any colour produced is not more intense than that of reference solution Y_2 (Appendix IX A, method 1).

Related substances Carry out the method for thin-layer chromatography (Appendix V B), using silica gel GF₂₅₄ as the coating substance and a mixture of chloroform-methanol-concentrate ammonia solution (80 : 20 : 2) as the mobile phase. Apply to the plate 5 µl of the solution containing 10 mg of the substance being examined per ml in dimethyl sulfoxide. After developing and removal of the plate, dry it in air and examine under ultra-violet light (254 nm), no spot other than the principle spot in the chromatogram is observed.

Guanine Dissolve about 50 mg, accurately weighed, in 5 ml of 0.4% sodium hydroxide solution in a 50 ml volumetric flask, dilute with water to volume and mix well, measure accurately 10 ml to a 50 ml volumetric flask, dilute with water to volume and mix well as a test solution. Dissolve 10

mg of guanine CRS, accurately weighed, in 0.4% sodium hydroxide solution in a 100 ml volumetric flask, dilute to volume and mix well as guanine stock reference solution, measure accurately 2 ml to a 100 ml volumetric flask, dilute with water to volume and mix well as guanine reference solution. Carry out the method described under Assay. Inject separately 20 μ l each of the test solution and guanine reference solution into the column, and record the chromatogram for twice the retention time of the principal peak. The peak area of guanine in the chromatogram obtained with the test solution is not greater than that of guanine in the chromatogram obtained with the guanine reference solution (1.0%).

Loss on drying When dried to constant weight at 105°C, loses not more than 6.0% of its weight (Appendix VIII L).

Residue on ignition Not more than 0.1% (Appendix VIII N), using 1.0 g.

Heavy metals Carry out the limit test for heavy metals (Appendix VIII H, method 2), using the residue obtained in the test for Residue on ignition; not more than 0.001%.

Assay Carry out the method for high performance liquid chromatograph (Appendix V D), using a column packed with octadecylsilane bonded silica gel and a mixture of methanol-water (10 : 90) as the mobile phase. Detection wavelength is 254 nm. Add 1 ml of guanine stock reference solution under Guanine to 5 ml of aciclovir reference solution and mix well. Inject 20 μ l of the resulting solution into the column and record the chromatogram. The resolution factor between peaks of aciclovir and guanine complies with the related requirements.

Procedure Dissolve about 50 mg, accurately weighed, in 5 ml of 0.4% sodium hydroxide solution in a 50 ml volumetric flask, dilute with water to volume and mix well, measure accurately 2 ml to a 100 ml volumetric flask, dilute with water to volume and mix well as test solution. Inject 20 μ l of the test solution into the column, and record the chromatogram. Repeat the operation, using aciclovir CRS instead of the substance being examined to produce the aciclovir reference solution of 20 μ g per ml. Calculate the content of $C_8H_{11}N_5O_3$ with respect to the peak area obtained in the chromatogram by the external standard method.

Category Antiviral.

Storage Preserve in tightly closed containers, protected from light.

Preparation

- (1) Aciclovir Capsules
- (2) Aciclovir chewable Tablets
- (3) Aciclovir Cream
- (4) Aciclovir Eye Drops
- (5) Aciclovir for Injection
- (6) Aciclovir Granules
- (7) Aciclovir Tablets

Aciclovir Capsules

Aciclovir Capsules contain not less than 93.0% and not more than 107.0% of the labelled amount of aciclovir ($C_8H_{11}N_5O_3$).

Description Capsules containing white to almost white powder.

Identification Comply with the tests (1), (2) for Identification described under Aciclovir Tablets.

Guanine The successive filtrate obtained under the Assay as

test solution complies with Guanine described under Aciclovir.

Dissolution Carry out the dissolution test (Appendix X C method 1), using 900 ml of 0.1 mol/L hydrochloric acid solution as the dissolution medium, adjust the rotational speed of the basket to 100 rpm. Withdraw 10 ml of the solution after exactly 30 minutes and filter. Dilute a quantity of the successive filtrate, accurately measured, with 0.1 mol/L hydrochloric acid solution to produce a solution containing about 10 μ g per ml. Measure the absorbance of the solution at 254 nm (Appendix IV A) immediately. Measure the absorbance of a solution containing 10 μ g of aciclovir CRS per ml in the same manner. Calculate the dissolution of $C_8H_{11}N_5O_3$ from each capsules. Not less than 80% of the labelled amount is dissolved.

Other requirements Comply with the general requirements for Capsules (Appendix I E).

Assay Weigh accurately a quantity of the mixed contents, equivalent to about 50 mg of aciclovir, obtained in the test for weight variation. Carry out the Assay described under Aciclovir Tablets, calculate the content of $C_8H_{11}N_5O_3$.

Category As described under Aciclovir.

Strength 0.2 g

Storage Preserve in tightly closed containers.

Aciclovir Chewable Tablets

Aciclovir Chewable Tablets contain not less than 93.0% and not more than 107.0% of the labelled amount of aciclovir ($C_8H_{11}N_5O_3$).

Description White or almost white tablets; taste, sweet.

Identification Comply with the tests (1), (2) for Identification described under Aciclovir Tablets.

Guanine Carry out the method as described under Aciclovir. The successive filtrate obtained under the Assay as test solution complies with Guanine described under Aciclovir.

Other requirements Comply with the general requirements for tablets (Appendix I A), except Disintegration.

Assay Weigh accurately and powder 10 tablets. Weigh accurately a quantity of the powder equivalent to about 50 mg of aciclovir. Carry out the Assay described under Aciclovir Tablets, calculate the content of $C_8H_{11}N_5O_3$.

Category As described under Aciclovir.

Strength 0.4 g

Storage Preserve in tightly closed containers, stored in a dry place.

Aciclovir Cream

Aciclovir Cream contains not less than 90.0% and not more than 110.0% of the labelled amount of aciclovir ($C_8H_{11}N_5O_3$).

Description A white cream.

Identification (1) Complies with the test (1) for Identification described under Aciclovir Eye Drops, using 50 ml of the successive filtrate obtained under the Assay as test solution.

(2) The retention time of the principal peak of the substance being examined in the chromatogram obtained in the Assay is identical with that of the principal peak obtained in the chromatogram of the reference solution.

Guanine The successive filtrate obtained under the Assay as test solution complies with Guanine described under Aciclovir.

Other requirements Complies with the general requirements for Cream (Appendix I F).

Assay Weigh accurately a quantity of the cream, equivalent to about 50 mg of acyclovir, into a beaker, add 5 ml of 0.4% sodium hydroxide solution, shake thoroughly for 1 minutes in a hot water bath, add 5 g of sodium chloride with stirring, transfer to 250 ml volumetric flask with a quantity of hot water and shake for 10 minutes in a hot water bath, cool to room temperature, dilute with water to volume, mix well and filter. Dilute a quantity of the successive filtrate, accurately measured, with water to produce a solution containing about 20 µg per ml as test solution. Carry out the Assay described under Aciclovir, calculate the content of $C_8H_{11}N_5O_3$.

Category As described under Aciclovir.

Strength 10 g : 0.3 g

Storage Preserve in tightly closed containers, stored in a dry, cool and dark place.

Aciclovir Eye Drops

Aciclovir Eye Drops contain not less than 90.0% and not more than 110.0% of the labelled amount of aciclovir ($C_8H_{11}N_5O_3$).

Description A clear, colourless liquid.

Identification (1) Evaporate 20 ml to dryness over a water bath. To the residue add 2 ml of hydrochloric acid and evaporate to dryness. Add 1 ml of hydrochloric acid and about 30 mg of potassium chlorate, evaporate to dryness, to the residue add ammonia TS dropwise, a violet-red colour is produced, add a few drops of sodium hydroxide TS again, the violet-red colour disappears.

(2) The retention time of the principal peak of the substance being examined in the chromatogram obtained in the Assay is identical with that of the principal peak obtained in the chromatogram of the reference solution.

pH value 7.5-9.0 (Appendix VI H).

Guanine Dilute an accurately measured quantity with water to produce a solution containing 200 µg of aciclovir per ml as test solution. The solution complies with Guanine described under Aciclovir.

Other requirements Comply with the general requirements for Ophthalmic preparations (Appendix I G).

Assay Dilute an accurately measured quantity with water to produce a solution containing 20 µg of aciclovir per ml. Carry out the Assay described under Aciclovir, calculate the content of $C_8H_{11}N_5O_3$.

Category As described under Aciclovir.

Strength 8 ml : 8 mg

Storage Preserve in tightly closed containers, stored in a cool and dark place.

Aciclovir for Injection

Aciclovir for Injection is a sterile lyophilized product with sodium hydroxide solution. It contains not less than 90.0% and not more than 110.0% of the labelled amount of aciclovir ($C_8H_{11}N_5O_3$), calculated on the basis of the average contents.

Description A white, loose agglomerates or powder.

Identification (1) To about 20 mg add 2 ml of hydrochloric acid and evaporate to dryness over a water bath. Add 1 ml of hydrochloric acid and about 30 mg of potassium chlorate, evaporate to dryness in the same manner, to the residue add ammonia TS dropwise, a violet-red colour is produced, add a few drops of sodium hydroxide TS, the violet-red colour disappears.

(2) To a quantity of the contents, equivalent to about 10 mg of acyclovir, add 10 ml of water, shake to dissolve acyclovir, add a few drops of ammoniated silver nitrate TS; a curdy, white precipitate is formed.

(3) The retention time of the principal peak of the substance being examined in the chromatogram obtained in the Assay is identical with that of the principal peak obtained in the chromatogram of the reference solution.

(4) Yields the flame reaction of sodium salts (Appendix III). Carry out the identification (1) (3) (4) or (2) (3) (4)

Alkalinity Dissolve the content of 1 container in 20 ml of water and mix well, pH 10.5-11.5 (Appendix VI H).

Clarity of solution Dissolve the content of 1 container in 5 ml of water, the solution is clear; any opalescence produced is not more pronounced than that of reference suspension II (Appendix IX B).

Guanine Weigh accurately a quantity of the mixed contents, equivalent to about 50 mg of acyclovir, obtained in the test for weight variation into a 250 ml volumetric flask, dissolve and dilute with water to volume, mix well, use the resulting solution as test solution. The solution complies with Guanine described under Aciclovir.

Pyrogens Complies with the test for pyrogens (Appendix XI D), using 1 ml of a solution of 16 mg per ml in Water for Injections per kg of rabbit's weight.

Other requirements Complies with the general requirements for Injection (Appendix I B).

Assay Weigh accurately a quantity of the mixed contents, equivalent to about 50 mg of acyclovir, obtained in the test for weight variation into a 250 ml volumetric flask, dissolve and dilute with water to volume, shake thoroughly, dilute an accurately measured quantity with water to produce a solution containing 20 µg of aciclovir per ml. Carry out the Assay described under Aciclovir, calculate the content of $C_8H_{11}N_5O_3$.

Category As described under Aciclovir.

Strength 0.25 g

Storage Preserve in well closed containers, protected from light.

Aciclovir Granules

Aciclovir Granules contain not less than 90.0% and not more than 110.0% of the labelled amount of

aciclovir ($C_8H_{11}N_5O_3$).

Description White to almost white granules; taste, slightly sweet.

Identification Comply with the tests (1), (2) for Identification described under Aciclovir Tablets.

Loss on drying When dries to constant weight at 105°C , loses not more than 6.0% of its weight (Appendix VIII L).

Guanine The successive filtrate obtained under the Assay as test solution complies with Guanine described under Aciclovir.

Other requirements Comply with the general requirements for Granules (Appendix I N).

Assay Weigh accurately a quantity of the powdered and mixed contents, equivalent to about 50 mg of acyclovir, obtained in the test for weight variation. Carry out the Assay described under Aciclovir Tablets, calculate the content of $C_8H_{11}N_5O_3$.

Category As described under Aciclovir.

Strength 0.2 g

Storage Preserve in tightly closed containers.

Aciclovir Tablets

Aciclovir Tablets contain not less than 93.0% and not more than 107.0% of the labelled amount of aciclovir ($C_8H_{11}N_5O_3$).

Description White tablets.

Identification (1) To a quantity of the powdered tablets, equivalent to about 10 mg of the acyclovir, add 10 ml of water, shake thoroughly and filter. To the filtrate add a few drops of ammoniated silver nitrate TS; a curdy, white precipitate is formed.

(2) The retention time of the principal peak of the substance being examined in the chromatogram obtained in the Assay is identical with that of the principal peak obtained in the chromatogram of the reference solution.

Guanine The successive filtrate obtained under the Assay as test solution complies with Guanine described under Aciclovir.

Dissolution Carry out the dissolution test (Appendix X C, method 2), using 900 ml of 0.1 mol/L hydrochloric acid solution as the dissolution medium, adjust the rotational speed of the paddle to 50 rpm. Withdraw 10 ml of the solution after exactly 30 minutes and filter. Dilute a quantity of the successive filtrate, accurately measured, with 0.1 mol/L hydrochloric acid solution to produce a solution containing about $10\text{ }\mu\text{g}$ per ml. Measure the absorbance of the solution at 254 nm (Appendix IV A) immediately. Measure the absorbance of a solution containing $10\text{ }\mu\text{g}$ of aciclovir CRS per ml in the same solution. Calculate the dissolution of $C_8H_{11}N_5O_3$ from each tablet. Not less than 80% of the labelled amount is dissolved.

Other requirements Comply with the general requirements for tablets (Appendix I A).

Assay Weigh accurately and powder 20 tablets. Weigh accurately a quantity of the powder, equivalent to about 50 mg of acyclovir into a 250 ml volumetric flask, add 5 ml of 0.4% sodium hydroxide solution and sonicate for 1 minute, add a quantity of water and shake for 10 minutes in a hot water bath, cool to room temperature, dilute with water to volume, mix well and filter. Dilute a quantity of the

successive filtrate, accurately measured, with water to produce a solution containing about $20\text{ }\mu\text{g}$ per ml. Carry out the Assay described under Aciclovir, calculate the content of $C_8H_{11}N_5O_3$.

Category As described under Aciclovir.

Strength (1) 0.1 g (2) 0.2 g

Storage Preserve in tightly closed containers.

Adenosine Disodium Triphosphate

$C_{10}H_{14}N_5Na_2O_{13}P_3 \cdot 3H_2O$ 605.19 [987-65-5]

Adenosine disodium triphosphate is adenosine-5'-triphosphate disodium salt trihydrate. It contains not less than 95.0% of $C_{10}H_{14}N_5Na_2O_{13}P_3$, calculated on the anhydrous basis.

Description A white or almost white powder or crystals; odourless; taste, salty; hygroscopic. Freely soluble in water, practically insoluble in ethanol, chloroform, or ether.

Identification (1) Dissolve 20 mg in 2 ml of dilute nitric acid, add 1 ml of ammonium molybdate TS, heat, cool, a yellow turbidity is formed.

(2) To 3 ml of its aqueous solution ($3 \rightarrow 10000$), add 0.2 ml of 3,5-dihydroxy-methylbenzene ethanol solution ($1 \rightarrow 10$) and 3 ml of ammonium ferric sulfate solution ($1 \rightarrow 1000$), heat for 10 minutes in a water bath, a green colour is produced.

(3) The infrared absorption spectrum is concordant with the reference spectrum of adenosine disodium triphosphate (Appendix XVI).

(4) Yields the flame reaction characteristic of sodium salts (Appendix III).

Acidity Dissolve 0.5 g in 10 ml of water, pH 2.5-3.5 (Appendix VI H).

Clarity and colour of solution A solution of 0.15 g in 10 ml of water is clear and colourless; any colour produced is not more intense than that of reference solution Y_1 (Appendix IX A, method 1).

Related substance Carry out the method as described under Weight ratio of adenosine disodium triphosphate of Assay, calculate as follows: not more than 5.0%.

$$\text{Related substance (\%)} = \frac{0.671T_1 + 0.855T_2 + T_x}{0.671T_1 + 0.855T_2 + T_3 + T_x} \times 100\%$$

Water 6.0%-12.0% (Appendix VIII M, A of method 1), dissolving an accurately weighed quantity in ethylene glycol-dehydrated methanol (60 : 40).

Chloride Carry out the limit test for chloride (Appendix VIII A), using 0.10 g. Any opalescence produced is not more pronounced than that of a reference solution using 5 ml of sodium chloride standard solution (0.05%).

Iron Carry out the limit test for iron (Appendix VIII G), using 1.0 g. Any colour produced is not more intense than that of a reference solution using 1.0 ml of iron standard solution (0.001%).

Heavy metals Dissolve 1.0 g in 23 ml of water, add 2 ml of acetate buffer (pH 3.5). Carry out the limit test for heavy metals (Appendix VIII H, method 1); not more than 0.001%.

Pyrogens Complies with the test for pyrogens (Appendix XI D), slowly injecting 1 ml of a solution of 2 mg per ml in Water for Injection per kg of rabbit's weight.

Assay

Total nucleotide Dissolve an accurately weighed quantity in 0.1 mol/L phosphate BS (to 35.8 g of disodium hydrogen phosphate, add water to 1000 ml, as solution A; to 13.6 g of dehydrated potassium dihydrogen phosphate, add water to 1000 ml, as solution B; adjust solution A to pH 7.0 with solution B) to produce a solution of 20 µg per ml, measure the absorbance at 259 nm (Appendix IV A). Calculate the content of $C_{10}H_{14}N_5Na_2O_{13}P_3$, taking 279 as the value of A (1%, 1 cm).

Weight ratio of adenosine disodium triphosphate Carry out the method for high performance liquid chromatography (Appendix V D), using a column packed with octadecylsilane bonded silica gel and 0.2 mol/L phosphate BS (Dissolve 35.8 g of disodium hydrogen phosphate and 13.6 g of potassium dihydrogen phosphate in 900 ml of water, adjust to pH 7.0 with 1 mol/L sodium hydroxide solution, add 1.61 g of tetrabutylammonium bromide, add water to 1000 ml and mix well)-methanol (95 : 5) as the mobile phase. Maintain the column temperature at 35°C. Detection wavelength is 259 nm and the number of theoretical plates of the column is not less than 1500, calculated with reference to the peak of adenosine disodium triphosphate. The elution order is adenosine sodium monophosphate, adenosine disodium diphosphate and adenosine disodium triphosphate. The resolution factor among peaks complies with related requirements.

Procedure Dissolve an accurately weighed quantity in mobile phase to produce a solution of 4 mg per ml. Inject 10 µl of the resulting solution into the column, calculate the weight ratio of adenosine disodium triphosphate to the total nucleotide as follows.

$$\text{Weight ratio of adenosine disodium triphosphate} = \frac{T_3}{0.671T_1 + 0.855T_2 + T_3 + T_x}$$

Where T_1 is peak area of adenosine sodium monophosphate
 T_2 is peak area of adenosine disodium diphosphate
 T_3 is peak area of adenosine disodium triphosphate
 T_x is area of the other peaks

0.671 is the molecular weight ratio of adenosine sodium monophosphate to adenosine disodium triphosphate

0.855 is the molecular weight ratio of adenosine disodium diphosphate to adenosine disodium triphosphate

Content of adenosine disodium triphosphate Calculate as follows.

$$\text{Content of adenosine disodium triphosphate (\%)} = \frac{\text{Total nucleotide} \times \text{Weight ratio of adenosine disodium triphosphate}}{\text{Total nucleotide}}$$

Category Medicines for improving cell metabolism.

Storage Preserve in tightly closed containers, stored in a cool, dark and dry place.

Preparation (1) Adenosine disodium triphosphate injection
 (2) Adenosine disodium triphosphate for injection

Adenosine Disodium Triphosphate for Injection

Adenosine disodium triphosphate for injection is a sterile lyophilized powder. It contains not less than 90.0% of the labelled amount of adenosine disodium triphosphate ($C_{10}H_{14}N_5Na_2O_{13}P_3$).

Description White lyophilized pieces or powder; hygroscopic; freely soluble in water.

Identification Complies with tests (1) and (2) for Identification described under Adenosine Disodium Triphosphate.

Acidity A solution of 10 mg per ml in water, pH 4.5-7.0 (Appendix VI H).

Clarity and colour of solution A solution of 10 mg per ml in water is clear and colourless.

Loss on drying When dried in vacuum over phosphorous pentoxide to constant weight at 100°C, loses not more than 5.0% of its weight (Appendix VIII L).

Pyrogens Complies with the test for Pyrogen described under Adenosine Disodium Triphosphate.

Other requirements Complies with the general requirements for injection (Appendix I B).

Assay Carry out the method for Assay under Adenosine Disodium Triphosphate.

Category As described under Adenosine Disodium Triphosphate.

Strength 20 mg

Storage Preserve in tightly closed containers, stored in a cool and dark place.

Adenosine Disodium Triphosphate Injection

Adenosine disodium triphosphate injection is a sterile solution of adenosine disodium triphosphate in Water for Injection. It contains not less than 90.0% of the labelled amount of adenosine disodium triphosphate ($C_{10}H_{14}N_5Na_2O_{13}P_3$).

Description A clear, colourless or almost colourless liquid.

Identification Complies with tests (1) and (2) for Identification described under Adenosine Disodium Triphosphate.

pH value pH 8.0-9.5 (Appendix VI H).

Colour of solution Not more intense than that of reference solution Y₂ (Appendix IX A, method 1).

Pyrogens Complies with the test for Pyrogen described under Adenosine Disodium Triphosphate.

Other requirements Complies with the general requirements for injection (Appendix I B).

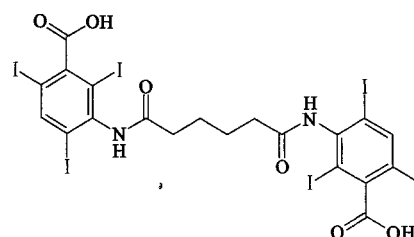
Assay Carry out the method for Assay under Adenosine Disodium Triphosphate.

Category As described under Adenosine Disodium Triphosphate.

Strength 2 ml : 20 mg

Storage Preserve in well tightly containers, stored in a cool and dark place.

Adipiodone



$C_{20}H_{14}I_6N_2O_6$ 1139.76

[606-17-7]

Adipiodone is 3,3'-[(1,6-dioxo-1,6-hexanediyl) diimino] bis [2,4,6-triiodo] benzoic acid. It contains not less than 98.0% of $C_{20}H_{14}I_6N_2O_6$, calculated on the dried basis.

Description A white powder; odourless; taste, slightly bitter.

Slightly soluble in ethanol; partially in alcohol, ether, chloroform or ether; soluble in sodium hydroxide solutions.

Identification (1) Heat gently about 10 mg in a crucible, the purple iodine vapour is evolved by decomposition. (2) Add separately a 0.08% methanolic sodium hydroxide solution to the substance being examined and adipiodone CRS to produce solutions of 1 mg per ml. Carry out the method for thin-layer chromatography (Appendix V B), using silica gel HF₂₅₄ as the coating substance and *n*-butanol-glacial acetic acid-water (4 : 1 : 5) as the mobile phase. Apply separately 10 µl each of the two solutions to the plate. Examine under an ultraviolet light (254 nm) after developing. The position of the principal spots in the chromatogram obtained with the two solutions are identical.

Clarity and colour of alkaline solution A solution of 2.0 g in 10 ml of sodium hydroxide TS is clear. Any opalescence produced is not more pronounced than that of reference suspension 2 (Appendix IX B) and any colour produced is not more intense than that of reference solution Y₂ or BR₂ (Appendix IX A, method 1).

Free iodine To 5 ml of the alkaline solution obtained in Clarity and colour of solution add water to produce 10 ml. Carry out the method described under Diatrizoic Acid, the result complies with the requirements.

Halide Dissolve 2.0 g in 4 ml of sodium hydroxide TS, add a mixture of 4 ml of dilute nitric acid and 30 ml of water, shake for a few minutes to precipitate adipiodone, filter. Wash the precipitate with a small amount of water. Combine the washings with filtrate and make up to 50 ml, shake well, refilter if necessary. Carry out the limit test for chlorides (Appendix VIII A), using 20 ml of filtrate. Any opalescence produced is not more pronounced than that of a reference, using 8.0 ml of sodium chloride standard solution (0.01%).

Amino-compound Dissolve 1.0 g in 5 ml of water and 5 ml of sodium hydroxide TS, add water to produce 100 ml. To 10 ml add 5 ml of sodium nitrite (0.1 mol/L) VS and 10 ml of hydrochloric acid solution (9→100), mix well and allow to stand for 10 minutes. Add 5 ml of 2.5% ammonium sulfamate solution, shake and allow to stand for 5 minutes. Add 2 ml of alkaline β-naphthol TS, 15 ml of sodium hydroxide TS and water to produce 50 ml, mix well. Measure the absorbance of the resulting solution at 485 nm (Appendix IV B); not greater than 0.34.

Loss on drying When dried to constant weight at 105°C, loses not more than 0.5% of its weight (Appendix VIII L).

Heavy metals Not more than 0.002% (Appendix VIII H, method 2), Using 1.0 g.

Iodide, Residue on ignition, Iron Carry out the corresponding tests described under Diatrizoic Acid and meet the requirement.

Assay Weigh accurately about 0.3 g, carry out the Assay described under Diatrizoic Acid. Each ml of silver nitrate (0.1 mol/L) VS is equivalent to 19.00 mg of $C_{20}H_{14}I_6N_2O_6$.

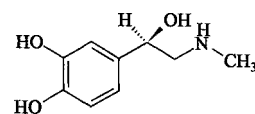
Category Diagnostic agent.

Storage Preserve in tightly closed containers, protected from light.

Preparation Meglumine Adipiodone Injection

Adrenaline

(Epinephrine)



$C_9H_{13}NO_3$ 183.21

[51-43-4]

Adrenaline is (*R*)-4-[2-(methylamino) 1-hydroxyethyl]-1, 2-benzenediol. It contains not less than 98.5% of $C_9H_{13}NO_3$, calculated on the dried basis.

Description A white or almost white crystalline powder; odourless; taste, bitter. Deteriorated on exposure to air or light; unstable in neutral or alkaline water solution; saturated aqueous solution exhibits a weak alkaline reaction. Very slightly soluble in water; insoluble in ethanol, chloroform, ether, fatty oils or volatile oils; freely soluble in solutions of mineral acids or sodium hydroxide solution; insoluble in ammonia or sodium carbonate solution.

Melting range 206-212°C, with decomposition (Appendix VI C).

Specific optical rotation -50.0° to -53.5°, in a solution of 20 mg per ml in hydrochloric acid solution (9→200) (Appendix VI E).

Identification (1) Dissolve about 2 mg in 2-3 drops of hydrochloric acid solution (9→1000), add 2 ml of water and 1 drop of ferric chloride TS; an emerald-green colour is produced, which changes firstly to violet and then to reddishviolet on the addition of 1 drop of ammonia TS. (2) Dissolve about 10 mg in 2 ml of hydrochloric acid solution (9→1000), add 10 drops of hydrogen peroxide TS and boil; a blood red colour is produced.

Clarity and colour of acid solution The solution obtained in the determination of Specific optical rotation is clear; any colour produced is not more intense than that of a reference solution prepared by adding 5 ml of water to 5 ml of reference solution Y₃ or OR₂ (Appendix IX A, method 1).

Phenones Measure the absorbance of a 2.0 mg per ml solution in hydrochloric acid solution (9→2000) at 310 nm (Appendix IV A); not greater than 0.05.

Loss on drying When dried in vacuum over phosphorus pentoxide for 18 hours, loses not more than 1.0% of its weight (Appendix VIII L).

Residue on ignition Not more than 0.1% (Appendix VIII N).

Assay Dissolve about 0.15 g, accurately weighed, in 10 ml of glacial acetic acid, add 1 drop of crystal violet IS, and titrate with perchloric acid (0.1 mol/L) VS until the solution becomes bluish-green. Perform a blank determination and make any necessary correction. Each ml of perchloric acid (0.1 mol/L) VS is equivalent to 18.32 mg of $C_9H_{13}NO_3$.

Category Adrenergic receptor stimulant.

Storage Preserve in hermetically sealed containers in vacuum, protected from light and stored in a cool place.

Preparation Adrenaline Hydrochloride Injection

Adrenaline Hydrochloride Injection

(Epinephrine Hydrochloride Injection)

Adrenaline Hydrochloride Injection is an isotonic sterile solution of adrenaline in Water for Injection containing a quantity of hydrochloric acid and sodium chloride. It contains not less than 85.0% and not more than 115.0% of the labelled amount of adrenaline ($C_9H_{13}NO_3$). It may contain suitable stabilizers.

Description A clear, colourless or almost colourless solution; deteriorated on exposure to air or light.

Identification To 2 ml add 1 drop of ferric chloride TS, an emerald-green colour is produced, it changes first to violet and then to reddish-violet on the addition of 1 drop of ammonia TS.

pH value 2.5–5.0 (Appendix VI H).

Other requirements Complies with the general requirements for injections (Appendix I B).

Assay Carry out the method for high performance liquid chromatography (Appendix V D), using a column packed with octadecylsilane bonded silica gel and a mixture of 0.14% sodium heptyl-sulfonate solution and methanol (65 : 35) and adjusting to pH 3.0 ± 0.1 with phosphoric acid as the mobile phase. Detection wavelength is 280 nm. The number of theoretical plates of the column is not less than 3000.

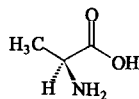
Procedure Dilute an accurately measured amount of the injection equivalent to 3 mg of adrenaline in a 25 ml volumetric flask, add acetic acid solution (1 → 25) to volume, mix well, inject 20 μ l into the column, record the peak areas correspondingly obtained in the chromatogram. Dissolve a quantity of adrenaline CRS, accurately weighed, in acetic acid solution (1 → 25) to produce a solution of 0.12 mg per ml. Repeat the operation, Calculate the content of $C_9H_{13}NO_3$ with respect to the peak area obtained in the chromatogram by external standard method.

Category As described under Adrenaline.

Strength (1) 0.5 ml : 0.5 mg (2) 1 ml : 1 mg

Storage Preserve in tightly closed containers, protected from light and stored in a cool place.

Alanine



$C_3H_7NO_2$ 89.09

Alanine is L-2-aminopropanoic acid. It contains not less than 98.5% of $C_3H_7NO_2$, calculated on the dried basis.

Description White crystals or crystalline powder; odour; taste, sweet.

Specific optical rotation $+14.0^\circ$ to $+15.0^\circ$, in a solution of about 50 mg per ml in 1 mol/L hydrochloric acid solution (Appendix VI E).

Identification The infrared absorption spectrum (Appendix

IV C) is concordant with the reference spectrum of Alanine (Appendix XVI).

Acidity Dissolve 1.0 g in 20 ml of water, pH is 5.5–7.0 (Appendix VI H).

Transmittance of solution Dissolve 1.0 g in 20 ml of water, the transmittance at 430 nm is not less than 98.0% (Appendix IV A).

Chloride Carry out the limit test for chloride (Appendix VIII A), using 0.30 g. Any opalescence produced is not more pronounced than that of a reference solution using 6.0 ml of sodium chloride standard solution (0.02%).

Sulfate Carry out the limit test for sulfate (Appendix VIII A), using 1.0 g. Any opalescence produced is not more pronounced than that of a reference solution using 2.0 ml of potassium sulfate standard solution (0.02%).

Ammonium Carry out the limit test for ammonium (Appendix VIII K), using 0.10 g. Any colour produced is not more intense than that of a reference solution using 2.0 ml of ammonium chloride standard solution (0.02%).

Other amino acids Carry out the method for thin-layer chromatography (Appendix V B), using silica gel G as the coating substance and *n*-butanol-water-acetic acid (5 : 2 : 1) as the mobile phase. Apply to the plate 5 μ l of a solution of 20 mg of the substance being examined per ml in water. After developing and removal of the plate, dry it in air and dry at 90°C for 10 minutes and spray with ninhydrin solution (dissolve 1 g ninhydrin in 50 ml of acetone) and heat at 90°C until the colour is produced. There is only one purple spot in the chromatogram.

Loss on drying When dried at 105°C for 3 hours, loses not more than 0.2% of its weight (Appendix VIII L).

Residue on ignition Not more than 0.1% (Appendix VIII N).

Iron Carry out the limit test for iron (Appendix VIII G), using 1.0 g. Any colour produced is not more intense than that of a reference solution using 1.0 ml of iron standard solution (0.001%).

Heavy metals Dissolve 2.0 g in 23 ml of water, add 2 ml of acetate BS (pH 3.5). Carry out the limit test for heavy metals (Appendix VIII H, method 1); not more than 0.001%.

Arsenic Dissolve 2.0 g in 23 ml of water, add 5 ml of hydrochloric acid, carry out the limit test for arsenic (Appendix VIII J, method 1); not more than 0.0001%.

Bacterial endotoxin Carry out the test for bacterial endotoxin (Appendix XI E); less than 0.02 EU per mg (for parenteral administration).

Assay Dissolve about 80 mg, accurately weighed, in 2 ml of dehydrated formic acid, add 30 ml of glacial acetic acid.

^y
V A), titrate with ^pperchloric acid (0.1 mol/L) ^{pp}VS. Perform a blank determination and make any necessary correction. Each ml of perchloric acid (0.1 mol/L) VS is equivalent to 8.909 mg of $C_3H_7NO_2$.

Category Amino acid.

Storage Preserve in tightly closed containers.

Alarelin Acetate

5-oxoPro-His-Trp-Ser-Tyr-D-Ala-Leu-Arg-Pro-NHCH₂CH₃, CH₃COOH

$C_{56}H_{78}N_{16}O_{12} \cdot n C_2H_4O_2$ 1227.39

Alarelin acetate is 5-oxo-L-prolyl-L-histidyl-L-tryptophyl-L-seryl-L-tyrosyl-D-alanyl-L-leucyl-L-arginyl-L-prolyl-ethylamine acetate. It contains not less than 95.0% and not more than 103.0% of $C_{56}H_{78}N_{16}O_{12}$, calculated with reference to the anhydrous, acetic acid-free substance.

Description A white or almost white powder; odourless; hygroscopic.

Soluble in water; sparingly soluble in methanol; soluble in 1% acetic acid solution.

Specific optical rotation -46° to -56° , calculated with reference to the anhydrous and acetic acid-free substance, in a solution of 5 mg per ml in 1% acetic acid solution (Appendix VI E).

Specific absorbance Measure the absorbance of a solution of 0.1 mg per ml in water at 279 nm (Appendix IV A), the value of A (1%, 1 cm) is 52-57, calculated with reference to the anhydrous, acetic acid-free substance.

Identification (1) The retention time of the principal peak of alarelin acetate in the substance being examined in the chromatogram obtained in the Assay is identical with that of the principal peak of alarelin acetate CRS in the chromatogram of the reference solution.

(2) Dilute the substance being examined and alarelin acetate CRS separately with water to produce test solution and reference solution both containing about 2 mg per ml. Carry out the thin-layer chromatography (Appendix V B), using silica gel G as the coating substance and a mixture of chloroform-methanol-glacial acetic acid-water (60 : 45 : 6 : 14) as the mobile phase. Apply separately to the plate 2 μ l of each of above two solutions, after developing and removal of the plate, dry it in air, leave it in contact with the chlorine vapour (add to a beaker, which is in a well closed container, 10 ml of 5% potassium permanganate solution and 3ml of hydrochloric acid). Dry it in air again. Spray with potassium iodide starch IS. The colour and position of the principal spot in the chromatogram obtained with the test solution correspond to the principal spot obtained with reference solution.

Clarity and colour of solution Dissolve 20 mg in 2 ml of water, the solution is clear and colourless; any colour produced is not more intense than that of reference solution Y_2 (Appendix IX A).

Acetic acid Dissolve a quantity of the substance being examined, accurately weighed, in the diluent (a mixture of 95 volumes of mobile phase A and 5 volumes of mobile phase B) to produce a solution of about 10 mg per ml as test solution. Dissolve a quantity of glacial acetic acid, accurately weighed, in the diluent to produce a reference solution of about 0.60 mg per ml. Carry out the method for high performance liquid chromatography (Appendix V D), using a column packed with octadecylsilane bonded silica gel, phosphoric acid solution (dilute 0.7 ml of phosphoric acid to 1000 ml with water; adjust to pH 3.0 with sodium hydroxide TS) as mobile phase A, and methanol as mobile phase B and performing the gradient elution program. Detection wavelength is 210 nm and the number of the theoretical plates of the column is not less than 2000, calculated with reference to the peak of acetic acid.

Time (min)	Mobile phase A (percent V/V)	Mobile phase B (percent V/V)
0	95	5
5	50	50
20	50	50
25	95	5

Inject separately 20 μ l of each of the reference solution and the test solution into the column, record the chromatogram. Calculate the content of acetic acid with respect to the peak area obtained in the chromatogram by the external standard method; not more than 7.5%.

Amino acids Add a quantity of 6 mol/L hydrochloric acid solution to the substance being examined. After hydrolyzing by heating at 110°C for 24 hours, examine by means of an amino-acid analyzer or suitable high performance liquid chromatography. Express the content of each amino acid in moles. Calculate the relative proportions of the amino acids taking the number of moles of alanine as equal to one. The values fall within the following limits: serine 0.7 to 1.0; glutamic acid 0.9 to 1.1; proline 0.8 to 1.0; leucine 0.9 to 1.1; tyrosine 0.9 to 1.1; histidine 0.9 to 1.1; arginine 0.9 to 1.1.

Related substance Dissolve a quantity of the substance being examined in water to produce a solution of 0.5 mg per ml as the test solution. Transfer 1 ml of the test solution, measured accurately, into a 100 ml volumetric flask, dilute with water to volume, mix well, and use this solution as the reference solution. Carry out the method as described under the Assay. Inject 20 μ l of the reference solution into the column. Adjust the attenuation so that the principal peak height in the chromatogram is 50% of the scale of the chart. Inject separately 20 μ l of each of the reference solution and the test solution into the column, and record the chromatogram for twice the retention time of the principal peak. The area of any peak other than the peaks of solvent and the principal peak in the chromatogram obtained with the test solution is not greater than twice the area of the principal peak in the chromatogram obtained with the reference solution. The sum of the areas of all peaks other than the peaks of solvent and the principal peak in the chromatogram obtained with the test solution are not greater than five times the area of principal peak in the chromatogram obtained with the reference solution (Disregard any peak with an area less than 0.05 times that of the principal peak in the chromatogram obtained with reference solution).

Water Not more than 7.0% (Appendix VIII M, method 1 A).

Assay Carry out the method for high performance liquid chromatography (Appendix V D), using a column packed with octadecylsilane bonded silica gel and a mixture of 0.1 mol/L phosphoric acid solution (adjust to pH 3.0 with triethylamine)-acetonitrile (80 : 20) as the mobile phase. Detection wavelength is 220 nm and the number of the theoretical plates of the column is not less than 2000, calculated with reference to the peak of alarelin acetate.

Procedure Dissolve a quantity of the substance being examined, accurately weighed, in mobile phase to produce a solution of about 0.5 mg per ml, mix well. Inject 10 μ l into the column. Repeat the operation, using alarelin acetate CRS instead of the substance being examined. Calculate the content of $C_{56}H_{78}N_{16}O_{12}$ with respect to the peak area obtained in the chromatogram by the external standard method.

Category Gonadotrophin-releasing hormone.

Storage Preserve in tightly closed containers, stored in a dry place and protected from light.

Preparation Alarelin acetate for injection

Alarelin Acetate for Injection

Alarelin acetate for injection is a sterile, freeze-dried preparation of alarelin acetate with mannitol. It contains

not less than 90.0% and not more than 110.0% of the labelled amount of alarelin ($C_{56}H_{78}N_{16}O_{12}$).

Description A white, friable mass or powder.

Identification The retention time of the principal peak of alarelin acetate in the substance being examined in the chromatogram obtained in the Assay is identical with that of the principal peak of alarelin acetate CRS in the chromatogram of the reference solution.

Acidity Add 2 ml of water separately to each of 5 containers, mix together, pH 4.5 to 7.0 (Appendix VI H).

Content uniformity Complies with the requirements for content uniformity (Appendix X E), using the individual results obtained in the Assay.

Sterility Complies with the requirements for sterility (Appendix XI H, membrane filtration method), dilute the substance being examined with sodium chloride injection.

Other requirements Complies with the general requirements for injections (Appendix I B).

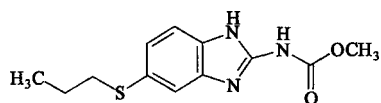
Assay Dissolve the contents of each of 10 containers in water to produce a solution of 0.1 mg per ml as test solution. Dissolve a quantity of alarelin acetate CRS, accurately weighed, in water to produce a solution of 0.1 mg per ml as reference solution. Carry out the method described under Assay in alarelin acetate. Calculate the content of $C_{56}H_{78}N_{16}O_{12}$ from the average of the 10 individual results.

Category As described under Alarelin acetate.

Strength (1) 25 μg (2) 150 μg

Storage Preserve in well closed containers and protected from light.

Albendazole



$C_{12}H_{15}N_3O_2S$ 265.34

[54965-21-9]

Albendazole is [5-(propylthio)-1*H*-benzimidazol-2-yl] carbamic acid methyl ester. It contains not less than 98.5% of $C_{12}H_{15}N_3O_2S$, calculated on the dried basis.

Description A white or almost white powder; odourless; tasteless.

Slightly soluble in acetone or chloroform; practically insoluble in ethanol; insoluble in water; soluble in glacial acetic acid.

Melting range 206–212°C, with decomposition (Appendix VI C).

Specific Absorbance Dissolve about 10 mg, accurately weighed, in 5 ml of glacial acetic acid in a 100 ml volumetric flask. Dilute with ethanol to volume, mix well. Transfer 5 ml, accurately measured, to a 50 ml volumetric flask, dilute with ethanol to volume, mix well. Measure the absorbance at 295 nm. The value of *A* (1%, 1 cm) is 430–458 (Appendix IV A).

Identification (1) Ignite about 0.1 g, fumes are evolved which stain lead acetate TP black.

(2) Dissolve about 0.1 g in warm dilute sulfuric acid, add potassium iodobismuthate TS, a reddish-brown precipitate is

produced.

(3) The light absorption of the solution obtained in the measurement of specific absorbance exhibits a maximum at 295 nm, a minimum at 277 nm (Appendix IV A).

(4) The infrared absorption spectrum (Appendix IV C) is concordant with the reference spectrum of albendazole (Appendix XVI). If the absorption peak at 1380 cm^{-1} is not concordant with the reference spectrum, dissolve a quantity of the substance in dehydrated ethanol, evaporate to dryness on a water bath and dry in vacuum. Record the infrared absorption spectrum of the dried substance.

Related substances Carry out the method for thin-layer chromatography (Appendix V B), using silica gel G as the coating substance and a mixture of chloroform-ether-glacial acetic acid (30 : 7 : 3) as the mobile phase. Apply separately to the plate 5 μl each of two solutions of the substance being examined in chloroform-glacial acetic acid (9 : 1) containing (1) 5.0 mg per ml, (2) 75 μg per ml. After developing and removal of the plate, dry it in the air and examine under an ultra-violet light (254 nm). Any spot other than the principal spot in the chromatogram obtained with solution (1) is not more intense than the principal spot obtained with solution (2).

Loss on drying When dried to constant weight at 105°C, loses not more than 0.5% of its weight (Appendix VIII L).

Residue on ignition Not more than 0.2% (Appendix VIII N), using 1.0 g.

Iron To the residue obtained in the test for Residue on ignition add 2 ml of hydrochloric acid, evaporate to dryness on a water bath. Dissolve the residue in 4 ml of dilute hydrochloric acid by warming, add 30 ml of water and 50 mg of ammonium persulfate. Carry out the limit test for iron (Appendix VIII G), the colour produced is not more intense than that produced by treating 3.0 ml of standard iron solution in the same manner (0.0030%).

Assay Dissolve about 0.2 g, accurately weighed, in 20 ml of glacial acetic acid, add 1 drop of crystal violet IS. Titrate with perchloric acid (0.1 mol/L) VS until the colour changes to green. Perform a blank determination and make any necessary correction. Each ml of perchloric acid (0.1 mol/L) VS is equivalent to 26.53 mg of $C_{12}H_{15}N_3O_2S$.

Category Anthelmintic.

Storage Preserve in tightly closed containers.

Preparation (1) Albendazole Capsules
(2) Albendazole Granules
(3) Albendazole Tablets

Albendazole Capsules

Albendazole Capsules contain not less than 90.0% and not more than 110.0% of the labelled amount of albendazole ($C_{12}H_{15}N_3O_2S$).

Identification (1) A quantity of the contents of the capsules equivalent to about 0.2 g of albendazole, complies with tests (1) and (2) for Identification described under Albendazole. (2) The light absorption of the solution obtained in the Assay exhibits maximum at 295 nm and a minimum at 277 nm (Appendix IV A).

Other requirements Comply with the general requirements for capsules (Appendix I E), except that the disintegration test is not required.

Assay To a quantity of the mixed contents obtained in the

test for weight variation of content equivalent to about 20 mg of albendazole, accurately weighed, in a 100 ml volumetric flask, add 10 ml of glacial acetic acid, shake thoroughly. Dilute with ethanol to volume, mix well, filter if necessary, and discard the initial filtrate. Transfer 5 ml of the successive filtrate, accurately measured to another 100 ml volumetric flask, dilute with ethanol to volume, mix well. Measure the absorbance of the resulting solution at 295 nm (Appendix IV A). Calculate the content of $C_{12}H_{15}N_3O_2S$, taking 444 as the value of A (1%, 1 cm).

Category As described under Albendazole.

Strength (1) 0.1 g (2) 0.2 g

Storage Preserve in tightly closed containers.

Albendazole Granules

Albendazole Granules contain not less than 90.0% and not more than 110.0% of the labelled amount of albendazole ($C_{12}H_{15}N_3O_2S$).

Description Granules with colour; odour, fragrant.

Identification (1) Dissolve a quantity of powdered granules, equivalent to about 0.2 g of albendazole, in 30 ml of ethanol by warming on a water bath. Filter and evaporate the filtrate to dryness on a water bath. The residue complies with test (2) for Identification described under Albendazole. (3) The light absorption of the solution obtained in the Assay exhibits a maximum at 295 nm and a minimum at 277 nm (Appendix IV A).

Other requirements Comply with the general requirements for granules (Appendix I N).

Assay Dissolve an accurately weighed quantity of powdered granules equivalent to about 20 mg of albendazole in 100 ml volumetric flask with 10 ml of glacial acetic acid, shake well. Dilute to volume with ethanol, mix well and filter. Transfer accurately measured 5 ml of the successive filtrate into 100 ml volumetric flask. Dilute to volume with ethanol, mix well. Measure the absorbance of the resulting solution at 295 nm (Appendix IV A), calculate the content of $C_{12}H_{15}N_3O_2S$, taking 444 as the value of A (1%, 1 cm).

Category As described under Albendazole.

Strength (1) 1 g : 0.1 g (2) 1 g : 0.2 g

Storage Preserve in tightly closed containers, stored in a dry place.

Albendazole Tablets

Albendazole Tablets contain not less than 90.0% and not more than 110.0% of the labelled amount of albendazole ($C_{12}H_{15}N_3O_2S$).

Description Almost white tablets, sugar coated tablets or film coated tablets, with white or almost white core.

Identification (1) Dissolve a quantity of powdered tablets, equivalent to about 0.2 g of albendazole, in 30 ml of ethanol by warming on a water bath. Filter and evaporate the filtrate on a water bath to dryness. The residue complies with tests (1) and (2) for Identification described under Albendazole. (2) The light absorption of the solution obtained in the Assay exhibits a maximum at 295 nm and a minimum at 277 nm (Appendix IV A).

Dissolution Carry out the dissolution test (Appendix X C, method 2), using 900 ml of 0.1 mol/L hydrochloric acid solution as the dissolution medium, adjust the rotational speed of the paddle to 75 rpm. Withdraw the solution after exactly 45 minutes and filter. Dilute an accurately measured quantity of the successive filtrate with 0.1 mol/L sodium hydroxide solution to produce a solution of 10 µg per ml as the test solution. Dissolve about 20 mg of albendazole CRS, accurately weighed, into 100 ml volumetric flask with 5 ml of 2% methanolic hydrochloric acid solution, shake well. Dilute to volume with 0.1 mol/L hydrochloric acid solution, mix well. Measure accurately 5 ml into a 100 ml volumetric flask, dilute to volume with 0.1 mol/L sodium hydroxide solution and mix well, as the reference solution. Measure the absorbance at 308 nm (Appendix IV A). Calculate the dissolution of $C_{12}H_{15}N_3O_2S$ from each tablet. Not less than 65% of the labelled amount is dissolved.

Other requirements Comply with the general requirements for tablets (Appendix I A).

Assay Weigh accurately and powder 20 tablets with sugar coating removed if the tablets are sugar coated. To a quantity of the powder equivalent to about 20 mg of albendazole, accurately weighed, in a 100 ml volumetric flask, add 10 ml of glacial acetic acid, shake thoroughly. Dilute with ethanol to volume, mix well and filter. Measure accurately 5 ml of the successive filtrate and transfer to another 100 ml volumetric flask, dilute with ethanol to volume and mix well. Measure the absorbance of the resulting solution at 295 nm (Appendix IV A), calculate the content of $C_{12}H_{15}N_3O_2S$, taking 444 as the value of A (1%, 1 cm).

Category As described under Albendazole.

Strength (1) 0.1 g (2) 0.2 g (3) 0.4 g

Storage Preserve in tightly closed containers.

Albumin Aggregated and Stannous Chloride for Injection

Albumin Aggregated and Stannous Chloride for Injection is a sterile, nonpyrogen and lyophilized preparation of stannous chloride and heat denatured human serum albumin. It contains not less than 85.0% and not more than 110.0% of the labelled amount of human serum albumin.

Description A white lyophilized powder, white particle suspension is produced in water or Sodium Chloride Injection, the particles aggregate at the bottom of the bottle after standing.

Identification (1) Dissolve the content of 1 bottle in 1 ml of water, mix well, add 1 drop of ninhydrin TS and heat, a violet blue is produced.

(2) Dissolve the content of 1 bottle in a quantity of water, add 1 drop of ammonium phosphomolybolic acid TS, a light blue colour is produced gradually, which changes dark blue after heating.

Acidity and alkalinity Suspend the content of 1 bottle in 5 ml of Sodium Chloride Injection, pH 5.0-7.5 (Appendix VI H).

Particle size Dilute the content of 1 bottle in a quantity of Sodium Chloride Injection to produce a suspension of about 1000 particles per ml, shake thoroughly to disperse the particles, immediately withdraw a drop with a pipette on a blood cell counting chamber, examine under a microscope.

Examining not less than 100 particles, particles from 10 μm up to 90 μm in maximum dimension are not less 90% and no particle of larger than 150 μm is observed.

Stannous To each of the content of 5 bottles, add 3 ml of 1 mol/L hydrochloric acid solution saturated with nitrogen respectively. Carry out the method for potentiometric titration (Appendix VII A), titrate with potassium iodate (0.001667 mol/L) VS under nitrogen current. Not less than 0.02 ml of potassium iodate (0.001667 mol/L) VS is consumed for per bottle. Repeat the test with 5 additional bottles if 1 bottle fails, All of the bottles should comply with the requirements.

Bacterial endotoxin Mix the content of 1 bottles with 5 ml of water-BET. Carry out the test for bacterial endotoxin (Appendix XI E); not more than 75 Eu per bottle.

Other requirements Complies with the general requirements for Injection (Appendix I B).

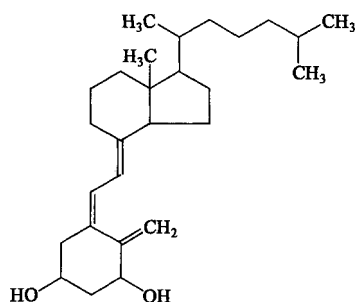
Assay Transfer the contents of 2 bottles with 4 ml of Sodium Chloride Injection to a centrifuging in portions, centrifuge, discard the supernatant liquid, wash the precipitation with 4 ml of Sodium Chloride Injection. Centrifuge and discard the supernatant liquid, add 2 ml of Sodium Chloride Injection, shake well as a test solution. Transfer 2 ml of human serum albumin solution (2 mg per ml) to another centrifuging as a reference solution. Transfer 2 ml of sodium chloride solution, measure accurately, to a third centrifuging as a blank solution. To each of the three solutions, add accurately 4 ml of alkaline cupric tartaric acid solution (Dissolve 1.5 g cupric sulfate and 6.0 g of sodium potassium tartrate in 500 ml of water in a 1000 ml volumetric flask, add 300 ml of 10% sodium hydroxide solution free from carbonate, mix well, and dilute with water to volume) respectively, mix well, heat in a 50-60°C water bath for 30 minutes. Measure the absorbance at 540 nm (Appendix IV B), and calculate the content of human serum albumin.

Category For preparation of Technetium [$^{99\text{m}}\text{Tc}$] Albumin Aggregated injection.

Strength 2 mg of human serum albumin and 0.15 mg of stannous chloride ($\text{SnCl}_2 \cdot 2\text{H}_2\text{O}$).

Storage Preserve in tightly closed containers, stored in a temperature between 2°C to 8°C in a dark place.

Alfacalcidol



$\text{C}_{27}\text{H}_{44}\text{O}_2$ 400.65

[41294-56-8]

Alfacalcidol is 9,10-Secosteroid-5,7,10 (19)-triene-1 α , 3 β -diol. It contains not less than 97.5% and not more than 102.0% of $\text{C}_{27}\text{H}_{44}\text{O}_2$.

Description A white, crystalline powder; odourless; tasteless, deteriorated on exposure to light, moisture or heat. Freely soluble in ethanol or dichloromethane; soluble in

ether; practically insoluble in water.

Melting range 137-142°C, with decomposition (Appendix VI C).

Specific optical rotation +46° to +52°, in a solution of 1.25 mg per ml in anhydrous ethanol (Appendix VI E).

Specific absorbance Measure the absorbance of a solution of 10 μg per ml in anhydrous ethanol at 265 nm (Appendix IV A), the value of A (1%, 1 cm) is 420-447.

Identification (1) Dissolve about 0.02 mg with 0.2 ml of chloroform, add 3 drops of acetic acid and 1 drop of sulfuric acid, shake; a yellow colour is produced which turns to red immediately and to yellow-green gradually.

(2) The retention time of the principal peak of the substance being examined in the chromatogram of the Assay corresponds to that of the reference substance.

(3) The infrared absorption spectrum (Appendix IV C) is concordant with the reference spectrum of alfacalcidol CRS.

Related substances Dissolve a quantity of the substance being examined in mobile phase to produce a solution of 0.1 mg per ml (solution 1) and 1 μg per ml (solution 2). Carry out the method as described under Assay. Inject 20 μl of the solution 2 into the column. Adjust the attenuation so that the principal peak height in the chromatogram is 10% of the full scale of the chart. Inject separately 20 μl of solution 1 and solution 2 into the column, and record the chromatogram for twice the retention time of the principal peak. The sum of the area of all peaks other than the principal peak in the chromatogram with solution 1 is not greater than 1.5 times the area of the principal peak in the chromatogram obtained with solution 2.

Assay Carry out the method for high performance liquid chromatography (Appendix V D), using a column packed with silica gel and a mixture of ethyl acetate-petroleum ether (60-90°C)-chloroform (42 : 44 : 14) as the mobile phase. Detection wavelength is 265 nm and the number of the theoretical plates of the column is not less than 2000, calculated with reference to the peak of alfacalcidol. The resolution factor between the peaks of alfacalcidol and internal standard is not less than 3.5.

Internal standard solution Dissolve about 15 mg of diazepam in mobile phase in a 50 ml volumetric flask, dilute to volume, shake well; and dilute 2 ml of the solution with mobile phase to volume in a 100 ml volumetric flask, shake well.

Procedure Dissolve a quantity of the substance being examined with mobile phase to produce a solution of 10 μg per ml as a test solution; transfer 5 ml each of the test solution and the internal standard solution, both measured accurately, in a 50 ml volumetric flask, dilute with mobile phase to volume, mix well. Inject 20 μl of the resulting solution into the column. And then dissolve a quantity of alfacalcidol CRS, accurately weighed, repeat the operation, calculate the content of $\text{C}_{27}\text{H}_{44}\text{O}_2$ with respect to the peak area obtained in the chromatogram by the internal standard method.

Category Calcium metabolism regulator.

Storage Preserve in tightly closed containers filled with nitrogen, stored in a cold place and protected from light.

Preparation Alfacalcidol Tablets.

Alfacalcidol Tablets

Alfacalcidol Tablets contain not less than 85.0% and not more than 115.0% of the labelled amount

of alfacalcidol ($C_{27}H_{44}O_2$).

Description White tablets.

Identification The retention time of the principal peak of the substance being examined in the chromatogram of the Assay corresponds to that of the reference substance.

Content uniformity Comply with the requirements (Appendix X E). Transfer 1 tablet to a stoppered centrifugal tube and powder. Add 1 ml of the internal standard solution (2) described under the Assay, measure accurately, stopper, treat vortically and ultrasonically for 4 minutes alternately, centrifuge in high speed. The supernatant is used as the test solution. Carry out the method described under the Assay and calculate the content of alfacalcidol. The limit of content uniformity is $\pm 25\%$.

Other requirements Comply with the general requirements for tablets (Appendix I A).

Assay Carry out the method for high performance liquid chromatography (Appendix V D), using a column packed with silica gel and a mixture of ethyl acetate-petroleum ether (60-90°C)-chloroform (42 : 44 : 14) as the mobile phase. Detection wavelength is 265 nm, and the number of the theoretical plates of the column is not less than 2000, calculated with reference to the peak of alfacalcidol. The resolution factor between the peaks of alfacalcidol and internal standard is not less than 1.5.

Internal standard solution Dissolve about 15 mg of diazepam in mobile phase in a 50 ml volumetric flask, dilute to volume, shake well; and measure accurately 2 ml of the solution to a 100 ml volumetric flask, dilute with mobile phase to volume, shake well as internal standard solution (1). Measure accurately 5 ml of the internal standard solution (1) to a 100 ml volumetric flask, dilute with a mixture of mobile phase-dichloromethane (1 : 1) to volume, shake well as internal standard solution (2).

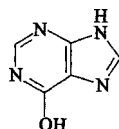
Procedure Weigh accurately and powder 20 tablets. Weigh accurately a quantity, equivalent to about 1 μg of alfacalcidol, to a stoppered centrifugal tube, add 2 ml of the internal standard solution (2), treat vortically and ultrasonically for 4 minutes alternately, centrifuge in high speed. Inject 20 μl of the supernatant into the column. Dissolve a quantity of alfacalcidol CRS with mobile phase to produce a solution of 10 μg per ml; transfer 5 ml each of the solution and the internal standard solution (1), both measured accurately, in a 100 ml of volumetric flask, dilute with mobile phase to volume, mix well. And then repeat the operation, calculate the content of $C_{27}H_{44}O_2$ with respect to the peak area obtained in the chromatogram by the internal standard method.

Category As described under Alfacalcidol.

Strength (1) 0.25 μg (2) 0.5 μg

Storage Preserve in tightly closed containers, stored in a dry, cool and dark place and protected from light.

Allopurinol



$C_5H_4N_4O$ 136.11

[315-30-0]

Allopurinol is 1*H*-pyrazolo [3,4-*d*] pyrimidin-4-ol. It contains not less than 97.0% and not more than 102.0% of $C_5H_4N_4O$, calculated on the dried basis.

Description A white or almost white crystalline powder; almost odourless.

Very slightly soluble in ethanol or water; insoluble in chloroform or ether; freely soluble in sodium hydroxide or potassium hydroxide solution.

Identification (1) To about 50 mg add 5 ml of 5% sodium hydroxide solution and 1 ml of alkali potassium mercuric iodide TS, heat to boil, a yellow precipitate is formed on standing.

(2) The light absorption of the solution obtained in Assay exhibits a maximum at 250 nm and a minimum at 231 nm. The ratio of the absorbance at 231 nm to that at 250 nm is 0.52-0.60 (Appendix IV A).

(3) The infrared absorption spectrum (Appendix IV C) is concordant with the reference spectrum of allopurinol (Appendix XVI).

Related substances Carry out the method for thin-layer chromatography (Appendix V B), using microcrystalline cellulose powder (F_{254}) as the coating substance and *n*-butanol saturated with ammonia TS as the mobile phase. Apply separately to the plate 5 μl each of two solutions in 10% diethylamine solution containing (1) 50 mg per ml, (2) 0.10 mg per ml of the substance being examined. After developing and removal of the plate, dry it in the air, examine under ultra-violet light (254 nm). Any spot other than the principal spot in the chromatogram obtained with solution (1) is not more intense than the principal spot obtained with solution (2).

Loss on drying When dried to constant weight at 105°C, loses not more than 0.5% of its weight (Appendix VIII L).

Assay Weigh accurately about 20 mg and dissolve in 10 ml of 0.4% sodium hydroxide solution with warming, if necessary. Add hydrochloric acid solution (9→1000) to produce a solution of 10 μg per ml. Measure the absorbance at 250 nm (Appendix IV A), calculate the content of $C_5H_4N_4O$, taking 571 as the value of *A* (1%, 1 cm).

Category Gout suppressant.

Storage Preserve in tightly closed containers, protected from light.

Preparation Allopurinol Tablets

Allopurinol Tablets

Allopurinol Tablets contain not less than 93.0% and not more than 107.0% of the labelled amount of allopurinol ($C_5H_4N_4O$).

Description White tablets.

Identification (1) To a quantity of the powdered tablets equivalent to about 0.1 g of allopurinol add 10 ml of 5% sodium hydroxide solution, shake to dissolve allopurinol, filter. The filtrate complies with test (1) for Identification describe 'r A''-p r' ol.

(2) The solution obtained in Assay complies with test (2) for Identification described under Allopurinol.

Dissolution Carry out the dissolution test (Appendix X C, method 2), using 1000 ml of hydrochloric acid solution (9→1000) as the dissolution medium, adjust the rotational speed of the paddle to 100 r/min. Withdraw 10 ml of the solution

after exactly 45 minutes and filter. Dilute 5 ml of successive filtrate, accurately measured, with hydrochloric acid solution (9 → 1000) to 50 ml, mix well. Measure the absorbance at 250 nm (Appendix IV A), calculate the dissolution of $C_5H_4N_4O$ from each tablet, taking 571 as the value of A (1%, 1 cm). Not less than 70% of the labelled amount is dissolved.

Other requirements Comply with the general requirements for tablets (Appendix I A).

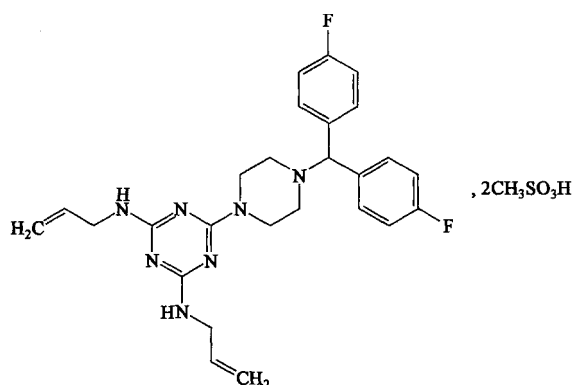
Assay Weigh accurately and powder 20 tablets. To a quantity of the powdered tablets equivalent to about 0.1 g of allopurinol, accurately weighed, in a 100 ml volumetric flask add 20 ml of 0.2% sodium hydroxide solution, shake for 15 minutes to dissolve allopurinol, add water to volume and mix well. Filter, transfer 5 ml of the successive filtrate, accurately measured, to a 500 ml volumetric flask, add hydrochloric acid solution (9 → 1000) to volume and mix well. Measure the absorbance at 250 nm (Appendix IV A). Calculate the content of $C_5H_4N_4O$, taking 571 as the value of A (1%, 1 cm).

Category As described under Allopurinol.

Strength 0.1 g

Storage Preserve in tightly closed containers, protected from light.

Almitrine Bismesylate



Almitrine Bismesylate is bis-2,4-allylamino-6-[4-bis-(4-fluorophenyl) methyl]-1-piperazinyl-S-triazine bismesylate. It contains not less than 98.0% and not more than 102.0% of $C_{26}H_{29}F_2N_7 \cdot 2CH_3SO_3H$, calculated on the dried basis.

Description A white or almost white crystalline powder; odourless; tasteless. Freely soluble in methanol, chloroform; soluble in ethanol; slightly soluble in acetone; insoluble in water.

Identification (1) Transfer about 0.2 g to a test tube, a gas is evolved by gentle heating, which turns wet lead acetate TP black.

(2) The light absorption of a solution of 8 µg per ml in ethanol exhibits a maximum at 223 nm (Appendix IV A).

(3) The infrared absorption spectrum (Appendix IV C) is concordant with the reference spectrum of almitrine bismesylate (Appendix XVI).

Acidity Dissolve 0.50 g in 50 ml of water, shake for 10 minutes and filter, the successive filtrate is as the test solution, pH 2.0-3.5 (Appendix VI H)

Fluorine Weigh accurately about 35 mg and carry out the limit test for Fluorine (Appendix VIII E). The fluorine content is not less than 5.1% and not more than 6.3%.

Related substances Carry out the method for thin-layer chromatography (Appendix V B) using silica gel GF₂₅₄ as the coating substance and the supernatant liquid of a mixture of *n*-Hexane-dichloromethane-ether-concentrated ammonia solution (38 : 25 : 12 : 10) as mobile phase. Apply separately to the plate 5 µl each of four solutions in methanol containing (1) 20 mg per ml, (2) 0.10 mg per ml, (3) 0.20 mg per ml, (4) 0.40 mg per ml of substance being examined. After developing and removal of the plate, dry it in air and expose it to iodine vapour until the spots appear. The number of spots in the chromatogram other than the principal spot obtained with solution (1) is not more than 3. The intensity of any secondary spot in the chromatogram obtained with solution (1) is compared with that of the principal spots obtained with solution (2), (3), (4), the total impurity is not more than 2.0%.

Toluene Dissolve a quantity, accurately weighed, in dimethyl-sulfoxide to produce a solution of 20 mg per ml and complies with the determination of residual solvents (Appendix VIII P).

Chloride Dissolve about 0.50 g in 25 ml of ethanol and carry out the limit test for chloride (Appendix VIII A) except diluting with ethanol. Any opalescence produced is not more pronounced than that of a reference using 5.0 ml of sodium chloride standard solution (0.01%).

Sulfate Dissolve about 0.50 g in 50 ml of water, boil gently for 2 minutes, cool, add water to original volume, mix well and filter. Carry out the limit test for sulfate (Appendix VIII B), using 40 ml of the successive filtrate. Any opalescence produced is not more pronounced than that of a reference using 2.0 ml of potassium sulfate standard solution (0.05%).

Loss on drying When dried to constant weight at 105°C, loses not more than 0.5% of its weight (Appendix VIII L).

Residue on ignition Not more than 0.15% (Appendix VIII N).

Heavy metals Carry out the limit test for heavy metals (Appendix VIII H, method 2), using the residue obtained in the test for Residue on ignition; not more than 0.002%.

Assay Carry out the method for high performance liquid chromatography (Appendix V D), using a column packed with octadecylsilane bonded silica gel and a mixture of methanol-water (85 : 15) (add 5 µl of diethylamine per 1000 ml) as the mobile phase. Detection wavelength is 222 nm and the number of theoretical plates of the column is not less than 900, calculated with reference to the peak of almitrine bismesylate.

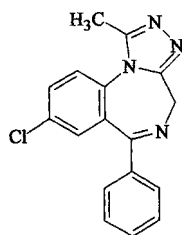
Procedure Dissolve a quantity, accurately weighed, in the mobile phase to produce the solution of 0.12 mg per ml. Inject 20 µl of the resulting solution, accurately measured, into the column and record the peak areas corresponding obtained in the chromatogram. Weigh accurately almitrine bismesylate CRS and repeat the operation. Calculate the content of $C_{26}H_{29}F_2N_7 \cdot 2CH_3SO_3H$.

Category Central stimulant.

Storage Preserve in tightly closed containers, protected from light.

Preparation Compound Almitrine Tablets

Alprazolam



$C_{17}H_{13}ClN_4$ 308.77

[28981-97-7]

Alprazolam is 8-chloro-1-methyl-6-phenyl-4*H*-s-triazolo [4,3- α] [1,4] benzodiazepine. It contains not less than 98.0% of $C_{17}H_{13}ClN_4$, calculated on the dried basis.

Description A white or almost white crystalline powder. Freely soluble in chloroform; sparingly soluble in ethanol or acetone; practically insoluble in water or ether.

Identification (1) Dissolve about 5 mg in 2 ml of hydrochloric acid solution (9→1000), divide to two portions. Add 1 drop of silicotungstic acid TS in one portion, a white precipitate is formed. Add 1 drop of potassium iodobismuthate TS in another portion, an orange red precipitate is produced.

(2) The light absorption of a solution of 12 μ g per ml in hydrochloric acid solution (9→1000) exhibits a maximum at 264 nm (Appendix IV A).

(3) The infrared absorption spectrum (Appendix IV C) is concordant with the reference spectrum of Alprazolam (Appendix XVI).

Chloride To 0.50 g add 50 ml of water, shake for 10 minutes and filter. Carry out the limit test for chloride (Appendix VIII A), using 25 ml of the filtrate. Any opalescence produced is not more pronounced than that of a reference solution using 5.0 ml of sodium chloride standard solution (0.02%).

Related substance Carry out the method for thin-layer chromatography (Appendix V B), using silica gel GF₂₅₄ as the coating substance and a mixture of chloroform-methanol (9 : 1) as the mobile phase. Apply separately to the plate 10 μ l of each of two solutions of the substance being examined in ethanol containing (1) 10 mg per ml, (2) 0.1 mg per ml. After developing and removal of the plate, dry it in air and examine under ultra-violet light (254 nm). Any spot, other than the principal spot, obtained with solution (1) is not more intense than the principal spot obtained with solution (2).

Loss on drying When dried to constant weight at 105°C, loses not more than 0.5% of its weight (Appendix VIII L).

Residue on ignition Not more than 0.3% (Appendix VIII N).

Assay Dissolve about 0.15 g, accurately weighed, in 10 ml of acetic anhydride, add 1 drop of crystal violet IS, titrate with perchloric acid (0.1 mol/L) VS, until the colour changes to yellowish green. Perform a blank determination and make any necessary correction. Each ml of perchloric acid (0.1 mol/L) VS is equivalent to 15.44 mg of $C_{17}H_{13}ClN_4$.

Category Hypnotic, sedative.

Storage Preserve in tightly closed containers, protected from light.

Preparation Alprazolam Tablets

Alprazolam Tablets

Alprazolam Tablets contain not less than 90.0% and not more than 110.0% of the labelled amount of alprazolam ($C_{17}H_{13}ClN_4$).

Description White tablets.

Identification (1) To a quantity of powdered tablets equivalent to about 2 mg of alprazolam add 3 ml of hydrochloric acid solution (9→1000), shake thoroughly and filter. The filtrate complies with the test (1) for Identification described under Alprazolam.

(2) The light absorption of a solution obtained in the Assay exhibits a maximum at 264 nm (Appendix IV A).

Content uniformity Comply with the requirements (Appendix X E). Dissolve 1 tablet with a quantity of hydrochloric acid solution (9→1000) and transfer to a 50 ml volumetric flask, shake well, dilute with hydrochloric acid solution (9→1000) to volume, shake and filter. Measure the absorbance of the successive filtrate, proceed as described under Assay, calculate the content of $C_{17}H_{13}ClN_4$, taking 407 as the value of A (1%, 1 cm).

Dissolution Carry out the dissolution test (Appendix XC, method 1), using 500 ml of phosphate BS (dissolve 16 g of potassium dihydrogen phosphate and 4 g of dipotassium hydrogen phosphate in water, dilute to 2000 ml with water, adjust the pH value to 6.0 ± 0.1 with phosphoric acid) as the dissolution medium, adjust the rotational speed of the paddle to 100 rpm. Withdraw a quantity of solution after exactly 30 minutes and filter, using the successive filtrate as the test solution. Carry out the method for high performance liquid chromatography (Appendix VD), using a column packed with octadecylsilane bonded silica gel and a mixture of phosphate BS-acetonitrile-tetrahydrofuran (60 : 35 : 5) as the mobile phase. Detection wavelength is 254 nm. Inject 100 μ l of the successive filtrate into the column, accurately measured, record the chromatogram. Dissolve a quantity of alprazolam CRS, accurately measured, in methanol to produce a solution of 16 μ g per ml. Transfer 5 ml of the solution into a 100 ml volumetric flask, accurately measured, dilute with the phosphate BS to volume and mix well, repeat the operation. Calculate the dissolution of $C_{17}H_{13}ClN_4$ from each tablet with respect to the peak area obtained in the chromatogram by the external standard method. Not less than 80% of the labelled amount is dissolved.

Other requirements Comply with the general requirements for tablets (Appendix I A).

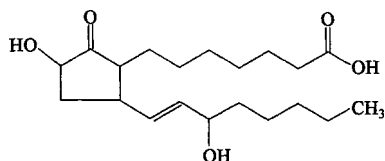
Assay Weigh and powder 20 tablets. To an accurately weighed quantity of powder (equivalent to about 3 mg of alprazolam) in a 50 ml volumetric flask, add a quantity of hydrochloric acid solution (9→1000), shake thoroughly, dilute with hydrochloric acid solution (9→1000) to volume, mix well and filter. Measure accurately 10 ml of the successive filtrate to another 50 ml volumetric flask, dilute with hydrochloric acid solution (9→1000) to volume and mix well. Measure the absorbance of the resulting solution at 264 nm (Appendix IV A), calculate the content of $C_{17}H_{13}ClN_4$, taking 407 as the value of A (1%, 1 cm).

Category As described under Alprazolam.

Strength 0.4 mg

Storage Preserve in tightly closed containers, protected from light.

Alprostadil



$C_{20}H_{34}O_5$ 354.48

[745-65-3]

Alprostadil is 11 α , 15(S)-dihydroxy-9-oxoprost-13-en-1-oic acid. It contains not less than 95.0% and not more than 105.0% of $C_{20}H_{34}O_5$, calculated on the dried basis.

Description White acicular crystals or a crystalline powder. Freely soluble in ethanol; slightly soluble in water; soluble in phosphate BS (pH 7.4-8.0).

Melting point 113-118°C (Appendix VI C).

Specific optical rotation -60° to -70° , in a solution of 10 mg per ml in ethanol (Appendix VI E).

Identification (1) The retention time of principal peak of alprostadil in the substance being examined in the chromatogram obtained in the Assay is identical with that of the principal peak of alprostadil CRS in the chromatogram of the reference solution.

(2) The infrared absorption spectrum (Appendix IV C) is concordant with the reference spectrum of alprostadil (Appendix XVI).

Related substance Dissolve a quantity of the substance being examined in the mobile phase to produce a solution of 1 mg per ml as the test solution. Transfer 5 ml of the test solution, measured accurately, into a 100 ml volumetric flask, dilute with the mobile phase to volume, mix well. Use this solution as the reference solution. Carry out the method as described under Assay. Inject 10 μ l of the reference solution into the column. Adjust the attenuation so that the principal peak height in the chromatogram is 10%-15% of full scale of the chart. Inject separately 10 μ l each of the test solution and the reference solution into the column, and record the chromatogram for three times the retention time of the principal peak. The area of the peak of prostaglandin A_1 in the chromatogram obtained with test solution is divided by 7.28, the sum of the result and the areas of all peaks other than the principal peak are not greater than that of the principal peak in the chromatogram obtained with reference solution (5.0%).

Loss on drying When dried in vacuum over phosphorous pentoxide to constant weight, loses not more than 1.0% of its weight (Appendix VIII L).

Assay Carry out the method for high performance liquid chromatography (Appendix V D), using a column packed with octadecylsilane bonded silica gel and a mixture of acetonitrile-0.02 mol/L potassium dihydrogen phosphate solution (pH 4.9) (40 : 60) as the mobile phase. Detection wavelength is 214 nm. To 2.0 ml of alprostadil CRS solution obtained in the Procedure, add 1 drop of 0.1 mol/L sodium hydroxide solution, mix well and allow to stand for 1 hour. Inject 10 μ l of the resulting solution into the column. The resolution factor between the peaks of Alprostadil and prostaglandin A_1 complies with the requirements (The relative retention time of the peak of prostaglandin A_1 is about 2.2-2.7).

Procedure Transfer about 10 mg, accurately weighed, into a 50 ml volumetric flask, dilute with mobile phase to volume, and mix well. Inject 10 μ l into the column, record the peak area obtained in the chromatogram. Repeat the operation, using alprostadil CRS instead of the substance being examined. Calculate the content of $C_{20}H_{34}O_5$ with respect to the peak area obtained in the chromatogram by the external standard method.

Category Medicine for prostaglandin.

Storage Preserve in tightly closed containers, stored in a cold place.

Preparation Alprostadil for Injection

Alprostadil for Injection

Alprostadil for injection is a sterile, freeze-dried preparation of alprostadil. It contains not less than 85.0% and not more than 120.0% of the labelled amount of alprostadil ($C_{20}H_{34}O_5$).

Description A white friable mass or powder

Identification The retention time of the principal peak of alprostadil in the substance being examined in the chromatogram obtained in the Assay is identical with that of the principal peak of alprostadil CRS in the chromatogram of the reference solution.

Related substance Dissolve a quantity of the substance being examined in 25% ethanol solution to produce a solution of 0.1 mg of alprostadil per ml as the test solution. Transfer 5 ml of the test solution, measured accurately, into a 50 ml volumetric flask, dilute with 25% ethanol solution to volume, mix well. Use this solution as the reference solution and carry out the test described under Alprostadil. The area of the peak of prostaglandin A_1 in the chromatogram obtained with test solution is divided by 7.28, the result is not greater than that of the principal peak in the chromatogram obtained with reference solution (10.0%).

Content uniformity Complies with the requirements for content uniformity except the limit is $\pm 20\%$ (Appendix X E). Carry out the method described under the Assay, using the contents of one container.

Undue toxicity Complies with the test for Undue toxicity (Appendix XI C), using a solution of 0.1 mg per ml in a sodium chloride injection, injected intravenously.

Bacterial endotoxin Carry out the test for bacterial endotoxin (Appendix XI E): not more than 0.25 EU per μ g of alprostadil.

Sterility Complies with the test for sterility (Appendix XI H), using a solution by dissolving a quantity of the substance being examined in a sodium chloride injection.

Other requirements Complies with the general requirements for the injections (Appendix I B).

Assay Dissolve a quantity of the substance being examined in 25% ethanol solution to produce a solution of 0.1 mg of alprostadil per ml as the test solution. Carry out the Assay described under Alprostadil and calculate the content of $C_{20}H_{34}O_5$.

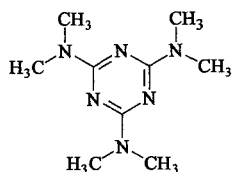
Category As described under alprostadil.

Strength (1) 20 μ g (2) 30 μ g (3) 80 μ g (4) 100 μ g (5) 200 μ g

Storage Preserve in tightly closed containers, protected

from light and stored in a cool place.

Altretamine



$C_9H_{18}N_6$ 210.28

[645-05-6]

Altretamine is 2,4,6-Tri-(dimethylamino)-1,3,5-triazine. It contains not less than 98.5% of $C_9H_{18}N_6$, calculated on the dried basis.

Description A white crystalline powder; odourless; sublimate, it may sublime.

Freely soluble in chloroform; sparingly soluble in ethanol; insoluble in water; freely soluble in dilute hydrochloric acid.

Melting range 170-174°C (Appendix VI C).

Identification (1) Dissolve 15 mg in 5 ml of 0.14% iodine petroleum ether solution, the colour of solution changes from purple to red.

(2) The light absorption of a solution of 2 µg per ml in ethanol exhibits a maximum at 227 nm (Appendix IV A).

(3) The infrared absorption spectrum of this substance or its sublimate are concordant with the spectrum of altretamine (Appendix XVI).

Chlorinated compound Weigh accurately 0.1 g, carry out the method for oxygen flask combustion (Appendix VII C), using 2 ml of sodium hydroxide TS and 10 ml of water as the absorbing liquid, when the combustion is completed, shake the flask vigorously to complete the absorption, add 10 ml of dilute nitric acid and transfer to a 50 ml nessler cylinder, carry out the limit test for chloride (Appendix VIII A). Any opalescence produced is not more pronounced than that of a reference solution using 2 ml of sodium chloride standard solution (0.01%).

Loss on drying When dried to constant weight at 105°C, loses not more than 0.5% of its weight (Appendix VIII L).

Residue on ignition Not more than 0.1% (Appendix VIII N).

Assay Dissolve about 0.15 g, accurately weighed, in each 10 ml of glacial acetic acid and acetic anhydride, add 1 drop of crystal violet IS, titrate with perchloric acid (0.1 mol/L) VS, until the colour changes to blue. Perform a blank determination and make any necessary correction. Each ml of perchloric acid (0.1 mol/L) VS is equivalent to 21.03 mg of $C_9H_{18}N_6$.

Category Antineoplastic.

Storage Preserve in tightly closed containers, protected from light.

Preparation (1) Altretamine Capsules
(2) Altretamine Tablets

Altretamine Capsules

Altretamine capsules contain not less than 90.0% and not more than 110.0% of the labelled amount of altretamine ($C_9H_{18}N_6$).

Identification To a quantity of the contents of capsules equivalent to about 0.1 g of Altretamine add a quantity of chloroform, filter and evaporate the filtrate to dryness on a water bath. The residue complies with test (1) and (2) for Identification described under Altretamine.

Dissolution Carry out the dissolution test (Appendix X C, method 1), using 900 ml of hydrochloric acid solution (0.9→1000) as the dissolution medium, adjust the rotational speed of the basket to 100 rpm. Withdraw 10 ml of the solution after exactly 30 minutes and filter. Measure accurately 2 ml of the successive filtrate to a 25 ml volumetric flask (strength 50 mg), to a 50 ml volumetric flask (strength 100 mg) or to a 100 ml volumetric flask (strength 200 mg), dilute with the same dissolution medium to volume and mix well. Dissolve an accurately weighed quantity of altretamine CRS in the dissolution medium to produce a solution of 4.4 µg per ml. Measure the absorbance of the resulting solutions at 241 nm (Appendix IV A), calculate the dissolution of $C_9H_{18}N_6$ from each capsule. Not less than 80% of the labelled amount is dissolved.

Other requirements Comply with the general requirements for capsules (Appendix I E).

Assay Weigh accurately a quantity of mixed contents obtained in the test for weight variation of contents equivalent to about 0.15 g of Altretamine, and carry out the Assay described under Altretamine.

Category As described under Altretamine.

Strength (1) 50 mg (2) 100 mg (3) 200 mg

Storage Preserve in tightly closed containers, protected from light.

Altretamine Tablets

Altretamine tablets contain not less than 90.0% and not more than 110.0% of the labelled amount of altretamine ($C_9H_{18}N_6$).

Description White tablets.

Identification To a quantity of powdered tablets equivalent to about 0.1 g of altretamine add a quantity of chloroform, shake thoroughly, filter and evaporate the filtrate to dryness on a water bath. The residue complies with test (1) and (2) for Identification described under Altretamine.

Dissolution Carry out the dissolution test (Appendix X C, method 1), using 900 ml of hydrochloric acid solution (0.9→1000) as the dissolution medium, adjust the rotational speed of the basket to 100 rpm. Withdraw 10 ml of the solution after exactly 30 minutes and filter. Measure accurately 2 ml of the successive filtrate to a 25 ml volumetric flask (strength 50 mg) or to a 50 ml volumetric flask (strength 100 mg), dilute with the same dissolution medium to volume and mix well. Dissolve an accurately weighed quantity of altretamine CRS in the dissolution medium to produce a solution of 4.4 µg per ml. Measure the absorbance of the resulting solutions at 241 nm (Appendix IV A), calculate the dissolution of $C_9H_{18}N_6$ from each tablet. Not less than 75% of the labelled amount is dissolved.

Other requirements Comply with the general requirements for tablets (Appendix I A).

Assay Weigh accurately and powder 20 tablets. Weigh accurately a quantity of the powder equivalent to about 0.15 g of altretamine, and carry out the Assay described under Altretamine.

Category As described under Altretamine.

Strength (1) 50 mg (2) 100 mg

Storage Preserve in tightly closed containers, protected from light.

Aluminium Hydroxide

Aluminium Hydroxide contains not less than 48.0% of Al_2O_3 .

Description A white powder, odourless and tasteless. Insoluble in water or ethanol; soluble in dilute mineral acids and sodium hydroxide solution.

Identification Heat and dissolve about 0.5 g in 10 ml of dilute hydrochloric acid, the solution yields the reactions characteristic of aluminium salts (Appendix III).

Neutralizing capacity To about 0.12 g, accurately weighed, in a 250 ml conical flask with stopper add 50 ml of hydrochloric acid (0.1 mol/L) VS, accurately measured, stopper the flask and shake for 1 hour continuously at 37°C. Allow the solution to cool, add 6-8 drops of bromophenol blue IS, titrate with sodium hydroxide (0.1 mol/L) VS. The volume of hydrochloric acid (0.1 mol/L) VS consumed is not less than 230 ml for each g of the substance being examined.

Alkali carbonate Mix 0.20 g with 10 ml of freshly boiled and cooled water and filter. To the filtrate add 2 drops of phenolphthalein IS. If the solution is pink, add 0.10 ml of hydrochloric acid (0.1 mol/L) VS, the pink colour disappears.

Chloride Boil and dissolve 0.10 g in 6 ml of dilute nitric acid, allow to cool, dilute to 20 ml with water and filter. Carry out the limit test for chlorides (Appendix VIII A), using 5 ml of the filtrate. Any opalescence produced is not more pronounced than that of a reference using 5.0 ml of sodium chloride standard solution (0.2%).

Sulfate Boil and dissolve 0.10 g in 3 ml of dilute hydrochloric acid, allow to cool, dilute to 50 ml with water and filter. Carry out the limit test for sulfates (Appendix VIII B), using 25 ml of the filtrate. Any opalescence produced is not more pronounced than that of a reference using 5.0 ml of potassium sulfate standard solution (0.1%).

Heavy metals To 1.0 g add 5 ml of hydrochloric acid, evaporate to dryness on a water bath. Add 5 ml of water, stir thoroughly, continue to evaporate towards dryness, stir to produce a dry powder. Dissolve it in 2 ml of acetate BS (pH 3.5) and 10 ml of water by gently heat, filter. To the filtrate add a quantity of water to produce 25 ml. Carry out the limit test for heavy metals (Appendix VIII H, method 1): not more than 0.003%.

Arsenic Boil 0.20 g in 10 ml of dilute sulfuric acid, allow to cool, add 5 ml of hydrochloric acid and a quantity of water to produce 28 ml. Complies with the limit test for arsenic (Appendix VIII J, method 1) (0.001%).

Assay Dissolve by heat about 0.6 g, accurately weighed, in 10 ml each of hydrochloric acid and water, cool to room temperature and filter. Transfer the filtrate to a 250 ml volumetric flask, wash the filter with water, combine the washings to the flask, dilute with water to volume and mix well. Measure accurately 25 ml of the resulting solution, neutralize with ammonia TS until the precipitate is just dissolved, add 10 ml of ammonium acetate BS (pH 6.0) and then 25 ml of disodium edetate (0.05 mol/L) VS, accurately measured. Boil the solution for 3-5 minutes, cool

to room temperature, add 1 ml of xylene orange IS, titrate with zinc (0.05 mol/L) VS until the solution changes from yellow to red. Perform a blank determination and make any necessary correction. Each ml of disodium edetate (0.05 mol/L) VS is equivalent to 2.549 mg of Al_2O_3 .

Category Antacid.

Storage Preserve in tightly closed containers.

Preparation (1) Aluminium Hydroxide Gel
(2) Aluminium Hydroxide Tablets
(3) Compound Aluminium Hydroxide Tablets

Aluminium Hydroxide Gel

Aluminium Hydroxide Gel is an suspension gel, form with colloid particles of aluminium hydroxide dispense in water. It contains not less than 3.60% and not more than 4.40% of aluminium hydroxide, calculated as Al_2O_3 .

A quantity of flavouring agent and preservatives may be added.

Description A white, viscous suspension gel; a thin layer of the suspension is translucent; a small amount of water may separate on standing; it exhibits a weak reaction to red or blue litmus paper, and no reaction to phenolphthalein IS.

Identification Heat and dissolve 5 ml in 10 ml of dilute hydrochloric acid, the solution yields the reactions characteristic of aluminium salts (Appendix III).

Neutralizing capacity To about 1.5 g, accurately weighed, in a 250 ml conical flask with stopper add 50 ml of hydrochloric acid (0.1 mol/L) VS, accurately measured, stopper the flask, shake for 1 hour continuously at 37°C. Add 6-8 drops of bromophenol blue IS, titrate with sodium hydroxide (0.1 mol/L) VS until the solution becomes blue. The volume of hydrochloric acid (0.1 mol/L) consumed is 12.5-25.0 ml for each g of the substance being examined.

Chloride Boil and dissolve 0.40 g in 6 ml of dilute nitric acid, allow to cool, dilute to 50 ml with water and filter. Carry out the limit test for chlorides (Appendix VIII A), using 25 ml of the filtrate. Any opalescence produced is not more pronounced than that of a reference using 7.0 ml of sodium chloride standard solution (0.035%).

Sulfate Boil and dissolve 1.0 g in 1 ml of dilute hydrochloric acid, allow to cool, dilute to 50 ml with water and filter. Carry out the limit test for sulfates (Appendix VIII B), using 20 ml of filtrate. Any opalescence produced is not more pronounced than that of a reference using 5.0 ml of potassium sulfate standard solution (0.125%).

Heavy metals To 5.0 g add 5 ml of hydrochloric acid, evaporate to dryness on a water bath; add 5 ml of water, stir, continue to evaporate towards dryness, stir to produce a dry powder. Dissolve it by heat gently in 2 ml of acetate BS (pH 3.5) and 10 ml of water, filter. To the filtrate add a quantity of water to produce 25 ml. Carry out the limit test for heavy metals (Appendix VIII H, method 1): not more than 0.0005%.

Arsenic Boil 2.5 g in 10 ml of dilute sulfuric acid, allow to cool, add 5 ml hydrochloric acid and a quantity of water to produce 28 ml. Complies with the limit test for arsenic (Appendix VIII J, method 1) (0.00008%).

Assay Weigh accurately about 8 g and carry out the Assay described under Aluminium Hydroxide beginning at the words "in 10 ml each of hydrochloric acid...", Each ml of

disodium edetate (0.05 mol/L) VS is equivalent to 2.549 mg of Al_2O_3 .

Category As described under Aluminium Hydroxide.

Storage Preserve in tightly closed containers, protected from freezing.

Aluminium Hydroxide Tablets

Aluminium Hydroxide Tablets contain not less than 0.135 g of aluminium oxide (Al_2O_3) in each tablet.

Description White tablets.

Identification To a quantity of the powdered tablets equivalent to about 0.5 g of aluminium hydroxide add 10 ml of dilute hydrochloric acid, heat to dissolve and filter, the filtrate yields the reactions characteristic of aluminium salts (Appendix III).

Neutralizing capacity Weigh accurately a quantity of the powdered tablets equivalent to about 0.15 g of aluminium hydroxide to a 250 ml conical flask with stopper, add accurately 50 ml of hydrochloric acid (0.1 mol/L) VS, stopper the flask and shake for an hour continuously at 37°C. Allow to cool, add 6-8 drops of bromophenol blue IS, titrate with sodium hydroxide (0.1 mol/L) VS. The volume of hydrochloric acid (0.01 mol/L) VS consumed is not less than 60 ml for each tablet.

Other requirements Comply with the general requirements for tablets (Appendix I A), except the disintegration test.

Assay Weigh accurately and powder 10 tablets. Weigh accurately a quantity equivalent to about 0.6 g of aluminium hydroxide, carry out the Assay described under Aluminium Hydroxide. Each ml of disodium edetate (0.05 mol/L) VS is equivalent to 2.549 mg of Al_2O_3 .

Category As described under Aluminium Hydroxide.

Strength 0.3 g

Storage preserve in tightly closed containers, stored in a dry place.

Compound Aluminium Hydroxide Tablets

Compound Aluminium Hydroxide Tablets contain not less than 0.116 g of aluminium oxide (Al_2O_3). And not less than 0.020 g of magnesium oxide (MgO) in each tablet.

Formula	Aluminium Hydroxide	245 g
	Magnesium Trisilicate	105 g
	Belladonna Liquid Extract	2.6 ml
	to make	1000 tablets

Description White tablets.

Identification To about 6 powdered tablets add 30 ml of dilute hydrochloric acid, warm gently and filter. The filtrate complies with the following tests:

(1) Make 4 ml alkaline with ammonia TS, a gelatinous white precipitate is formed; add a few drops of sodium alizarin sulfonate IS, the precipitate becomes cherry red in colour.

(2) Make 4 ml alkaline with sodium hydroxide TS, a gelatinous white precipitate is produced, which is partially

soluble in 3 ml of sodium hydroxide TS. Filter and wash the precipitate with water, it is produced reddish brown colour on the addition of iodine TS.

(3) Make 20 ml alkaline with ammonia TS, extract with ether, evaporate the ether extract to dryness. To the residue add 3-4 drops of fuming nitric acid and evaporate on a water bath to dryness. Cool, to the residue add a small pellet of potassium hydroxide and a few drops of dehydrated ethanol; a violet colour is produced.

Neutralizing capacity Transfer accurately a quantity of the powdered tablets equivalent to a quarter of one tablet to a 250 ml glass-stoppered flask. Add accurately 50 ml of hydrochloric acid (0.1 mol/L) VS and shake continuously, maintaining the temperature at 37°C for 1 hour. Allow to cool, add 0.5 ml of bromophenol blue IS and titrate the excess acid with sodium hydroxide (0.1 mol/L) VS. The volume of hydrochloric acid (0.1 mol/L) VS consumed is not less than 60 ml per tablet.

Other requirements Comply with the general requirements for tablets (Appendix I A); but the disintegration time is not more than 10 minutes, using hydrochloric acid solution (9→1000) instead of water.

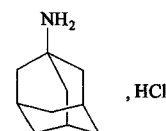
Assay Aluminium oxide Weigh accurately and powder 10 tablets. To an accurately weighed quantity of the powder equivalent to about a quarter of one tablet add 50 ml of water and 2 ml of hydrochloric acid. Heat to boiling, cool and filter. Wash the residue with water, combine the washings with the filtrate, add ammonia TS until a precipitate is just formed and redissolve it by adding dropwise, dilute hydrochloric acid. Add 10 ml of acetic acid ammonium acetate BS (pH 6.0) and 25.0 ml of disodium edetate (0.05 mol/L) VS, heat to boil for 10 minutes. Cool, add 1 ml of xylenol orange IS and titrate with zinc (0.05 mol/L) VS until the colour changes from yellow to red. Perform a blank determination and make any necessary correction. Each ml of disodium edetate (0.05 mol/L) VS is equivalent to 2.549 mg of Al_2O_3 .

Magnesium oxide Weigh accurately a quantity of the powdered tablets equivalent to about 1 tablet, add 50 ml of water and 5 ml of hydrochloric acid, heat to boil, cool. Add 1 drop of methyl red IS, and then add ammonia TS dropwise until the colour changes from red to yellow. Boil again for 5 minutes, filter while hot, wash the residue with 30 ml of 2% ammonium chloride solution. Combine the washings with the filtrate and cool. Add 10 ml of ammonia TS, 5 ml of triethanolamine solution (1→2) and a small quantity of eriochrome black T indicator, titrate with disodium edetate (0.05 mol/L) VS until the colour changes to pure blue. Each ml of disodium edetate (0.05 mol/L) VS is equivalent to 2.015 mg of MgO .

Category Antacid.

Storage Preserve in tightly closed containers, stored in a dry place.

Amantadine Hydrochloride



$\text{C}_{10}\text{H}_{17}\text{N} \cdot \text{HCl}$ 187.71

[665-66-7]

Amantadine Hydrochloride is tricyclo [3.3.1.^{1,3,7}]

decan-1-amine hydrochloride. It contains not less than 99.0% of $C_{10}H_{17}N \cdot HCl$, calculated on the dried basis.

Description White crystals or a crystalline powder; odourless; taste, bitter. Freely soluble in water or ethanol; soluble in chloroform.

Identification (1) Dissolve 10 mg in 2 ml of water, acidify with hydrochloric acid, add silicotungstic acid TS dropwise; a white precipitate is produced.

(2) The infrared absorption spectrum (Appendix IV C) is concordant with the reference spectrum of amantadine hydrochloride (Appendix XVI).

(3) The aqueous solution yields the reactions characteristic of chlorides (Appendix III).

Acidity Dissolve 2.0 g in 10 ml of water, pH 3.5-5.0 (Appendix VI H).

Clarity and colour of solution A solution of 1.0 g in 10 ml of water is clear and colourless. Any opalescence produced is not more pronounced than that of reference suspension 1 (Appendix IX B), and any colour produced is not more intense than that of reference solution Y_2 (Appendix IX A, method 1).

Loss on drying When dried to constant weight at 105°C, loses not more than 0.5% of its weight (Appendix VIII L).

Residue on ignition Not more than 0.1% (Appendix VIII N).

Heavy metals Dissolve 2.0 g in 23 ml of water, add 2 ml of acetate BS (pH 3.5), carry out the limit test for heavy metals (Appendix VIII H, method 1); not more than 0.0005%.

Assay Dissolve about 0.12 g, accurately weighed, in 30 ml of glacial acetic acid and 5 ml of mercuric acetate TS, add 2 drops of crystal violet IS. Titrate with perchloric acid (0.1 mol/L) VS until the colour changes to blue. Perform a blank determination and make any necessary correction. Each ml of perchloric acid (0.1 mol/L) VS is equivalent to 18.77 mg of $C_{10}H_{17}N \cdot HCl$.

Category Anti-parkinsonian and antiviral.

Storage Preserve in tightly closed containers, protected from light.

Preparation (1) Amantadine Hydrochloride Capsules
(2) Amantadine Hydrochloride Tablets
(3) Amantadine Hydrochloride Granules
(4) Amantadine Hydrochloride Syrup

Amantadine Hydrochloride Capsules

Amantadine Hydrochloride Capsules contain not less than 90.0% and not more than 110.0% of the labelled amount of amantadine hydrochloride ($C_{10}H_{17}N \cdot HCl$).

Identification (1) Dissolve 10 mg of the contents of the capsules in 2 ml of water, acidify with hydrochloric acid and add dropwise silicotungstic acid TS; a white precipitate is produced.

(2) The aqueous solution yields the reactions characteristic of chlorides (Appendix III).

Other requirements Comply with the general requirements for capsules (Appendix I E).

Assay Dissolve an accurately weighted quantity of the mixed

contents obtained in the test for weight variation, equivalent to about 0.12 g of amantadine hydrochloride, in 30 ml of glacial acetic acid and 5 ml of mercuric acetate TS, add 2 drops of crystal violet IS. Titrate with perchloric acid (0.1 mol/L) VS until the colour changes to blue, perform a blank determination and make any necessary correction. Each ml of perchloric acid (0.1 mol/L) VS is equivalent to 18.77 mg of $C_{10}H_{17}N \cdot HCl$.

Category As described under Amantadine Hydrochloride.

Strength 0.1 g

Storage Preserve in tightly closed containers, protected from light.

Amantadine Hydrochloride Granules

Amantadine Hydrochloride Granules contain not less than 93.0% and not more than 107.0% of the labelled amount of amantadine hydrochloride ($C_{10}H_{17}N \cdot HCl$).

Description White granules; taste sweet.

Identification (1) To a quantity of the granules, equivalent to about 0.1 g of amantadine hydrochloride, add 5 ml of water, shake to dissolve amantadine hydrochloride and filter. Acidify the filtrate with hydrochloric acid, add dropwise silicotungstic acid TS; a white precipitate is formed.

(2) The aqueous solution yields the reactions characteristic of chlorides (Appendix III).

Other requirements Comply with the general requirements for granules (Appendix I N).

Assay Triturate the contents of 20 packages, weigh accurately. Weigh accurately a quantity of the powdered granules, equivalent to about 0.3 g of amantadine hydrochloride, in a conical flask with stopper. Add 50 ml of ethanol, accurately measured, shake for 20 minutes to dissolve amantadine hydrochloride. Filter through a dry filter paper, transfer 20 ml of the successive filtrate, accurately measured, to a conical flask, and evaporate on a water bath to dryness. Dry the residue at 105°C for 30 minutes, cool. Carry out the Assay as described under Amantadine Hydrochloride, beginning at the words "in 30 ml of glacial acetic acid". Calculate the content of $C_{10}H_{17}N \cdot HCl$.

Category As described under Amantadine Hydrochloride.

Strength (1) 6 g : 60 mg (2) 12 g : 140 mg

Storage Preserve in tightly closed containers, protected from light.

Amantadine Hydrochloride Syrup

Amantadine Hydrochloride Syrup contains not less than 93.0% and not more than 107.0% of the labelled amount of amantadine hydrochloride ($C_{10}H_{17}N \cdot HCl$).

Formula	Amantadine Hydrochloride	5 g
	Sucrose	650 g
	Citric Acid	4 g
	Sodium Benzoate	3 g
	Flavouring agent	1 ml

Colouring matter	a quantity
Water	a quantity
To make	1000 ml

Description A clear, coloured viscous liquid.

Identification To 5 ml add 1 ml of 20% sodium hydroxide solution, mix well. Add 5 ml of ethyl acetate, shake thoroughly, allow to separate into two layers. To ethyl acetate layer add 5 ml of 1 mol/L hydrochloric acid solution, shake thoroughly, allow to separate into two layers. To 2 ml of the aqueous layer add dropwise silicotungstic acid TS; a white precipitate is formed.

pH value 3.0-4.0 (Appendix VI H).

Relative density Not less than 1.240 (Appendix VI A).

Other requirements Complies with the general requirements for syrup (Appendix I K).

Assay Measure accurately 50 ml with a "to contain" pipette, equivalent to about 250 mg of amantadine hydrochloride, into a separator. Wash the inner wall of the pipette with water in several portions. Combine the washings into the separator, add 13 ml of 20% sodium hydroxide solution, and mix well. Add accurately 40 ml of ethyl acetate, shake thoroughly for 15 minutes, allow it to separate. Measure accurately 20 ml of the ethyl acetate layer into 50 ml of glacial acetic acid in a conical flask, add 2 drops of crystal violet IS. Titrate with perchloric acid (0.1 mol/L) VS until the colour changes from violet to blue. Perform a blank determination and make any necessary correction. Each ml of perchloric acid (0.1 mol/L) VS is equivalent to 18.77 mg of $C_{10}H_{17}N \cdot HCl$.

Category As described under Amantadine Hydrochloride.

Storage Preserve in tightly closed containers, protected from light.

Amantadine Hydrochloride Tablets

Amantadine Hydrochloride Tablets contain not less than 93.0% and not more than 107.0% of the labelled amount of amantadine hydrochloride ($C_{10}H_{17}N \cdot HCl$).

Description White tablets.

Identification To a quantity of the powdered tablets equivalent to about 0.1 g of amantadine hydrochloride add 5 ml of water, shake and filter. The filtrate complies with tests (1) and (3) for Identification described under Amantadine Hydrochloride.

Other requirements Complies with the general requirements for tablets (Appendix I A).

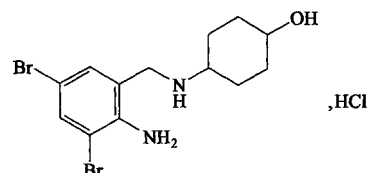
Assay Weigh accurately and powder 20 tablets. To a quantity of the powder equivalent to about 0.3 g of amantadine hydrochloride, accurately weighed, in a 50 ml volumetric flask, add about 35 ml of ethanol, shaking for 20 minutes, dilute to volume with ethanol, mix well. Filter through a dry filter paper, transfer 20 ml of the successive filtrate, accurately measured, to a conical flask, and evaporate on a water bath to dryness. Dry the residue at 105°C for 30 minutes, cool. Carry out the Assay described under Amantadine Hydrochloride, beginning at the words "in 30 ml of glacial acetic acid...". Each ml of perchloric acid (0.1 mol/L) VS is equivalent to 18.77 mg of $C_{10}H_{17}N \cdot HCl$.

Category As described under Amantadine Hydrochloride.

Strength 0.1 g

Storage Preserve in tightly closed containers, protected from light.

Ambroxol Hydrochloride



$C_{13}H_{18}Br_2N_2O \cdot HCl$ 414.57

Ambroxol Hydrochloride is trans-4-[(2-Amino-3,5-dibromobenzyl) amino] cyclohexanol hydrochloride. It contains not less than 99.0% of $C_{13}H_{18}Br_2N_2O \cdot HCl$, calculated on the dried basis.

Description A white to slightly yellow crystalline powder; practically odourless.

Soluble in methanol; sparingly soluble in water; slightly soluble in ethanol.

Specific absorbance Measure the absorbance of a solution of 25 μ g per ml in 0.01 mol/L hydrochloric acid at 244 nm (Appendix IV A), the value of E (1%, 1 cm) is 233-247.

Identification (1) The light absorption of a solution of 15 μ g per ml in 0.01 mol/L hydrochloric acid solution exhibits two maximum at 244 nm and 308 nm (Appendix IV A).

(2) The infrared absorption spectrum (Appendix IV C) is concordant with the reference spectrum of Ambroxol Hydrochloride (Appendix XVI).

(3) Yields the reactions characteristic of chlorides (Appendix III).

Acidity Dissolve 0.20 g in 20 ml of water, pH 4.5-6.0 (Appendix VI H).

Clarity and colour of methanol solution Dissolve 0.50 g in 10 ml of methanol, the solution is clear and colourless; any opalescence produced is not more pronounced than that of reference suspension I (Appendix IX B); any colour produced is not more intense than that of reference solution Y₃ (Appendix IX A, method 2).

Related substances Dissolve a quantity in the mobile phase to produce a solution of 1 mg per ml (test solution). Transfer 1 ml of the test solution in a 100 ml volumetric flask, dilute with the mobile phase, mix well (reference solution). Dissolve 5 mg in 0.2 ml of methanol, add 40 μ l of formaldehyde solution (1 \rightarrow 100), mix well, heat at 60°C for 5 minutes, dry it in nitrogen, dissolve the residue in 5 ml of water, dilute with the mobile phase to 20 ml, inject 20 μ l into the column. Carry out the method for high performance liquid chromatography (Appendix V D), using a column packed with octadecylsilane bonded silica gel and a mixture of 0.01 mol/L diammonium hydrogen phosphate solution (adjust the pH value to 7.0 with phosphate acid)-acetonitrile (50 : 50) as the mobile phase. Detection wavelength is 248 nm. The resolution factor between the peaks of ambroxol hydrochloride and the secondary B (the relative retention time is 0.8) is more than 4.0. Inject 20 μ l of reference solution into the column, adjust the sensitivity of the detector so that the principal peak height in the chromatogram is 20%-25% of the full scale of the recorder.

Inject accurately 20 μ l of test solution and reference solution into the column respectively, and record the chromatogram for twice the retention time of the principal peak. The sum of the areas of all secondary peaks in the chromatogram obtained with the test solution is not greater than 1/3 of the principal peak area in the chromatogram obtained with the reference solution.

Residual solvents Dissolve a quantity, accurately weighed, in dimethylsulfoxide to produce a solution of 100 mg per ml (test solution). Dissolve a quantity of methanol and acetone, accurately weighed, in dimethylsulfoxide to produce a solution of 0.3 mg of methanol and 0.5 mg of acetone per ml (reference solution), transfer 1 ml of the reference solution in vaporization chamber. Carry out the test for residual solvents (Appendix VIII P method 2), using a column packed with (5%) diphenyl-(95) dimethyl silane polymer as the stationary phase, and maintain the injector temperature at 120°C and the detection temperature at 260°C. Temperature program: maintain the initial temperature of the column at 50°C for 5 minutes, then raising the temperature at a rate of 8°C per minute to 145°C, then raising the temperature at a rate of 35°C per minute to 260°C and maintain it at 260°C for 5 minutes. The relative deviation is not more than 10.0%. Inject the test solution into the column, measure in the same manner, the content of methanol and acetone complies with the related requirements.

Loss on drying When dried to constant weight at 105°C, loses not more than 0.5% of its weight (Appendix VIII L).

Residue on ignition Not more than 0.1% (Appendix VIII N), using 1.0 g.

Heavy metals Carry out the limit test for heavy metals (Appendix VIII H, method 2), using the residue obtained in the test for Residue on ignition; not more than 0.002%.

Arsenic Dissolve 1.0 g in 10 ml of water and 15 ml of hydrochloric acid. Carry out limit test for arsenic (Appendix VIII J, method 1); not more than 0.0002%.

Assay Dissolve about 0.3 g, accurately weighed, in 5 ml of methanol, add 20 ml of glacial acetic acid, 5 ml mercuric acetate TS and 1 drop of crystal violet IS, titrate with perchloric acid VS (0.1 mol/L) until the colour changes to blue. Perform a blank determination and make any necessary correction. Each ml of perchloric acid VS (0.1 mol/L) is equivalent to 41.46 mg of $C_{13}H_{18}Br_2N_2O \cdot HCl$.

Category Extensorant.

Storage Preserve in tightly closed containers, protected from light.

Preparations (1) Ambroxol Hydrochloride Oral Solution (2) Ambroxol Hydrochloride Tablets (3) Ambroxol Hydrochloride Capsules (4) Ambroxol Hydrochloride Sustained-release Capsules

Ambroxol Hydrochloride Capsules

Ambroxol Hydrochloride Capsules contain not less than 90.0% and not more than 110.0% of ambroxol hydrochloride ($C_{13}H_{18}Br_2N_2O \cdot HCl$).

Description Capsules containing white or almost white particles or powder.

Identification (1) The retention time of principal peak of the substance being examined in the chromatogram obtained in the Assay is identical with that of the principal peak of ambroxol hydrochloride CRS in the chromatogram of the

reference solution.

(2) The light absorption of a solution under Dissolution exhibits two maximum at 244 nm and 308 nm (Appendix IV A).

Related substances Dissolve a quantity of the mixed content in the mobile phase to produce a solution of 1 mg of ambroxol hydrochloride per ml as the test solution and a solution of 10 μ g of ambroxol hydrochloride per ml as the reference solution. Carry out the chromatogram conditions as described under Assay. Inject 20 μ l of reference solution into the column, adjust the sensitivity of the detector so that the principal peak height in the chromatogram is 20%-25% of the full scale of the recorder. Inject accurately 20 μ l of test solution and reference solution into the column respectively, and record the chromatogram for twice the retention time of the principal peak. The sum of the areas of all secondary peaks in the chromatogram obtained with the test solution is not greater than the principal peak area in the chromatogram obtained with the reference solution.

Dissolution Carry out the dissolution test (Appendix X C, method 1), using 900 ml of hydrochloric acid solution (9→1000) as the dissolution medium, adjust the rotational speed of the paddle to 75 rpm. Withdraw 10 ml of the solution after exactly 30 minutes and filter. Dilute 5 ml of the successive filtrate, accurately measured, with the dissolution medium to 10 ml, mix well. Carry out the method for spectrophotometry (Appendix IV A), measure the absorbance at 244 nm. Dissolve a quantity of ambroxol hydrochloride CRS, accurately weighed, in the dissolution medium to produce a solution of 15 μ g per ml, measure the absorbance in the same manner. Calculate the dissolution of $C_{13}H_{18}Br_2N_2O \cdot HCl$ from each capsules, not less than 80% of the labelled amount is dissolved.

Other requirements Comply with the general requirements for capsules (Appendix I E).

Assay Carry out the method for High performance liquid chromatography (Appendix V D), using a column packed with octadecylsilane bonded silica gel and a mixture of 0.01 mol/L diammonium hydrogen phosphate solution (adjust the pH value to 7.0 with phosphate acid)-acetonitrile (50 : 50) as the mobile phase. Detection wavelength is 248 nm. Dissolve about 5 mg of ambroxol hydrochloride CRS in 0.2 ml of methanol, add 40 μ l of formaldehyde solution (1→100), mix well, heat at 60°C for 5 minutes, dry it in nitrogen, dissolve the residue in 5 ml of water, dilute with the mobile phase to 20 ml, inject 20 μ l into the column. The resolution factor between the peaks of ambroxol hydrochloride and the secondary B (the relative retention time is 0.8) is more than 4.0.

Procedure Weigh and powder a quantity of the contents. Dissolve a quantity of the powder, accurately measured, in mobile phase to produce a solution of 30 μ g of ambroxol hydrochloride per ml, filter. Inject 20 μ l of the successive filtrate into the column and record the peak areas correspondingly obtained in the chromatogram. Dissolve about a quantity of ambroxol hydrochloride CRS, accurately weighed, in mobile phase to produce a solution of 30 μ g per ml, inject the reference solution into the column, measure in the same manner. Calculate the content of $C_{13}H_{18}Br_2N_2O \cdot HCl$ with respect to the peak area obtained in the chromatogram by the external standard method.

Category As described under Ambroxol Hydrochloride.

Strength 30 mg

Storage Preserve in tightly closed containers, protected from light.

Ambroxol Hydrochloride Oral Solution

Ambroxol Hydrochloride Oral Solution contains not less than 95.0% and not more than 105.0% of ambroxol hydrochloride ($C_{13}H_{18}Br_2N_2O \cdot HCl$).

Description A clear, colourless or almost colourless viscous liquid; a clear, colourless or almost colourless liquid (sugarless).

Identification (1) The retention time of principal peak of the substance being examined in the chromatogram obtained in the Assay is identical with that of the principal peak of ambroxol hydrochloride CRS in the chromatogram of the reference solution.

(2) The light absorption of a solution of 30 μg per ml in 0.1 mol/L hydrochloric acid solution exhibits a maximum at 308 nm (Appendix IV A).

Relative density 1.090-1.200 (Appendix VI A) (contain sugar).

pH value 2.5-5.0 or 4.0-6.0 (sugarless) (Appendix VI H).

Clarity and colour A clear, colourless liquid; any opalescence produced is not more pronounced than that of reference suspension I (Appendix IX B); any colour produced is not more intense than that of reference solution Y_2 (Appendix IX A, method 2).

Other requirements Complies with the general requirements for oral solution (Appendix I O).

Assay Carry out the method for high performance liquid chromatography (Appendix V D), using a column packed with octadecylsilane bonded silica gel and a mixture of 0.01 mol/L diammonium hydrogen phosphate solution (adjust the pH value to 7.0 with phosphate acid)-acetonitrile (50 : 50) as the mobile phase. Detection wavelength is 248 nm. Dissolve about 5 mg of ambroxol hydrochloride CRS in 0.2 ml of methanol, add 40 μl of formaldehyde solution (1 \rightarrow 100), mix well, heat at 60°C for 5 minutes, dry it in nitrogen, dissolve the residue in 5 ml of water, dilute with the mobile phase to 20 ml, inject 20 μl into the column. The resolution factor between the peaks of ambroxol hydrochloride and the secondary B (the relative retention time is 0.8) is more than 4.0.

Procedure Measure accurately a quantity (viscous liquid with a "to contain" pipette), in mobile phase to produce a solution of 30 μg per ml. Inject 20 μl into the column and record the peak areas correspondingly obtained in the chromatogram. Dissolve a quantity of ambroxol hydrochloride CRS, accurately weighed, in mobile phase to produce a solution of 30 μg per ml, inject the reference solution into the column, measure in the same manner. Calculate the content of $C_{13}H_{18}Br_2N_2O \cdot HCl$ with respect to the peak area obtained in the chromatogram by the external standard method.

Category As described under Ambroxol Hydrochloride.

Strengths (1) 5 ml : 15 mg (2) 60 ml : 180 mg
(3) 105 ml : 0.3 g (4) 100 ml : 0.3 g (sugarless)

Storage Preserve in tightly closed containers, protected from light.

Ambroxol Hydrochloride Sustained-release Capsules

Ambroxol Hydrochloride Sustained-release Capsules

contain not less than 95.0% and not more than 105.0% of ambroxol hydrochloride ($C_{13}H_{18}Br_2N_2O \cdot HCl$).

Description Capsules containing white or almost white small pills.

Identification (1) The retention time of principal peak of the substance being examined in the chromatogram obtained in the Assay is identical with that of the principal peak of ambroxol hydrochloride CRS in the chromatogram of the reference solution.

(2) The light absorption of a solution under Assay exhibits a maximum at 244 nm (Appendix IV A).

Related substances Dissolve a quantity of power of the mixed content in the mobile phase to produce a solution of 1 mg of ambroxol hydrochloride per ml as the test solution. Transfer 1 ml of the test solution in a 100 ml volumetric flask, dilute with the mobile phase, mix well as the reference solution. Carry out the chromatogram conditions as described under Assay. Inject 20 μl of reference solution into the column, adjust the sensitivity of the detector so that the principal peak height in the chromatogram is 20%-25% of the full scale of the recorder. Inject accurately 20 μl of test solution and reference solution into the column respectively, and record the chromatogram for twice the retention time of the principal peak. The sum of the areas of all secondary peaks in the chromatogram obtained with the test solution is not greater than the principal peak area in the chromatogram obtained with the reference solution.

Drug release Carry out the method for drug release test (Appendix X D, method 1), with the apparatus of dissolution test (Appendix X C, method 2), using 1000 ml of sodium chloride hydrochloric acid solution (dissolve 2 g of sodium chloride in a quantity of water, add 7 ml of hydrochloric acid, dilute with water to 1000 ml, pH value is 1.2) as the release medium, adjust the rotational speed of the paddle to 50 rpm. Withdraw 10 ml of the solution after exactly 30 minutes and filter. The successive filtrate are used as the test solution (1). Replace the basket into 1000 ml phosphate BS (dissolve 6.805 g potassium dihydrogen phosphate in 22.4 ml of 1 mol/L sodium hydroxide, dilute with water to 1000 ml, pH value 6.8) as the release medium. Withdraw a sample of 5 ml of the solution at exact 2 and 4 hours respectively, filter and supply 5 ml of release medium accordingly in the vessel immediately. Transfer 2 ml of the successive filtrate in a 10 ml volumetric flask and dilute with the sodium chloride hydrochloric acid solution separately, mix well as the test solution (2) and (3). Carry out the method for spectrophotometry (Appendix IV A), measure the absorbance at 244 nm. Dissolve a quantity of ambroxol hydrochloride CRS, accurately weighed, in the sodium chloride hydrochloric acid solution to produce a solution of 25 μg per ml. Measure the absorbance in the same manner. Calculate the content of $C_{13}H_{18}Br_2N_2O \cdot HCl$ released from each capsule at 1, 2 and 4 hours separately. The dissolution of ambroxol hydrochloride complies with the requirement: the quantity released of each capsule is not less than 15%-45%, 45%-80% and over 80% of the labelled amount of $C_{13}H_{18}Br_2N_2O \cdot HCl$ at 1, 2 and 4 hours respectively.

Other requirements Comply with the general requirements for capsules (Appendix I E).

Assay Carry out the method for high performance liquid chromatography (Appendix V D), using a column packed with octadecylsilane bonded silica gel and a mixture of 0.01 mol/L diammonium hydrogen phosphate solution (adjust the pH value to 7.0 with phosphate acid)-acetonitrile (50 : 50) as the mobile phase. Detection wavelength is 248 nm. Dissolve about 5 mg of ambroxol hydrochloride CRS in 0.2

ml of methanol, add 40 μ l of formaldehyde solution (1 \rightarrow 100), mix well, heat at 60°C for 5 minutes, dry it in nitrogen, dissolve the residue in 5 ml of water, dilute with the mobile phase to 20 ml, inject 20 μ l into the column. The resolution factor between the peaks of ambroxol hydrochloride and the secondary B (the relative retention time is 0.8) is more than 4.0.

Procedure Weigh and powder a quantity of the contents obtained in the test of Weigh Variation. Dissolve a quantity of the powder, accurately measured, in mobile phase to produce a solution of 30 μ g of ambroxol hydrochloride per ml, filter. Inject 20 μ l of the successive filtrate into the column and record the peak areas correspondingly obtained in the chromatogram. Dissolve a quantity of ambroxol hydrochloride CRS, accurately weighed, in mobile phase to produce a solution of 30 μ g per ml, inject the reference solution into the column, measure in the same manner. Calculate the content of $C_{13}H_{18}Br_2N_2O \cdot HCl$ with respect to the peak area obtained in the chromatogram by the external standard method.

Category As described under Ambroxol Hydrochloride.

Strength 75 mg

Storage Preserve in tightly closed containers, protected from light.

Ambroxol Hydrochloride Tablets

Ambroxol Hydrochloride Tablets contain not less than 95.0% and not more than 105.0% of ambroxol hydrochloride ($C_{13}H_{18}Br_2N_2O \cdot HCl$).

Description White or almost white tablets.

Identification (1) The retention time of principal peak of the substance being examined in the chromatogram obtained in the Assay is identical with that of the principal peak of ambroxol hydrochloride CRS in the chromatogram of the reference solution.

(2) The light absorption of a solution under Dissolution exhibits two maximum at 244 nm and 308 nm (Appendix IV A).

Related substances Dissolve a quantity of powdered tablets in the mobile phase to produce a solution of 1 mg of ambroxol hydrochloride per ml, filter and using the successive filtrate as the test solution. Transfer 1 ml of the test solution in a 100 ml volumetric flask, dilute with the mobile phase, mix well. Carry out the assay under the following conditions as described under Assay. Inject 20 μ l of reference solution into the column, adjust the sensitivity of the detector so that the principal peak height in the chromatogram is 20%-25% of the full scale of the recorder. Inject accurately 20 μ l of test solution and reference solution into the column respectively, and record the chromatogram for twice the retention time of the principal peak. The sum of the areas of all secondary peaks in the chromatogram obtained with the test solution is not greater than the principal peak area in the chromatogram obtained with the reference solution.

Dissolution Carry out the dissolution test (Appendix X C, method 2), using 900 ml of hydrochloric acid solution (9 \rightarrow 1000) as the dissolution medium, adjust the rotational speed of the paddle to 75 rpm. Withdraw a quantity of the solution after exactly 30 minutes and filter. Dilute 5 ml of the successive filtrate, accurately measured, with the dissolution medium to 10 ml, mix well. Carry out the method for spectrophotometry (Appendix IV A), measure the absorbance at 244 nm. Dissolve a quantity of ambroxol

hydrochloride CRS, accurately weighted, in the dissolution medium to produce a solution of 15 μ g per ml. Measure the absorbance in the same manner. Calculate the dissolution of $C_{13}H_{18}Br_2N_2O \cdot HCl$ from each tablet, not less than 75% of the labelled amount is dissolved.

Other requirements Comply with the general requirements for tablets (Appendix I A).

Assay Carry out the method for high performance liquid chromatography (Appendix V D), using a column packed with octadecylsilane bonded silica gel and a mixture of 0.01 mol/L diammonium hydrogen phosphate solution (adjust the pH value to 7.0 with phosphate acid)-acetonitrile (50 : 50) as the mobile phase. Detection wavelength is 248 nm. Dissolve about 5 mg of ambroxol hydrochloride CRS in 0.2 ml of methanol, add 40 μ l of formaldehyde solution (1 \rightarrow 100), mix well, heat at 60°C for 5 minutes, dry it in nitrogen, dissolve the residue in 5 ml of water, dilute with the mobile phase to 20 ml, inject 20 μ l into the column. The resolution factor between the peaks of ambroxol hydrochloride and the secondary B (the relative retention time is 0.8) is more than 4.0.

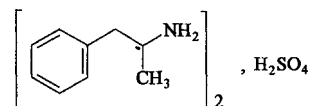
Procedure Weigh accurately and powder 20 tablets. Dissolve a quantity of the powder, accurately measured, in mobile phase to produce a solution of 30 μ g of ambroxol hydrochloride per ml, filter. Inject 20 μ l of the successive filtrate into the column and record the peak areas correspondingly obtained in the chromatogram. Dissolve about a quantity of ambroxol hydrochloride CRS, accurately weighed, in mobile phase to produce a solution of 30 μ g per ml, inject the reference solution into the column, measure in the same manner. Calculate the content of $C_{13}H_{18}Br_2N_2O \cdot HCl$ with respect to the peak area obtained in the chromatogram by the external standard method.

Category As described under Ambroxol Hydrochloride.

Strength 30 mg

Storage Preserve in tightly closed containers, protected from light.

Amphetamine Sulfate



$C_{18}H_{26}N_2 \cdot H_2SO_4$ 368.49

[60-13-9]

Amphetamine sulfate is (\pm)- α -methyl-benzene-ethanamine sulfate. It contains not less than 98.0% and not more than 100.5% of $C_{18}H_{26}N_2 \cdot H_2SO_4$, calculated on the dried basis.

Description A white crystalline powder; odourless; taste, slightly bitter and then numbing. Freely soluble in water; slightly soluble in ethanol; insoluble in ether.

Identification (1) Dissolve about 0.1 g in 5 ml of water, add 5 ml of sodium hydroxide TS, cool to 10-15°C, add 1 ml of a mixture of benzoyl chloride-dehydrated ether (1 : 2), stopper and shake for 3 minutes. Filter, wash the precipitate with 10 ml of cold water, and recrystallize twice with dilute ethanol, the crystals of the benzoyl derivative of amphetamine is produced. Dry at 80°C for 2 hours, it melts at 131-135°C (Appendix VI C).

(2) Dissolve about 5 mg in 4 ml of water, add 1 ml of 1 mol/L hydrochloric acid solution, 2 ml of diazotized *p*-nitroaniline TS, 4 ml of sodium hydroxide solution (1 mol/L) and 2 ml of butanol. Shake and allow to stand until two separate layers are produced, the colour of butanol layer is red.

(3) The aqueous solution yields the reactions characteristic of sulfates (Appendix III).

Acidity or alkalinity Dissolve 0.50 g in 25 ml of water, add 0.1 ml of methyl red IS, not more than 0.1 ml of hydrochloric acid (0.01 mol/L) VS or sodium hydroxide (0.01 mol/L) VS is required to change the colour of solution.

Clarity and colour of solution A Solution of 0.2 g in water is clear and colourless.

Loss on drying When dried to constant weight at 105°C, loses not more than 1.0% of its weight (Appendix VIII L).

Residue on ignition Not more than 0.2% (Appendix VIII N).

Assay Dissolve about 0.3 g, accurately weighed, in 20 ml of water in a separator, add 8 ml of sodium hydroxide TS, saturated with sodium chloride. Extract with 15 ml each of ether for 6 times, combine ether extracts, wash with 10 ml of water and extract the washing with 10 ml of ether. Combine ether extracts, add accurately 25 ml of sulfuric acid (0.05 mol/L) VS, shake thoroughly, expel ether on a water bath at a warm temperature, cool to room temperature. Add 2 drops of methyl red IS, titrate with sodium hydroxide (0.1 mol/L) VS. Each ml of sulfuric acid (0.05 mol/L) VS is equivalent to 18.42 mg of $C_{18}H_{26}N_2 \cdot H_2SO_4$.

Category Psychostimulant

Storage Preserve in tightly closed containers, protected from light.

Preparation (1) Amfetamine Sulfate Injection
(2) Amfetamine Sulfate Tablets

Amfetamine Sulfate Injection

Amfetamine Sulfate Injection is a sterile solution of amfetamine sulfate in water for Injection. It contains not less than 93.0% and not more than 107.0% of the labelled amount of amfetamine sulfate ($C_{18}H_{26}N_2 \cdot H_2SO_4$).

Description A clear, colourless liquid.

Identification Complies with tests (2) and (3) for Identification described under Amfetamine sulfate.

pH value 5.0-6.5 (Appendix VI H).

Other requirements Complies with the general requirements for Injections (Appendix I B).

Assay Measure accurately a quantity of the injection equivalent to about 50 mg of amfetamine sulfate in a separator, add a quantity of water to produce about 20 ml, and 3 ml of sodium hydroxide TS, saturated with sodium chloride. Extract with ether for 6 times, using 30 ml for the first time and then each of 15 ml. Combine the ether extracts, wash with 10 ml of water, extract the washing with 10 ml of ether. Combine ether extracts, add accurately 20 ml of sulfuric acid (0.01 mol/L) VS, shake thoroughly, heat on a warm water bath to remove ether and cool to room temperature. Add 1-2 drops of methyl red IS, titrate with sodium hydroxide (0.02 mol/L) VS. Each ml of sulfuric acid (0.01 mol/L) VS is equivalent to 3.685 mg of

$C_{18}H_{26}N_2 \cdot H_2SO_4$.

Category As described under amfetamine sulfate.

Strength (1) 1 ml : 5 mg (2) 1 ml : 10 mg

Storage Preserve in well closed containers, protected from light.

Amfetamine Sulfate Tablets

Amfetamine Sulfate Tablets contain not less than 90.0% and not more than 110.0% of the labelled amount of amfetamine sulfate ($C_{18}H_{26}N_2 \cdot H_2SO_4$).

Description White tablets; taste, slightly bitter.

Identification To a quantity of powdered tablets, equivalent to about 0.1 g of amfetamine sulfate, add 10 ml of water, macerate for 30 minutes, filter. The filtrate complies with tests for Identification described under Amfetamine Sulfate.

Other requirements Comply with the general requirements for tablets (Appendix I A).

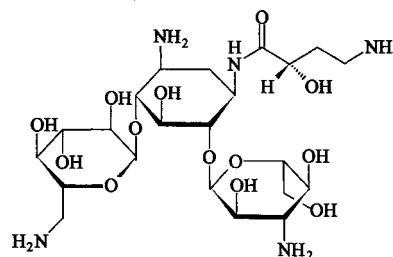
Assay Weigh accurately and powder 15 tablets (for 10 mg) or 25 tablets (for 5 mg). Transfer an accurately weighed quantity of the powder equivalent to about 50 mg of amfetamine sulfate to a conical flask. Add 30 ml of water and 1 ml of dilute sulfuric acid, shake and allow to stand for 2 hours with constantly shaking. Filter wash the residue with water. Combine the filtrate and washings, evaporate to about 20 ml on a water bath, cool to room temperature, add 5 ml of sodium hydroxide TS, saturated with sodium chloride. Extract with ether for 6 times, using 30 ml for the first time and then each of 15 ml. Combine the extracts, wash with 10 ml of water, extract the washing with 10 ml of ether. Combine ether extracts, add accurately 20 ml of sulfuric acid (0.01 mol/L) VS, shake thoroughly, heat on a warm water bath to remove ether, cool to room temperature. Add 1-2 drops of methyl red IS, titrate with sodium hydroxide (0.02 mol/L) VS. Each ml of sulfuric acid (0.01 mol/L) VS is equivalent to 3.685 mg of $C_{18}H_{26}N_2 \cdot H_2SO_4$.

Category As described under Amfetamine sulfate.

Strength (1) 5 mg (2) 10 mg

Storage Preserve in tightly closed containers, protected from light.

Amikacin



$C_{22}H_{43}N_5O_{13}$ 585.61

[37517-28-5]

Amikacin is O-3-amino-3-deoxy-α-D-glucopyranosyl-(1→6)-O-[(6-amino-6-deoxy-α-D-glucopyra-

nosyl-(1 → 4)]-N'-(4-amino-2-hydroxyl-1-oxobutyl)-2-deoxy-D-streptamine. It has a potency of not less than 910 amikacin Units per mg, calculated on the dried basis.

Description A white or almost white powder or crystalline powder; almost odourless; tasteless. Freely soluble in water; practically insoluble in ethanol.

Specific optical rotation +97° to +105°, in a solution of 20 mg per ml in water (Appendix VI E).

Identification (1) Dissolve 10 mg in 1 ml of water, add 4 ml of a 0.1% solution of anthrone in sulfuric acid; a bluish-purple colour is produced.

(2) Dissolve 10 mg in 1 ml of water, add 1 ml of a 4% solution of sodium hydroxide, mix well and add 2 ml of a 5% solution of cobaltous nitrate; a purple flocculent precipitate is produced.

(3) Carry out the method for thin-layer chromatography (Appendix V B) described under Related substances. Apply separately to the plate 2 µl each of the two solutions in water containing (1) 5 mg of the substance being examined per ml and (2) 5 mg of Amikacin RS per ml. The position and colour of the principal spot in the chromatogram obtained with solution (1) correspond to that of the principal spot in the chromatogram obtained with solution (2).

Alkalinity Dissolve 0.1 g in 10 ml of water, pH 9.5-11.5 (Appendix VI H).

Clarity and colour of solution Dissolve 0.6 g each of the 5 portions with sulfuric acid solution (0.5 mol/L) to produce solutions of 0.12 g per ml respectively, the solutions are clear and colourless; any opalescence produced is not more pronounced than that of reference suspension I (Appendix IX B); any colour produced is not more intense than that of reference solution Y₂ or YG₂ (Appendix IX A, method 1).

Related substance Carry out the method for thin-layer chromatography (Appendix V B), using silica gel H as the coating substance, and a mixture of chloroform-methanol-concentrate ammonia solution-water (1 : 4 : 2 : 1) as the mobile phase. Apply separately to the plate 2 µl each of three solutions in water containing (1) 10 mg of the substance being examined per ml, (2) 0.2 mg of the substance being examined per ml, (3) 3 mg of per ml of each of the amikacin RS and impurity A CRS, after developing and removal of the plate, allow it to dry in air and spray with a 0.2% solution of ninhydrin in n-butanol saturated with water and heat at 100°C for 10 minutes. The spot of amikacin and impurity in the chromatogram obtained with solution (3) is separated completely. Any spot other than principal in the chromatogram obtained with solution (1) is not more intense than the principal spot obtained with solution (2).

Loss on drying When dried to constant weight at 120°C, losses not more than 7.0% of its weight (Appendix VIII L).

Residue on ignition Not more than 0.5% (Appendix VIII N).

Bacterial endotoxin Carry out the test for bacterial endotoxin (Appendix XI E); not more than 2.2 EU per 1000 Amikacin Units.

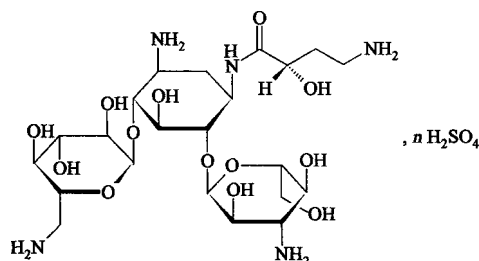
Assay Dissolve an accurately weighed quantity in sterile water to produce a solution of about 1000 Units per ml and carry out the Microbiological Assay of Antibiotics (Appendix XI A). 1000 Amikacin Units are equivalent to 1 mg of C₂₂H₄₃N₅O₁₃.

Category Aminoglycoside antibiotic

Storage Preserve in hermetically sealed containers, stored

in a dry place.

Amikacin Sulfate



C₂₂H₄₃N₅O₁₃ · 1.8 H₂SO₄ 762.15

C₂₂H₄₃N₅O₁₃ · 2 H₂SO₄ 781.76 [39831-28-5]

Amikacin Sulfate is O-3-amino-3-deoxy-α-D-glucopyranosyl-(1 → 6)-O-[6-amino-6-deoxy-α-D-glucopyranosyl-(1 → 4)]-N-(4-amino-2-hydroxy-1-oxobutyl)-2-deoxy-D-streptamine sulfate. It has a potency of not less than 690 Amikacin Units per mg (n=1.8) or not less than 674 Amikacin units per mg (n=2), calculated on the dried basis.

Description A white or almost white powder or crystalline powder; almost odourless; tasteless. Very soluble in water; practically insoluble in methanol, acetone, ether or chloroform.

Specific optical rotation +72° to +85°, in a solution of 20 mg per ml in water (Appendix VI E).

Identification (1) Carry out the method for thin-layer chromatography (Appendix V B), described under Related substances. Apply separately to the plate 2 µl each of two solutions in water containing (1) 5 mg per ml of substance being examined and (2) 5 mg per ml of Amikacin RS. The position and colour of the principal spot in the chromatogram obtained with solution (1) correspond to that of the principal spot in the chromatogram obtained with solution (2).

(2) The infrared absorption spectrum (Appendix IV C) is concordant with the reference spectrum of Amikacin Sulfate RS (Appendix XVI).

(3) The aqueous solution yields the reactions characteristic of sulfates (Appendix III).

Acidity or alkalinity Dissolve a quantity in water to produce a solution of 10 mg per ml, pH 6.0-7.5 (n=1.8) or 2.4-4.0 (n=2) (Appendix VI H).

Clarity and colour of solution To 0.3 g each of 5 portions add water to produce solutions of 0.06 g per ml, the solutions are clear and colourless; any opalescence produced is not more pronounced than that of reference suspension 1 (Appendix IX B); any colour produced is not more intense than that of reference solution Y₂ or YG₂ (Appendix IX A, method 1).

Related substances Carry out the method for thin-layer chromatography (Appendix V B), using silica gel H as the coating substance, and a mixture of chloroform-methanol-concentrate ammonia solution-water (1 : 4 : 2 : 1) as the mobile phase. Apply separately to the plate 2 µl each of three solutions in water containing (1) 10 mg of the substance being examined per ml, (2) 0.2 mg of the substance being examined per ml, (3) 3 mg per ml of each of the amikacin RS and impurity A CRS, after developing

and removal of the plate, allow it to dry in air and spray with a 0.2% solution of ninhydrin in n-butanol saturated with water and heat at 100°C for 10 minutes. The spot of amikacin and impurity in the chromatogram obtained with solution (3) is separated completely. Any spot other than principal in the chromatogram obtained with solution (1) is not more intense than the principal spot obtained with solution (2) (2%).

Sulfate Dissolve 0.25 g, accurately weighed, in 100 ml of water, adjust the pH to 11 with concentrated ammonia solution, add 10 ml of barium chloride (0.1 mol/L) VS and 5 drops of metaphthalein IS. Titrate with disodium edetate (0.05 mol/L) VS, when the colour of the solution begin to change slightly add 50 ml of ethanol and continue titration until the violet colour disappears. Perform a blank determination and make any necessary correction. Each ml of barium chloride (0.1 mol/L) VS is equivalent to 0.009 606 g of sulfate (SO_4). The content of sulfate is not less 21.0% and not more than 24.0% ($n=1.8$), or not less 22.8% and not more than 26.0% ($n=2$) calculated on the dried basis.

Loss on drying When dried over phosphorous pentoxide in vacuum at 110°C for 3 hours, loses not more than 13.0% (Appendix VIII L).

Bacterial endotoxin Carry out the test for bacterial endotoxin (Appendix XI E); not more than 2.2 EU per 1000 Amikacin Units.

Sterility Complies with the test for sterility (Appendix XI H, membrane filtration method), using not less than 2 portions each containing the maximum dose of the preparation being examined, to each portion add not less than 500 ml of 0.9% sterile sodium chloride solution to produce a solution.

Assay Dissolve an accurately weighed quantity in sterile water to produce a solution of 1000 Units per ml and carry out the Microbiological Assay of Antibiotics (Appendix XI A). 1000 Amikacin Units are equivalent to 1 mg of $\text{C}_{22}\text{H}_{43}\text{N}_5\text{O}_{13}$.

Category Aminoglycosides antibiotic.

Storage Preserve in hermetically sealed containers, stored in a dry place.

Preparation (1) Amikacin Sulfate for Injection
(2) Amikacin Sulfate Injection

Amikacin Sulfate for Injection

Amikacin Sulfate for Injection is a powder steril crystalline powder or sterile lyophilized preparation of amikacin sulfate. It contains not less than 93.0% and not more than 107.0% of the labelled potency of amikacin ($\text{C}_{22}\text{H}_{43}\text{N}_5\text{O}_{13}$), calculated on the basis of the average weight of contents.

Description A white or almost white powder or crystalline powder or loose masses.

Identification Complies with the Identification tests described under Amikacin Sulfate.

Clarity and colour of solution To each of 5 containers add 5 ml of water, the solutions are clear and colourless; any opalescence produced is not more pronounced than that of reference suspension 1 (Appendix IX B); any colour produced is not more intense than that of reference solution Y_3 or YG_3 (Appendix IX A, method 1).

Related substances Carry out the method for thin-layer chromatography (Appendix V B), using silica gel H as the coating substance, and a mixture of chloroform-methanol-concentrate ammonia solution-water (1 : 4 : 2 : 1) as the mobile phase. Apply separately to the plate 2 μl each of three solutions in water containing (1) 10 mg of the substance being examined per ml, (2) 0.3 mg of the substance being examined per ml, (3) 3 mg of per ml of each of the amikacin RS and impurity A CRS, after developing and removal of the plate, allow it to dry in air and spray with a 0.2% solution of ninhydrin in n-butanol saturated with water and heat at 100°C for 10 minutes. The spot of amikacin and impurity in the chromatogram obtained with solution (3) is separated completely. Any spot other than principal in the chromatogram obtained with solution (1) is not more intense than the principal spot obtained with solution (2).

Acidity or alkalinity, Loss on drying, Bacterial endotoxin, sterility Complies with the corresponding tests described under Amikacin Sulfate.

Other requirements Complies with the general requirements for injections (Appendix I B).

Assay Carry out the Assay described under Amikacin Sulfate, using an accurately weighed quantity of the mixed contents obtained from the test for Weight variation of contents.

Category As described under Amikacin Sulfate.

Strength 0.2 g (200000 Units)

Storage Preserve in well closed containers, stored in a dry place.

Amikacin Sulfate Injection

Amikacin Sulfate Injection is a sterile aqueous solution of amikacin sulfate. It contains not less than 90.0% and not more than 110.0% of the labelled amount of amikacin ($\text{C}_{22}\text{H}_{43}\text{N}_5\text{O}_{13}$).

Description A clear, colourless to slightly yellow liquid.

Identification (1) Complies with test (1) for Identification described under Amikacin, using a quantity of the substance being examined and Amikacin RS.

(2) The aqueous solution yields the reactions characteristic of sulfates (Appendix III).

pH value 4.0-7.0 (Appendix VI H).

Colour of solution The solution is colourless, any colour produced is not more intense than that of reference solution Y_3 or YG_3 (Appendix IX A, method 1).

Related substances Carry out the method for thin-layer chromatography (Appendix V B), using silica gel H as the coating substance, and a mixture of chloroform-methanol-concentrate ammonia solution-water (1 : 4 : 2 : 1) as the mobile phase. Apply separately to the plate 2 μl each of three solutions in water containing (1) 10 mg of the substance being examined per ml, (2) 0.3 mg of the substance being examined per ml, (3) 3 mg of per ml of each of the amikacin RS and impurity A CRS, after developing and the removal of the plate, allow it to dry in air and spray with a 0.2% solution of ninhydrin in n-butanol saturated with water and heat at 100°C for 10 minutes. The spot of amikacin and impurity in the chromatogram obtained with solution (3) is separated completely. Any spot other than principal in the chromatogram obtained with solution (1) is not more intense than the principal

spot obtained with solution (2).

Bacterial endotoxin Carry out the test for bacterial endotoxin (Appendix XI E); not more than 0.33 EU per 1000 Amikacin Units.

Sterility Complies with the test for Sterility (Appendix IX H, membrane filtration method), using not less than 2 portions. To each portion add not less than 500 ml of 0.9% sterile sodium chloride solution.

Other requirements Complies with the general requirements for injections (Appendix I B).

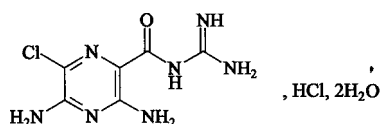
Assay Measure accurately a quantity and carry out the assay described under Amikacin Sulfate.

Category As described under Amikacin Sulfate.

Strength (1) 1 ml : 0.1 g (100000 Units)
(2) 2 ml : 0.2 g (200000 Units)

Storage Preserve in well closed containers, stored in a cool and dark place.

Amiloride Hydrochloride



$C_6H_8ClN_7O \cdot HCl \cdot 2H_2O$ 302.1

Amiloride hydrochloride is *N*-Amidino-3,5-diamino-6-chloropyrazine-2-carboxamide hydrochloride dihydrate. It contains not less than 98.5% of $C_6H_8ClN_7O \cdot HCl$, calculated on the dried basis.

Description A pale yellow or yellowish green powder; odourless or practically odourless; taste, bitter. Slightly soluble in water; very slightly soluble in ethanol; practically insoluble in chloroform or ether.

Identification (1) The light absorption of a solution of about 10 µg per ml in (0.1 mol/L) hydrochloric acid solution exhibits maxima at 285 nm and 362 nm (Appendix IV A).

(2) The infrared absorption spectrum (Appendix IV C) is concordant with the reference spectrum of Amiloride hydrochloride (Appendix XVI).

(3) Dissolve about 20 mg in 20 ml of water, add excessive nitric acid dropwise to precipitate entirely, filter, the filtrate yields reactions characteristic of chlorides (Appendix III).

Acidity Dissolve 0.10 g in 20 ml of water, pH 3.8-5.2 (Appendix VI H).

Related substances Carry out the method for thin-layer chromatography (Appendix V B), using silica gel G as the coating substance and a mixture of dioxane-diluted ammonia solution-water (90 : 6 : 6) as the mobile phase. Apply separately to the plate 10 µl each of the solutions in methanol containing (1) 2 mg per ml of the substance being examined, (2) 10 µg per ml and (3) 4 µg per ml of 3,5-diamino-6-chloropyrazine-2-carboxylic methyl ester CRS. After developing and removal of the plate, dry it in air and examine under ultra-violet light (365 nm). The fluorescence intensity of the spot in the chromatogram obtained with solution (1), corresponding to the spot obtained with solution (2), is not more intense than that of the principal spot obtained with solution (2). Any other secondary spots

in the chromatogram obtained with solution (1) is not more intense than the principal spot obtained with solution (3).

Loss on drying When dried in vacuum to constant weight at 100°C, loses not less than 11.0% and not more than 13.0% of its weight (Appendix VIII C).

Residue on ignition Not more than 0.1% (Appendix VIII N), using 1.0 g.

Heavy metals Carry out the limit test for heavy metals (Appendix VIII H, method 2), using the residue obtained in the test for Residue on ignition: not more than 0.002%.

Assay Dissolve about 0.2 g, accurately weighed, in a mixture of 50 ml of glacial acetic acid, 5 ml of mercuric acetate TS and 8 ml of dioxane, add 1 drop of crystal violet IS, titrate with perchloric acid (0.1 mol/L) VS until the colour changes to blue, perform a blank determination and make any necessary correction. Each ml of perchloric acid (0.1 mol/L) VS is equivalent to 26.61 mg of $C_6H_8ClN_7O \cdot HCl$.

Category Diuretics.

Storage Preserve in tightly closed containers, protected from light.

Preparation (1) Amiloride Hydrochloride Tablets
(2) Compound Amiloride Hydrochloride Tablets

Amiloride Hydrochloride Tablets

Amiloride Hydrochloride Tablets contain not less than 90.0% and not more than 110.0% of the labelled amount of amiloride hydrochloride ($C_6H_8ClN_7O \cdot HCl$).

Description Pale yellow tablets.

Identification (1) Dissolve a quantity of the powdered tablets in hydrochloric acid solution (0.1 mol/L) to produce a solution of 10 µg of amiloride hydrochloride per ml, filter, the light absorption of the filtrate exhibits maxima at 285 nm and 362 nm (Appendix IV A).

(2) Triturate 1 tablets, add 25 ml of methanol, shake thoroughly and filter, using the filtrate as a test solution. Dissolve a quantity of amiloride hydrochloride CRS in methanol to produce a reference solution of 0.2 mg per ml. Carry out the method for thin-layer chromatography (Appendix V B), using silica gel H as the coating substance and a mixture of dioxane-diluted ammonia solution-water (90 : 6 : 6) as the mobile phase. Apply separately to the plate 10 µl each of the resulting two solutions, after developing and removal of the plate, dry it in the air, and examined under ultra-violet light (365 nm). The fluorescence and position of the principal spot in the chromatogram obtained with the test solution corresponding to that of the principal spot obtained with the reference solution.

Content uniformity Transfer 1 powdered tablet to a 50 ml volumetric flask, carry out the method described under Assay and comply with the requirements for content uniformity (Appendix X E).

Dissolution Carry out the dissolution test (Appendix X C, method 2), using 0.1 mol/L hydrochloric acid solution as the dissolution medium, adjust the rotational speed of the paddle to 50 rpm, withdraw 10 ml of the solution after exactly 30 minutes and filter. Measure the absorbance of the filtrate at 362 nm (Appendix IV A). Dissolve an accurately weighed quantity of amiloride hydrochloride CRS in

(0.1 mol/L) hydrochloric acid solution to produce a solution of 2.5 µg per ml, measure the absorbance as the same procedure. Calculate the dissolution of $C_6H_8ClN_7O \cdot HCl$ from each tablet. Not less than 80% of the labelled amount is dissolved.

Other requirements Comply with the general requirements for tablets (Appendix I A).

Assay Weigh accurately and triturate 10 tablets, weigh accurately a quantity, equivalent to about 5 mg of amiloride hydrochloride, to a 100 ml volumetric flask, add 60 ml of 0.1 mol/L hydrochloric acid solution, heat in a water bath for about 30 minutes with shaking to dissolve amiloride hydrochloride, cool, dilute with 0.1 mol/L hydrochloric acid solution to volume, mix well. Transfer immediately a quantity to a centrifuging with stopper and centrifuge. Measure accurately 5 ml of the supernatant liquid into a 25 ml volumetric flask, dilute with 0.1 mol/L hydrochloric acid solution to volume, mix well. Measure the absorbance at 362 nm (Appendix IV A). Dissolve an accurately weighed quantity of amiloride hydrochloride CRS in 0.1 mol/L hydrochloric acid solution to produce a solution of 10 µg per ml, measure the absorbance as the same procedure. Calculate the content of $C_6H_8ClN_7O \cdot HCl$.

Category As described under Amiloride Hydrochloride.

Strength 2.5 mg

Storage Preserve in tightly closed containers, protected from light.

Compound Amiloride Hydrochloride Tablets

Compound Amiloride Hydrochloride Tablets contain not less than 2.25 mg and not more than 2.75 mg of amiloride hydrochloride ($C_6H_8ClN_7O \cdot HCl$) and not less than 22.5 mg and not more than 27.5 mg of hydrochlorothiazide ($C_7H_8ClNO_4S_2$).

Formula	Amiloride hydrochloride	2.5 g
	Hydrochlorothiazide	25 g
	to make	1000 tablets

Description Almost White tablets.

Identification The retention times of the principal peaks of amiloride hydrochloride and hydrochlorothiazide in the substance being examined in the chromatogram obtained in the Assay are identical with those of the principal peaks of amiloride hydrochloride CRS and hydrochlorothiazide CRS in the chromatogram of the reference solution correspondingly.

Content Uniformity Comply with the requirement for content uniformity (Appendix X E). Transfer 1 powdered tablet to a 25 ml volumetric flask, add 7.5 ml of methanol and 1 ml of 0.1 mol/L hydrochloric acid solution, carry out the method described under Assay, beginning at the words "Ultrasonicate to dissolve amiloride hydrochloride...".

Dissolution Carry out the "dissolution" test (Appendix X C, method 1), using 900 ml of 0.1 mol/L hydrochloric acid solution as the dissolution medium, adjust the rotational speed of the paddle to 100 rpm. Withdraw 20 ml of the solution after exactly 30 minutes and filter, carry out the following tests, using the filtrate.

Amiloride hydrochloride Measure the absorbance of the filtrate at 365 nm (Appendix IV A). Dissolve an accurately weighed quantity of amiloride hydrochloride CRS in 0.1 mol/L

hydrochloric acid solution to produce a solution of 2.5 µg per ml, measure the absorbance as the same procedure. Calculate the dissolution of $C_6H_8ClN_7O \cdot HCl$ from each tablet. Not less than 80% of the labelled amount is dissolved.

Hydrochlorothiazide Transfer 5 ml of the filtrate to a 50 ml volumetric flask, dilute with 0.1 mol/L hydrochloric acid solution to volume, mix well. Measure the absorbance at 272 nm (Appendix IV A). Dissolve an accurately weighed quantity of hydrochlorothiazide CRS in 0.1 mol/L hydrochloric acid solution to produce a solution of 2.5 µg per ml, measure the absorbance as the same procedure. Calculate the dissolution of $C_7H_8ClNO_4S_2$ from each tablet. Not less than 80% of the labelled amount is dissolved.

Other requirements Comply with the general requirements for tablets (Appendix I A).

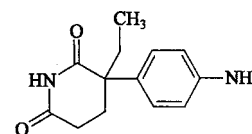
Assay Carry out the method for high performance liquid chromatography (Appendix V D), using a column packed with octadecylsilane bonded silica gel and a mixture of phosphate buffer solution (Dissolve 13.6 g of potassium dihydrogen phosphate in 80 ml of water, adjust the pH value to 3.0 with phosphoric acid, dilute with water to 100 ml)-methanol-water (4 : 25 : 71) as the mobile phase. Detection wavelength is 286 nm and the number of the theoretical plates of the column is not less than 1000, calculated with reference to the peak of amiloride hydrochloride. The resolution factor between amiloride hydrochloride and hydrochlorothiazide complies with the related requirements.

Procedure Weigh accurately and triturate 10 tablets, weigh accurately a quantity equivalent to about 5 mg of amiloride hydrochloride to a 50 ml volumetric flask, add 15 ml of methanol and 2 ml of 0.1 mol/L hydrochloric acid solution. Ultrasonicate to dissolve amiloride hydrochloride and hydrochlorothiazide, dilute with water to volume, mix well, filter. Inject 10 µl of the successive filtrate into the column and record the chromatogram. Dissolve 100 mg of hydrochlorothiazide CRS, accurately weighed, in 20 ml of methanol in a 100 ml volumetric flask, add accurately 10 ml of a solution of 1 mg of amiloride hydrochloride CRS per ml in methanol, add 4 ml of 0.1 mol/L hydrochloric acid solution, dilute with water to volume, inject 10 µl into the column. Calculate the content of $C_6H_8ClN_7O \cdot HCl$ and $C_7H_8ClNO_4S_2$ respectively with respect to the peak area obtained in the chromatogram by the external standard method.

Category Diuretics.

Storage Preserve in tightly closed containers, protected from light.

Aminoglutethimide



$C_{13}H_{16}N_2O_2$ 232.28

Aminoglutethimide is 2-(*p*-aminophenyl)-2-ethylglutarimide. It contains not less than 99.0% of $C_{13}H_{16}N_2O_2$, calculated on the dried basis.

Description A white crystalline powder.

Very soluble in acetone; soluble in methanol and chloro-

form; sparingly soluble in ethanol; practically insoluble in water.

Melting point 150-153°C (Appendix VI C).

Specific absorbance Measure the absorbance of a solution of 10 µg per ml in ethanol at 242 nm (Appendix IV A), the value of A (1%, 1 cm) is 489-519.

Identification (1) To about 10 mg add 3 drops of furfural solution (dissolve 10 drops of furfural in 10 ml of dehydrated ethanol, add 10 ml of glacial acetic acid, shake well), a red colour is produced.

(2) The infrared absorption spectrum (Appendix IV C) is concordant with the reference spectrum of Aminogluthethimide (Appendix XVI).

Acidity or alkalinity Dissolve 10 mg in 0.5 ml of methanol, add 10 ml of water, shake well. pH 6.2-7.3 (Appendix VI H).

Sulfate Dissolve 0.25 g in 1 ml of dilute hydrochloric acid and a quantity of water. Carry out the limit test for sulfate (Appendix VIII B), any opalescence produced is not more pronounced than that of a reference solution using 0.5 ml of potassium sulfate standard solution (0.02%).

Related substances Carry out the method for thin-layer chromatography (Appendix V B), using silica gel GF₂₅₄ as the coating substance and a mixture of chloroform-ethyl acetate (7 : 3) as the mobile phase. Apply separately to the plate 10 µl each of two solutions in chloroform containing (1) 10 mg per ml, (2) 0.2 mg per ml of the substance being examined. After developing and removal of the plate, dry it in air, repeat this operation for 3 times. Examine under ultra-violet light (254 nm). Any spot in the chromatogram other than the principal spot obtained with solution (1) is not more intense than the principal spot obtained with solution (2).

Loss on drying When dried to constant weight at 105°C, loses not more than 0.5% of its weight (Appendix VIII L).

Residue on ignition Not more than 0.1% (Appendix VIII), m.g l. . g.

Heavy metals Carry out the limit test for heavy metals (Appendix VIII H, method 2), using the residue obtained in the test for Residue on ignition; not more than 0.001%.

Assay Dissolve about 0.2 g, accurately weighed, in 30 ml of glacial acetic acid, add 1 drop of crystal violet IS, titrate with perchloric acid (0.1 mol/L) VS until the colour changes to green. Perform a blank determination and make any necessary correction. Each ml of perchloric acid (0.1 mol/L) VS is equivalent to 23.23 mg of C₁₃H₁₆N₂O₂.

Category Adrenocortical suppressant; antineoplastic.

Storage Preserve in tightly closed containers, protected from light.

Preparation Aminogluthethimide Tablets

Aminogluthethimide Tablets

Aminogluthethimide Tablets contain not less than 93.0% and not more than 107.0% of the labelled amount of aminogluthethimide (C₁₃H₁₆N₂O₂).

Description White tablets.

Identification (1) The powder, equivalent to 10mg of aminogluthethimide, complies with the test for Identification (1) described under Aminogluthethimide.

(2) The light absorption of the solution obtained in Assay exhibits a maximum at 242 nm (Appendix IV A).

Dissolution Carry out the dissolution test (Appendix X C, method 1), using 1000 ml of hydrochloric acid solution (7→1000) as the dissolution medium, adjust the rotational speed of the basket to 100 rpm. Withdraw 10 ml of the solution after exactly 30 minutes and filter. Dilute a quantity of the successive filtrate, accurately measured, with phosphate BS (pH 7.4) to produce a solution of 12.5 µg per ml. Dissolve 12.5 mg of aminogluthethimide CRS, in hydrochloric acid solution (7→1000) and dilute to 100 ml, transfer 5 ml to a 50 ml volumetric flask, dilute with phosphate BS (pH 7.4) to volume and mix well. Measure the absorbances of the resulting solutions at 237 nm (Appendix IV A). Calculate the dissolution of C₁₃H₁₆N₂O₂ from each tablet. Not less than 70% of the labelled amount is dissolved.

Other requirements Comply with the general requirements for tablets (Appendix I A).

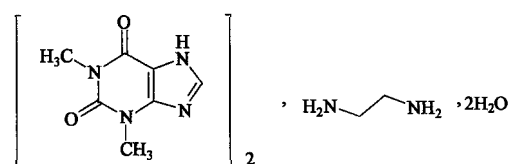
Assay Weigh accurately and powder 10 tablets. Weigh accurately a quantity of the powder equivalent to about 20 mg of aminogluthethimide into a 100 ml volumetric flask, add a quantity of ethanol, warm on a water bath for 10 minutes, cool, add ethanol to volume and mix well. Filter, transfer 5 ml of the successive filtrate, accurately measured, to a 100 ml volumetric flask, add ethanol to volume and mix well. Measure the absorbance of the resulting at 242 nm (Appendix IV A). Calculate the content of C₁₃H₁₆N₂O₂, taking 504 as the value of A (1%, 1 cm).

Category As described under Aminogluthethimide.

Strength (1) 0.125 g (2) 0.25 g

Storage Preserve in tightly closed containers, protected from light.

Aminophylline



C₂H₈N₂ (C₇H₈N₄O₂)₂ · 2H₂O 456.46 [5877-66-5]

Aminophylline is 3,7-dihydro-1,3-dimethyl-1H-Purine-2,6-dione, compound with 1,2-ethanediamine (2 : 1), dihydrate. It contains not less than 84.0% and not more than 87.4% of C₇H₈N₄O₂; not less than 13.5% and not more than 15.0% of C₂H₈N₂, calculated on anhydrous basis.

Description White to slightly yellow granules or a powder; odour, slightly ammoniacal; taste, bitter. Upon exposure to air it absorbs carbon dioxide with the liberation of free theophylline. Its aqueous solution is alkaline. Soluble in water; slightly soluble in ethanol; practically insoluble in ether.

Identification (1) Dissolve about 0.2 g in 10 ml of water, add dropwise, with constant stirring, 1 ml of dilute hydrochloric acid, filter, wash the precipitate with small portions of water and dry at 105°C for 1 hour. Complies with the tests for Identification described under Theophylline. (2) Dissolve 30 mg in 1 ml of water, add 2-3 drops of 1% cupric sulfate solution, shake; a violet colour is produced.

which turns to bluish-violet and finally to dark blue on the addition of cupric sulfate solution dropwise.

Clarity and colour of solution Dissolve 0.5 g in 10 ml of freshly boiled and cooled water by warming the solution is clear and colourless. Any colour produced is not more intense than that reference solution YG₂ (Appendix IX A, method 1).

Related Substances Carry out the method for thin-layer chromatography (Appendix V B), using silica gel GF₂₅₄ as the coating substance and a mixture of *n*-butanol-acetone-chloroform-concentrated ammonia solution (40 : 30 : 30 : 10) as the mobile phase. Dissolve 0.20 g of the substance being examined in 2 ml of water by warming, cool, dilute, with methanol to 10 ml (solution 1), measure accurately 1 ml, dilute with methanol to 200 ml (solution 2). Apply separately to the plate 10 µl each of solution (1) and (2), after developing and removal of the plate, dry it in the air, and examine under ultra-violet light (254 nm). Any spot other than the principal spot in the chromatogram obtained with solution (1) is not more intense than the principal spot obtained with solution (2).

Water Not more than 8.0% (Appendix VIII M, method 1 A).

Residue on ignition Not more than 0.1% (Appendix VIII N).

Assay *Ethylenediamine* Weigh accurately about 0.25 g, dissolve in 25 ml of water, add 8 drops of sodium alizarin-sulfonate IS, titrate with sulfuric acid (0.05 mol/L) VS until the colour changes to yellow. Each ml of sulfuric acid (0.05 mol/L) VS is equivalent to 3.005 mg of C₂H₈N₂.

Anhydrous Theophylline To above titrated solution add 20 ml of silver nitrate (0.1 mol/L) VS, shake, titrate with sodium hydroxide (0.1 mol/L) VS immediately, until the colour changes to red. Each ml of sodium hydroxide (0.1 mol/L) VS is equivalent to 18.02 mg of C₇H₈N₄O₂.

Category Smooth muscle relaxant and diuretic.

Storage Preserve in tightly closed containers, protected from light.

Preparation (1) Aminophylline Injection
(2) Aminophylline Sustained-release Tablets
(3) Aminophylline Tablets

Aminophylline Injection

Aminophylline Injection is a sterile solution of Aminophylline in Water for Injection. It contains anhydrous theophylline (C₇H₈N₄O₂) not less than 74.0% and not more than 84.0% of the labelled amount of aminophylline.

Description A clear colourless to slightly yellow liquid.

Identification Complies with the tests for Identification described under Aminophylline.

pH value Not more than 9.6 (Appendix VI H).

Colour of solution Dilute a quantity of the injection with water to produce a solution containing 12.5% of aminophylline, any colour produced is not more intense than that of reference solution Y₄ or YG₄ (Appendix IX A, method 1).

Other requirements Complies with the general requirements for Injections (Appendix I B).

Assay Dilute an accurately measured quantity of the injection, 0.01 mol/L with sodium hydroxide solution to

produce a solution of about 10 µg per ml. Measure the absorbance at 275 nm (Appendix IV A). Calculate the content of C₇H₈N₄O₂, taking 650 as the value of A (1%, 1 cm).

Category As described under Aminophylline.

Strength (1) 2 ml : 0.125 g (2) 2 ml : 0.25 g
(3) 2 ml : 0.5 g (4) 10 ml : 0.25 g

Storage Preserve in well closed containers, protected from light.

Aminophylline Sustained-release Tablets

Aminophylline Sustained-release Tablets contain aminophylline consisting of not less than 74.0% and not more than 84.0% of the labelled amount of anhydrous theophylline (C₇H₈N₄O₂) and ethylenediamine (C₂H₈N₂) contains not less than 11.25% of the labelled amount of aminophylline.

Description Film coated tablets with white to slightly yellow core.

Identification Triturate a quantity of the powdered tablets equivalent to about 0.5 g of aminophylline with 25 ml of water, filter. The filtrate exhibits alkaline reaction and complies with the tests for Identification described under Aminophylline.

Drug release Carry out the drug release test (Appendix X D, method 1), using the apparatus described under dissolution test method 1 and using 1000 ml of dilute hydrochloric acid (24 → 1000) as the dissolution medium, adjust the rotational speed of the basket to 50 rpm. Withdraw each 10 ml of the solution after exactly 2, 4 and 6 hours, respectively, add 10 ml of the same dissolution medium to the vessel to compensate the volume. Filter, to each 5 ml of the successive filtrate, accurately measured, add 4.5 ml of 0.1 mol/L sodium hydroxide solution, dilute with 0.01 mol/L sodium hydroxide solution to produce 25 ml or 50 ml and mix well. Measure the absorbance of the resulting solutions at 275 nm (Appendix IV A), calculate the drug release from each tablet at different time interval, taking 650 as the value of A (1%, 1 cm). The amount of aminophylline released in 2, 4 and 6 hours is 25%-45%, 35%-55% and not less than 50% of the labelled amount, respectively.

Other requirements Comply with the general requirements for tablets (Appendix I A).

Assay *Anhydrous Theophylline* Weigh accurately and powder 20 tablets. Transfer an accurately weighed quantity of the powdered tablets, equivalent to about 100 mg of aminophylline, to a 200 ml volumetric flask. Add 20 ml of sodium hydroxide solution (0.1 mol/L) and 60 ml of water, shake well for 10 minutes, dilute with water to volume and mix well. Filter. Transfer 5 ml of the successive filtrate, accurately measured, to a 250 ml volumetric flask, dilute with sodium hydroxide solution (0.01 mol/L) to volume and mix well. Measure the absorbance of the resulting solution at 275 nm (Appendix IV A). Calculate the content of C₇H₈N₄O₂, taking 650 as the value of A (1%, 1 cm).

Ethylenediamine Transfer an accurately weighed quantity of the powdered tablets, equivalent to about 0.8 g of aminophylline, to a 100 ml volumetric flask, shake with a quantity of water and warm, allow to cool, dilute with

water to volume and mix well. Filter, to 50 ml of the successive filtrate, accurately measured, add 8 drops of sodium alizarinsulfonate IS, titrate with hydrochloric acid (0.1 mol/L) VS until the colour changes to yellow. Each ml of hydrochloric acid (0.1 mol/L) VS is equivalent to 3.005 mg of $C_2H_8N_2$.

Category As described under Aminophylline.

Strength (1) 0.1 g (2) 0.2 g

Storage Preserve in tightly closed containers, protected from light.

Aminophylline Tablets

Aminophylline Tablets contain anhydrous theophylline ($C_7H_8N_4O_2$) not less than 74.0% and not more than 84.0% of the labelled amount of aminophylline; contains ethylenediamine ($C_2H_8N_2$) not less than 11.25% of the labelled amount of aminophylline.

Description White to slightly yellow tablets.

Identification Triturate a quantity of powdered tablets equivalent to 0.5 g of aminophylline with 20 ml of water, filter; the filtrate is alkaline. The filtrate complies with the tests for Identification described under Aminophylline.

Dissolution Carry out the dissolution test (Appendix X C, method 1), using 800 ml of water as the dissolution medium, adjust the rotational speed of the basket to 100 rpm. Withdraw 10 ml of the solution after exactly 10 minutes and filter. Dilute an accurately measured quantity of the successive filtrate with 0.01 mol/L sodium hydroxide solution to produce a solution of 10 µg per ml. Measure the absorbance at 275 nm (Appendix IV A). Calculate the dissolution of $C_7H_8N_4O_2$ from each tablet, taking 650 as the value of A (1%, 1 cm). Not less than 60% of the labelled amount is dissolved.

Other requirements Comply with the general requirements for tablets (Appendix I A).

Assay Anhydrous Theophylline Weigh accurately and powder 20 tablets. To a quantity of the powder equivalent to 100 mg of aminophylline, accurately weighed, in a 200 ml volumetric flask add 20 ml of 0.1 mol/L sodium hydroxide solution and 60 ml of water, shake for 10 minutes, dilute with water to volume and mix well. Filter, discard the initial filtrate. Measure accurately 5 ml of the successive filtrate into a 250 ml volumetric flask, dilute with 0.01 mol/L sodium hydroxide solution to volume and mix well. Measure the absorbance at 275 nm (Appendix IV A). Calculate the content of $C_7H_8N_4O_2$, taking 650 as the value of A (1%, 1 cm).

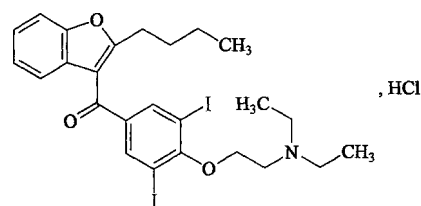
Ethylenediamine To a quantity of the powdered tablets equivalent to 0.5 g of aminophylline, accurately weighed, add 50 ml of water and warm to dissolve. Allow to cool, add 8 drops of sodium alizarinsulfonate IS, titrate with hydrochloric acid (0.1 mol/L) VS until the colour changes to yellow. Each ml of hydrochloric acid (0.1 mol/L) VS is equivalent to 3.005 mg of $C_2H_8N_2$.

Category As described under Aminophylline.

Strength (1) 20 mg (2) 30 mg (3) 0.1 g (4) 0.2 g

Storage Preserve in tightly closed containers, protected from light.

Amiodarone Hydrochloride



$C_{25}H_{29}I_2NO_3 \cdot HCl$ 681.78

Amiodarone Hydrochloride is 2-butyl-3-[3,5-diiodo-4-(2-diethylaminoethoxy)benzoyl]benzofuran hydrochloride. It contains not less than 98.5% of $C_{25}H_{29}I_2NO_3 \cdot HCl$ calculated on the dried basis.

Description A white to slightly yellow crystalline powder; odourless; tasteless.

Freely soluble in chloroform; soluble in ethanol; slightly soluble in acetone; practically insoluble in water.

Melting range 158-162°C, with decomposition (Appendix V C).

Identification (1) Dissolve 20 mg in 2 ml of ethanol, add 2 ml of a solution of 2,4-dinitrophenylhydrazine in perchloric acid (dissolve 1.2 g of 2,4-dinitrophenylhydrazine in 50 ml of 30% perchloric acid) and 5 ml of water; a yellow precipitate is formed.

(2) Heat gently 50 mg with 1 ml of sulfuric acid; violet iodine vapor is evolved.

(3) The light absorption of a solution of 10 µg per ml in ethanol exhibits a maximum at 242 nm and a minimum at 223 nm (Appendix IV A). The ratio of the absorbance at 242 nm to that at 223 nm is 1.47-1.61.

(4) The infrared absorption spectrum (Appendix IV C) is concordant with the reference spectrum of amiodarone hydrochloride (Appendix XVI).

(5) The ethanolic solution yields the reactions characteristic of chlorides (Appendix III).

Clarity and colour of methanol solution A solution of 1.0 g in 20 ml of methanol is clear and colourless. Any colour produced is not more intense than that of reference solution Y₃ (Appendix IX A, method 1).

Acidity Dissolve 0.50 g in 10 ml of water by warming, cool to room temperature, pH 3.4-3.9 (Appendix VI H).

Free iodine Shake 0.50 g with 10 ml of water for 30 seconds, allow to stand for 5 minutes and filter. To the filtrate, add 1 ml of dilute sulfuric acid and 2 ml of chloroform, shake well; the chloroform layer exhibits no colour.

Related substances Carry out the method for thin-layer chromatography (Appendix V B), using silica gel HF₂₅₄ as the coating substance and a mixture of chloroform-methanol-anhydrous formic acid (80 : 15 : 5) as the mobile phase. Apply separately to the plate 10 µl each of two solutions of the substance being examined in methanol containing (1) 20 mg per ml, (2) 0.10 mg per ml. After developing and removal of the plate, dry it in air and examine under ultra-violet light (254 nm). Any spot other than the principal spot in the chromatogram obtained with solution (1) is not more intense than the principal spot obtained with solution (2).

Iodine Weigh accurately about 20 mg, carry out the method for oxygen flask combustion (Appendix VII C), using 2 ml of sodium hydroxide TS and 10 ml of water as the

absorbing liquid. When the process is complete, add 10 ml of bromine-acetic acid solution (dissolve 10 g of potassium acetate in a quantity of glacial acetic acid, add 0.4 ml of bromine and dilute with glacial acetic acid to 100 ml). Stopper the flask, shake, allow the solution to stand for several minutes and add about 1 ml of formic acid. Wash the mouth of the flask with water and introduce an air stream into the flask for 3-5 minutes to expel the excess of bromine vapour. Then add 2 g of potassium iodide, stopper the flask, mix well and titrate with sodium thiosulfate (0.02 mol/L) VS. Add 1 ml of starch IS towards the end of titration and continue the titration until the blue colour just disappears. Perform a blank determination and make any necessary correction. Each ml of sodium thiosulfate (0.02 mol/L) VS is equivalent to 0.423 mg of iodine (I), not less than 36.0% and not more than 38.0% of iodine.

Loss on drying When dried in vacuum at 50°C for 4 hours, loses not more than 0.5% of its weight (Appendix VIII L).

Residue on ignition Not more than 0.1% (Appendix VIII N), using 1.0 g.

Heavy metals Carry out the limit test for heavy metals (Appendix VIII H, method 2), using the residue obtained in the test for Residue on ignition; not more than 0.001%.

Assay Dissolve about 0.50 g, accurately weighed, in 20 ml of glacial acetic acid by warming, add 6 ml of mercuric acetate TS and 1 drop of crystal violet IS, titrate with perchloric acid (0.1 mol/L) VS until a blue colour is produced. Perform a blank determination and make any necessary correction. Each ml of perchloric acid (0.1 mol/L) VS is equivalent to 68.18 mg of $C_{25}H_{29}I_2NO_3 \cdot HCl$.

Category Antiarrhythmic agent.

Storage Preserve in tightly closed containers, protected from light.

Preparation (1) Amiodarone Hydrochloride Capsules
(2) Amiodarone Hydrochloride Injection
(3) Amiodarone Hydrochloride Tablets

Amiodarone Hydrochloride Capsules

Amiodarone Hydrochloride Capsules contain not less than 90.0% and not more than 110.0% of the labelled amount of amiodarone hydrochloride ($C_{25}H_{29}I_2NO_3 \cdot HCl$).

Identification (1) Dissolve a quantity of the contents of the capsules equivalent to about 20 mg of amiodarone hydrochloride in 2 ml of ethanol, add 2 ml of a solution of 2,4-dinitrophenylhydrazine in perchloric acid (dissolve 1.2 g of 2,4-dinitrophenylhydrazine in 50 ml of 30% perchloric acid) and 5 ml of water; a yellow precipitate is formed.

(2) To a quantity of the contents of the capsules equivalent to about 50 mg of amiodarone hydrochloride add 1 ml of sulfuric acid and heat gently, the violet iodine vapour is evolved.

(3) Dissolve a quantity of the contents of the capsules in ethanol to produce a solution of 10 µg per ml, filter. The light absorption of the filtrate exhibits a maximum at 242 nm and a minimum at 223 nm (Appendix IV A).

(4) Shake a quantity of the contents of the capsules equivalent to about 50 mg of amiodarone hydrochloride with 5 ml of ethanol, filter. The filtrate yields the reactions characteristic of chlorides (Appendix III).

Related substances Dissolve a quantity of the contents of the capsules in methanol to produce a solution containing 20 mg per ml of amiodarone hydrochloride as the test solution

(filter if necessary). Dilute an accurately measured quantity of the test solution with methanol to produce a solution of 0.20 mg per ml as the reference solution. Proceed as described under Amiodarone Hydrochloride beginning at the words "carry out the method for thin-layer chromatography (Appendix V B)...". It complies with the requirements.

Loss on drying When dried in vacuum at 50°C for 4 hours, loses not more than 1.0% of its weight (Appendix VIII L).

Other requirements Comply with the general requirements for capsules (Appendix I E).

Assay Weigh accurately a quantity of the mixed contents obtained in the test for weight variation of contents, equivalent to about 0.1 g of amiodarone hydrochloride in a conical flask with stopper, add 20 ml of water, 50 ml of chloroform and 5 ml of dilute sulfuric acid. Then add 1 ml of dimethyl yellow solvent blue 19 IS and titrate with sodium dioctylsulfo-succinate TS, shake vigorously towards the end of titration and continue titration until the chloroform layer changes from green to reddish-grey. Perform a reference titration using 0.1 g of amiodarone hydrochloride CRS. Calculate the content of $C_{25}H_{29}I_2NO_3 \cdot HCl$ from the volume ratio of sodium dioctylsulfo succinate TS consumed in the two titrations.

Category As described under Amiodarone Hydrochloride.

Strength (1) 0.1 g (2) 0.2 g

Storage Preserve in tightly closed containers, protected from light.

Amiodarone Hydrochloride Injection

Amiodarone Hydrochloride Injection is a sterile solution of Amiodarone Hydrochloride in Water for Injection. It contains not less than 90.0% and not more than 110.0% of the labelled amount of amiodarone hydrochloride ($C_{25}H_{29}I_2NO_3 \cdot HCl$).

Description A clear, pale yellow liquid.

Identification To a quantity equivalent to about 0.2 g of amiodarone hydrochloride add 10 ml of chloroform, shake and filter the chloroform layer. Evaporate the filtrate to dryness, the residue complies with the test (1), (2), (3) and (5) for Identification described under Amiodarone Hydrochloride.

pH value 2.5-4.0 (Appendix VI H).

Related substances Carry out the method for thin-layer chromatography (Appendix V B), using silica gel HF₂₅₄ as the coating substance and a mixture of chloroform-methanol-anhydrous formic acid (85 : 15 : 5) as the mobile phase. Apply separately to the plate 10 µl each of two solutions of the substance being examined in methanol containing (1) 20 mg per ml, (2) 0.20 mg per ml. After developing and removal of the plate, dry it in air and examine under ultraviolet light (254 nm). Any spot other than the principal spot in the chromatogram obtained with solution (1) is not more intense than the principal spot obtained with solution (2).

Other requirements Complies with the general requirements for injections (Appendix I B).

Assay Transfer an accurately measured quantity equivalent to about 0.15 g of amiodarone hydrochloride to a conical flask with stopper, add 20 ml of water, 50 ml of chloroform and 5 ml of dilute sulfuric acid. Then add 1 ml of dimethyl yellow solvent blue 19 IS and titrate with sodium

dioctylsulfo-succinate TS, Shake vigorously towards the end of titration and continue titration until the chloroform layer changes from green to reddish-grey. Perform a reference titration using 0.15 g of amiodarone hydrochloride CRS. Calculate the content of $C_{25}H_{29}I_2NO_3 \cdot HCl$ from the volume ratio of sodium dioctylsulfo succinate TS consumed in the two titrations.

Category As described under Amiodarone Hydrochloride.

Strength (1) 2 ml : 150 mg (2) 3 ml : 150 mg

Storage Preserve in well closed containers, protected from light.

Amiodarone Hydrochloride Tablets

Amiodarone Hydrochloride Tablets contain not less than 95.0% and not more than 105.0% of amiodarone hydrochloride ($C_{25}H_{29}I_2NO_3 \cdot HCl$).

Description Almost white tablets.

Identification Triturate 1 tablet and shake with 10 ml of chloroform, filter and evaporate the filtrate to dryness. The residue complies with tests (1), (2), (3) and (5) for Identification described under Amiodarone Hydrochloride.

Related substances Dissolve a quantity of powdered tablets in methanol to produce two solution of the substance being examined, containing (1) 20 mg per ml (2) 0.20 mg per ml. Proceed as described under Amiodarone Hydrochloride beginning at the words "carry out the method for thin-layer chromatography (Appendix V B)...". It complies with the requirements.

Other requirements Comply with the general requirements for tablets (Appendix I A).

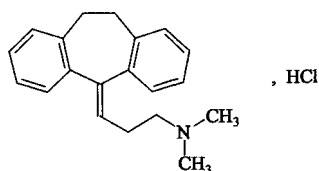
Assay Weigh accurately and powder 10 tablets. To a quantity of the powdered tablets, equivalent to 0.1 g of amiodarone hydrochloride, accurately weighed, in a glass stoppered flask, add 20 ml of water, 50 ml of chloroform and 5 ml of dilute sulfuric acid. Then add 1 ml of dimethyl yellow solvent blue 19 IS and titrate with sodium dioctylsulfo-succinate TS, Shake vigorously towards the end of titration and continue titration until the chloroform layer changes from green to reddish-grey. Perform a reference titration using 0.1 g of amiodarone hydrochloride CRS. Calculate the content of $C_{25}H_{29}I_2NO_3 \cdot HCl$ from the volume ratio of sodium dioctylsulfo succinate TS consumed in the two titrations.

Category As described under Amiodarone Hydrochloride.

Strength (1) 0.1 g (2) 0.2 g

Storage Preserve in tightly closed containers, protected from light.

Amitriptyline Hydrochloride



$C_{20}H_{23}N \cdot HCl$ 313.87

[549-18-8]

Amitriptyline Hydrochloride is 3-(10,11-dihydro-5H-dibenzo [*a,d*] cyclohepten-5-ylidene)-N,N-dimethyl-1-propanamine hydrochloride. It contains not less than 99.0% of $C_{20}H_{23}N \cdot HCl$, calculated on the dried basis.

Description Colourless crystals or a white to almost white powder; odourless or almost odourless; taste, bitter, hot and numbing. Freely soluble in water, methanol, ethanol or chloroform; practically insoluble in ether.

Melting range 195-199°C (Appendix VI C).

Identification (1) Dissolve 5 mg in 2 ml of sulfuric acid; a red colour is produced.

(2) The light absorption of a solution of 12 µg per ml in hydrochloric acid solution (9→1000) exhibits maximum at 239 nm, the absorbance is about 0.51-0.56 (Appendix IV A).

(3) The infrared absorption spectrum (Appendix IV C) is concordant with the reference spectrum of amitriptyline hydrochloride (Appendix XVI).

(4) The aqueous solution yields the reactions characteristic of chlorides (Appendix III).

Acidity Dissolve 0.10 g in 10 ml of water, pH 4.5-6.0 (Appendix VI H).

Clarity and colour of solution A solution of 0.20 g in 10 ml of water is clear and colourless. Any colour produced is not more intense than reference solution Y_2 or OY_2 (Appendix IX A, method 1).

Related substances Carry out the method for thin-layer chromatography (Appendix V B), using silica gel G as the coating substance and a mixture of chloroform-toluene (1 : 1) as the mobile phase. Apply to the plate 5 µl of a solution of 10 mg per ml in ethanol. After developing and removal the plate, dry it in the air and spray with formaldehyde-sulfuric acid (4 : 96). Examine immediately under an ultra-violet light (365 nm). No spot other than the principal spot is appeared in the chromatogram.

Loss on drying When dried in vacuum over phosphorus pentoxide at 60°C to constant weight, loses not more than 0.5% of its weight (Appendix VIII L).

Residue on ignition Not more than 0.1%; use 1.0 g (Appendix VIII N).

Heavy metals Carry out the limit test for heavy metals (Appendix VIII H, method 2), using the residue obtained in the test for Residue on ignition; not more than 0.0015%.

Assay Dissolve 0.3 g, accurately weighed, in 20 ml of glacial acetic acid by warming. Allow to cool, add 5 ml of mercuric acetate TS and 1 ml of crystal violet IS, titrate with perchloric acid (0.1 mol/L) VS until the colour changes to bright blue. Perform a blank determination and make any necessary correction. Each ml of perchloric acid (0.1 mol/L) VS is equivalent to 31.39 mg of $C_{20}H_{23}N \cdot HCl$.

Category Antidepressant

Storage Preserve in tightly closed containers, protected from light.

Preparation Amitriptyline Hydrochloride Tablets

Amitriptyline Hydrochloride Tablets

Amitriptyline Hydrochloride Tablets contain not less than 90.0% and not more than 110.0% of the

labelled amount of amitriptyline hydrochloride ($C_{20}H_{23}N \cdot HCl$).

Description Sugar coated tablets with white core.

Identification (1) The light absorption of the solution obtained in the Assay exhibits a maximum at 239 nm (Appendix IV A).

(2) Triturate 1 tablet with 4 ml of water, filter, to the filtrate add 2 drops of dilute nitric acid and 2 drops of silver nitrate TS; a white precipitate is formed.

Dissolution Carry out the dissolution test (Appendix X C, method 1), using 900 ml of hydrochloric acid solution (9→1000) as the dissolution medium, adjust the rotational speed of the basket to 100 rpm. Withdraw 10 ml of solution after exactly 45 minutes and filter. Dilute 5 ml of the successive filtrate, accurately measured, with the above dissolution medium to volume in a 10 ml volumetric flask, mix well. Proceed as described under assay beginning at the word "Measure the absorbance...". Calculate the dissolution from each tablet, not less than 75% of the labelled amount is dissolved.

Other requirements Comply with the general requirements for tablets (Appendix I A).

Assay Weigh accurately 20 tablets with the coating removed to a 200 ml volumetric flask. Add 100 ml of hydrochloric acid solution (9→1000), shake for 30 minutes to dissolve amitriptyline hydrochloride, dilute with hydrochloric acid solution (9→1000) to volume and mix well. Filter and dilute 5 ml of the successive filtrate, accurately measured, with hydrochloric acid solution (9→1000) to volume in a 100 ml volumetric flask and mix well. Transfer 10 ml of above solution into a 100 ml volumetric flask, accurately measured, dilute with the solution to volume and mix well. Measure the absorbance at 239 nm (Appendix IV A). Calculate the content of $C_{20}H_{23}N \cdot HCl$, taking 444 as the value of A (1%, 1 cm).

Category, Storage As described under Amitriptyline Hydrochloride.

Strength 25 mg

Dilute Ammonia Solution

Dilute Ammonia Solution contains 9.5%-10.5% (g/ml) of ammonia (NH_3).

Formula	Strong Ammonia Solution	420 ml
	Water	a quantity
	Total	1000 ml

Description A clear, colourless liquid; odour, pungent and characteristic; alkaline.

Relative density 0.955-0.962 (Appendix VI A).

Identification Dip a glass rod into hydrochloric acid and hold it above the surface of the substance being examined, dense white fumes are produced.

Assay To 5 ml, accurately measured, in a stoppered conical flask containing 25 ml of water add 2 drops of methyl red IS and titrate with sulfuric acid (0.5 mol/L) VS. Each ml of sulfuric acid (0.5 mol/L) VS is equivalent to 17.03 mg of NH_3 .

Category Stimulant.

Storage Preserve in tightly closed containers, stored at a temperature below 30°C.

Ammonium Chloride

NH_4Cl 53.49

[12125-02-9]

Ammonium Chloride contains not less 99.5% of NH_4Cl , calculated on the dried basis.

Description Colourless crystals or a white crystalline powder; odourless; taste, salty and chilly; hygroscopic. Freely soluble in water; slightly soluble in ethanol.

Identification The aqueous solution yields the reactions characteristic of ammonium salts (Appendix III) and chlorides (Appendix III).

Acidity Dissolve 2.0 g in 10 ml of water, pH 4.0-6.0 (Appendix IV H).

Barium Dissolve 4.0 g in 20 ml of water, filter. Divide the filtrate into 2 equal parts. To one part add 2 ml of dilute sulfuric acid and to the other part add 2 ml of water, allow to stand for 15 minutes. The solutions are equal in clarity.

Loss on drying When dried over sulfuric acid to constant weight, loses not more than 0.5% of its weight (Appendix VIII L).

Residue on ignition Not more than 0.1% (Appendix VIII N).

Iron Heat 1.0 g with a small flame until ammonium chloride is completely evaporated, cool, add 25 ml of water to the residue. Carry out the limit test for iron (Appendix VIII G). Any colour produced is not more intense than that of a reference, using 5.0 ml of iron standard solution (0.005%).

Heavy metals Dissolve 2.0 g in 2 ml of acetate BS (pH 3.5) and a quantity of water to produce 25 ml. Carry out the limit test for heavy metals (Appendix VIII H, method 1): not more than 0.001%.

Arsenic Dissolve 0.40 g in 23 ml of water, add 5 ml of hydrochloric acid. Carry out the limit test for arsenic (Appendix VIII J, method 1): not more than (0.0005%).

Assay Dissolve about 0.12 g, accurately weighed, in 50 ml of water, add 5 ml of dextran solution (1→50), 8 drops of fluorescein IS and 0.10 g of calcium carbonate, shake well. Titrate the solution with silver nitrate (0.1 mol/L) VS. Each ml of silver nitrate (0.1 mol/L) VS is equivalent to 5.349 mg of NH_4Cl .

Category Expectorant and auxiliary diuretics.

Storage Preserve in tightly closed containers, stored in a dry place.

Preparation Ammonium Chloride Tablets

Ammonium Chloride Tablets

Ammonium Chloride Tablets contain not less than 95.0% and not more than 105.0% of the labelled amount of ammonium chloride (NH_4Cl).

Description White tablets.

Identification Its aqueous solution yields the reactions characteristic of ammonium salts and chlorides (Appendix III).

Other requirements Comply with the general requirements for tablets (Appendix I A).

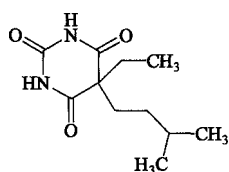
Assay Weigh accurately and powder 10 tablets. Weigh accurately a quantity of the powder equivalent to about 0.12 g of ammonium chloride and carry out the Assay described under Ammonium Chloride. Each ml of silver nitrate (0.1 mol/L) VS is equivalent to 5.349 mg of NH_4Cl .

Category As described under Ammonium Chloride.

Strength 0.3 g

Storage Preserve in tightly closed containers, stored in a dry place.

Amobarbital



$\text{C}_{11}\text{H}_{18}\text{N}_2\text{O}_3$ 226.28

[57-43-2]

Amobarbital is 5-ethyl-5-(3-methylbutyl)-2,4,6-(1*H*,3*H*,5*H*)-pyrimidinetrione. It contains not less than 98.5% of $\text{C}_{11}\text{H}_{18}\text{N}_2\text{O}_3$, calculated on the dried basis.

Description A white crystalline powder; odourless; taste, bitter.

Freely soluble in ethanol or ether; soluble in chloroform; very slightly soluble in water; soluble in aqueous solution of sodium hydroxide or sodium carbonate.

Melting point 155-158.5°C (Appendix VI C).

Identification (1) Yields the reactions characteristic of malonylureas (Appendix III).

(2) The infrared absorption spectrum (Appendix IV C) is concordant with the reference spectrum of amobarbital (Appendix XVI).

Clarity of solution Dissolve 1.0 g in 10 ml of sodium hydroxide solution TS, the solution is clear.

Chlorides Boil 0.30 g with 30 ml of water for 2 minutes, cool, filter, add water through the filter to produce 50 ml. Carry out the limit test for chlorides (Appendix VIII A), using 25 ml of this filtrate, any opalescence produced is not more pronounced than that of a reference using 7.0 ml of sodium chloride standard solution (0.047%).

Loss on drying When dried to constant weight at 105°C, loses not more than 1.0% of its weight (Appendix VIII L).

Residue on ignition Not more than 0.1% (Appendix VIII N).

Assay Weigh accurately about 0.2 g and dissolve in 40 ml of methanol, add 15 ml of freshly prepared 3% anhydrous sodium carbonate solution. Carry out the method for potentiometric titration (Appendix VII A), titrate with silver nitrate (0.1 mol/L) VS. Each ml of silver nitrate (0.1 mol/L) VS is equivalent to 22.63 mg of $\text{C}_{11}\text{H}_{18}\text{N}_2\text{O}_3$.

Category Hypnotic and anticonvulsant agent.

Storage Preserve in tightly closed containers.

Preparation Amobarbital Tablets

Amobarbital Tablets

Amobarbital Tablets contain not less than 94.0% and not more than 106.0% of the labelled amount of amobarbital ($\text{C}_{11}\text{H}_{18}\text{N}_2\text{O}_3$).

Description White tablets.

Identification Dissolve a quantity of the powdered tablets equivalent to about 0.5 g of amobarbital in 10 ml of sodium carbonate TS with gentle heating, filter. Add hydrochloric acid dropwise to the filtrate, until no more precipitate is formed, filter. The residue, washed with water and dried at 105°C, has a melting point of 155-158.5°C (Appendix VI C) and yields the reactions characteristic of malonylureas (Appendix III).

Dissolution Carry out the dissolution test (Appendix X C, method 1), using 500 ml of phosphate BS (pH 7.6) as the dissolution medium, adjust the rotational speed of the basket to 100 rpm. Withdraw 10 ml of the solution after exactly 30 minutes and filter. Measure accurately 5 ml of the successive filtrate to a 25 ml volumetric flask, dilute with phosphate BS to volume and mix well. Dissolve a quantity of amobarbital CRS, accurately weighed, in phosphate BS to produce a solution of 35 µg per ml. Measure the absorbance of the resulting solution at 239 nm (Appendix IV A). Calculate the dissolution of $\text{C}_{11}\text{H}_{18}\text{N}_2\text{O}_3$ from each tablet, not less than 70% of the labelled amount is dissolved.

Other requirements Comply with the general requirements for tablets (Appendix I A).

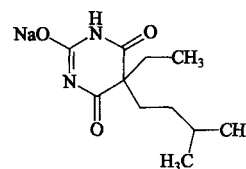
Assay Weigh accurately and powder 20 tablets. Add 40 ml of methanol to a quantity of the powder equivalent to about 0.2 g, accurately weighed, of amobarbital and shake to dissolve the amobarbital. Carry out the Assay described under Amobarbital beginning at the words "add 15 ml of freshly prepared 3% anhydrous sodium carbonate solution...". Each ml of silver nitrate (0.1 mol/L) VS is equivalent to 22.63 mg of $\text{C}_{11}\text{H}_{18}\text{N}_2\text{O}_3$.

Category As described under Amobarbital.

Strength 0.1 g

Storage Preserve in tightly closed containers.

Amobarbital Sodium



$\text{C}_{11}\text{H}_{17}\text{N}_2\text{NaO}_3$ 248.26

[64-43-7]

Amobarbital Sodium is 5-ethyl-5-(3-methylbutyl)-2,4,6-(1*H*,3*H*,5*H*)-pyrimidinetrione monosodium salt. It contains not less than 98.5% of $\text{C}_{11}\text{H}_{17}\text{N}_2\text{NaO}_3$, calculated on the dried basis.

Description White granules or a white powder; odourless; taste, bitter; hygroscopic. The aqueous solution yields alkaline reaction.

Very soluble in water; soluble in ethanol; practically insoluble in chloroform or ether.

Identification (1) Dissolve about 0.5 g in 10 ml of water, add 0.5 ml of hydrochloric acid, a white precipitate of amobarbital is produced. Filter, the residue, washed with water and dried at 105°C, has a melting point of 155-158.5°C (Appendix VI C).

(2) The infrared absorption spectrum (Appendix IV C) is concordant with the reference spectrum of amobarbital sodium (Appendix XVI).

(3) Yields the reactions characteristic of malonylureas (Appendix III).

(4) Ignite about 0.1 g, the residue yields the reactions characteristic of sodium salts (Appendix III).

Alkalinity Dissolve 1.0 g in 20 ml of water, pH 9.5-11.0 (Appendix VI H).

Loss on drying When dried to constant weight at 130°C, loses not more than 4.0% of its weight (Appendix VIII L).

Heavy metals Dissolve 1.0 g in 43 ml of water, add slowly 3 ml of dilute hydrochloric acid with constant shaking. Carry out the limit test for heavy metals (Appendix VIII H, method 1), using 23 ml of the successive filtrate, add 2 ml of acetate BS (pH 3.5); not more than 0.002%.

Sterility Dissolve a quantity of the powder in 10 ml of sterile water, complies with the test for sterility (Appendix XI H).

Assay Carry out the Assay described under Amobarbital, using about 0.2 g, accurately weighed. Each ml of silver nitrate (0.1 mol/L) VS is equivalent to 24.83 mg of $C_{11}H_{17}N_2NaO_3$.

Category Anticonvulsant.

Storage Preserve in hermetically sealed containers, protected from light.

Preparation Amobarbital Sodium for Injection

Amobarbital Sodium for Injection

Amobarbital Sodium for Injection is a sterile powder of Amobarbital Sodium. It contains not less than 93.0% and not more than 107.0% of the labelled amount of amobarbital sodium ($C_{11}H_{17}N_2NaO_3$), calculated on the basis of average weight of content.

Description White granules or a white powder.

Identification Complies with the tests (1), (3) and (4) for Identification described under Amobarbital Sodium.

Alkalinity Dissolve 0.50 g in 10 ml of water, pH 9.5-11.0 (Appendix VI H).

Loss on drying When dried to constant weight at 130°C, loses not more than 5.0% of its weight (Appendix VIII L).

Sterility Dissolve separately the contents of two containers in sterile water to produce two solutions of 50 mg per ml, the resulting solutions comply with the test for sterility (Appendix XI H).

Other requirements Complies with the general requirements for injections (Appendix I B).

Assay Carry out the Assay described under Amobarbital, using the mixed contents obtained from the test for weight variation of content. The content of $C_{11}H_{17}N_2NaO_3$, calculated on the dried basis, is not less than 98.5%. Then calculated on the basis of average weight of content. Each ml

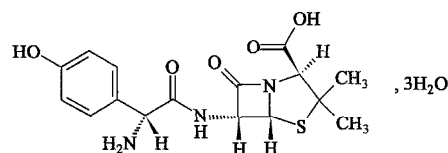
of silver nitrate (0.1 mol/L) VS is equivalent to 24.83 mg of $C_{11}H_{17}N_2NaO_3$.

Category As described under Amobarbital Sodium.

Strength (1) 0.1 g (2) 0.25 g

Storage Preserve in tightly closed containers, protected from light.

Amoxicillin



$C_{16}H_{19}N_3O_5S \cdot 3H_2O$ 419.46

[61336-70-7]

Amoxicillin is (2S,5R,6R) 6-[(R)-(–)-2-amino-2 (P-hydroxyphenyl) acetamido]-3,3-dimethyl-7-oxo-4-thia-azabicyclo [3.2.0] heptane-2-carboxylic acid trihydrate. It contains not less than 95.0% of $C_{16}H_{19}N_3O_5S$, calculated on the anhydrous basis.

Description A white or almost white crystalline powder; taste, slightly bitter.

Slightly soluble in water; practically insoluble in ethanol.

Specific optical rotation +290° to +315°, in a solution of 2 mg per ml in water (Appendix VI E).

Identification (1) The retention time of principal peak in the substance being examined in the chromatogram obtained in the Assay is identical with that the principal peak of amoxicillin CRS in the chromatogram of the reference solution correspondingly.

(2) The infrared absorption spectrum (Appendix IV C) is concordant with the reference spectrum of amoxicillin (Appendix XVI).

Acidity Dissolve a quantity in water by gently heating on a water bath at 50 °C to produce a solution of 5 mg per ml, pH 3.5-5.5 (Appendix VI H).

Clarity of solution To 5 portions each of 1.0 g add 10 ml of 0.5 mol/L hydrochloric acid solution and 2 mol/L ammonia solution separately, the solution is clear; any opalescence produced is not more pronounced than that of reference suspension II (Appendix IX B).

Related substances Dissolve a quantity of the substance being examined, accurately weighed, in mobile phase A to produce a solution of 2 mg per ml as the test solution; dissolve an accurately weighed quantity of amoxicillin CRS in mobile phase A to produce a solution of 20 µg per ml as the reference solution. Carry out the method for high performance liquid chromatography (Appendix V D), using a column packed with octadecylsilane bonded silica gel. A mixture of 0.05 mol/L phosphate buffer solution (0.05 mol/L potassium dihydrogen phosphate solution, adjust the pH value with 2 mol/L sodium hydroxide solution to 5.0) - acetonitrile (99 : 1) as mobile phase A; the mobile phase B is 0.05 mol/L phosphate buffer solution (pH 5.0) - acetonitrile (80 : 20). The flow rate is 1 ml per min and detection wavelength is 254 nm. Start the elution isocratically with a mobile phase ratio A : B of 92 : 8, immediately after elution of the amoxicillin peak start the following linear gradient.

Time(min)	Mobile phase A(%)	Mobile phase B(%)
0	92	8
25	0	100
40	0	100
41	92	8
55	92	8

The number of the theoretical plates of the column is not less than 2000 calculated with reference to the peak of amoxicillin. Inject 20 μ l of the reference solution into the column, adjust the attenuation so that the principal peak height in the chromatogram is 20%-25% of full scale of the chart. Inject separately 20 μ l each of the test solution and the reference solution and record the chromatogram. In the chromatogram obtained with the test solution; the area of any peak, apart from the principal peak, is not greater than the area of the principal peak in the chromatogram obtained with the reference solution (1 percent); the sum of the areas of all the peaks, apart from the principal peak, is not greater than three times the area of the principal peak in the chromatogram obtained with the reference solution (3 percent). Disregard any peak with an area less than 0.05 times that of the principal peak in the chromatogram obtained with the reference solution.

Amoxicillin polymer Carry out the method for size-exclusion chromatography (Appendix V H), using a column with 1.3-1.6 cm in internal diameter and 30-40 cm height packed with sephadex G-10 (40-120 μ m), a phosphate buffer solution [0.05 mol/L disodium hydrogen phosphate solution-0.05 mol/L sodium dihydrogen phosphate (95 : 5), pH 8.0] as mobile phase A and water as mobile phase B. The flow rate is 1.5 ml per minute and the detection wavelength is 254 nm. Inject 200 μ l of a solution of 0.1 mg/ml dextran blue 2000 per ml into the column, elute with mobile A and mobile B separately. The number of the theoretical plates of the column is not less than 700 and the tailing factor is not more than 2.0, calculated with reference to the peak of dextran blue 2000, using mobile phase A and B as eluent. The ratio of retention time of dextran blue 2000 peak in the two mobile phases is between 0.93-1.07, the ratio of retention time of the polymer peak of the test solution and the dextran blue 2000 peak in mobile phase A is between 0.93-1.07, the ratio of retention time of the principal peak of the reference solution and the dextran blue 2000 peak in mobile phase B is between 0.93-1.07. The relative standard deviation (RSD) of the areas of the principal peak in chromatogram obtained with 200 μ l of the reference solution for several replicate injections is not more than 5.0%, using mobile phase B as the eluent.

Reference solution Dissolve an accurately weighed quantity of benzylpenicillin CRS in water to produce a solution of 0.2 mg per ml.

Procedure Weigh accurately 0.2 g of the substance being examined in a 10 ml volumetric flask, add 4 ml of sodium carbonate solution (2%) to dissolve amoxicillin, dilute to volume with water, mix well as test solution. Inject immediately 200 μ l into the column and record the chromatogram, using mobile phase A as the eluent. Inject 200 μ l the reference solution into the column and record the chromatogram, using mobile phase B as the eluent. The content of amoxicillin polymer is not more than 0.15%, calculate as amoxicillin ($C_{16}H_{19}N_3O_5S$) with respect to the peak area obtained in the chromatogram by the external standard method (amoxicillin; benzylpenicillin=1 : 10).

Water 12.0%-15.0% (Appendix VIII M, method 1 A).

Assay Carry out the method for high performance liquid

chromatography (Appendix V D), using a column packed with octadecylsilane bonded silica gel and a mixture of 0.05 mol/L potassium dihydrogen phosphate solution (adjust the pH with 2 mol/L potassium hydroxide solution to 5.0)-acetonitrile (97.5 : 2.5) as the mobile phase. The flow rate is 1 ml per min. Detection wavelength is 254 nm and the number of the theoretical plates of the column is not less than 2000 calculated with reference to the peak of amoxicillin.

Procedure Dissolve about 25 mg of amoxicillin, accurately weighed, in 50 ml volumetric flask, dilute with the mobile phase to volume, mix well. Inject 20 μ l of the resulting solution into the column. Repeat the operation, using amoxicillin CRS instead of the substance being examined. Calculate the content of $C_{16}H_{19}N_3O_5S$ with respect to the peak area obtained in the chromatogram by the external standard method.

Category β -lactam antibiotic, penicillins.

Storage Preserve in tightly closed containers, protected from light.

Preparation (1) Amoxicillin Tablets
(2) Amoxicillin Capsules

Amoxicillin Capsules

Amoxicillin Capsules contain not less than 90.0% and not more than 110.0% of the labelled amount of amoxicillin ($C_{16}H_{19}N_3O_5S$).

Identification The retention time of principal peak in the substance being examined in the chromatogram obtained in the Assay is identical with that of the principal peak of amoxicillin CRS in the reference solution correspondingly.

Amoxicillin polymer Weigh accurately a quantity of the mixed contents, equivalent to about 200 mg of amoxicillin, to a 10 ml volumetric flask, add 5 ml of 2% sodium carbonate solution to dissolve the amoxicillin. Dilute to volume with water, mix well and filter, using the successive filtrate immediately as the test solution. Carry out the method described under Amoxicillin, the content of amoxicillin polymer is not more than 0.2%, calculate as amoxicillin ($C_{16}H_{19}N_3O_5S$).

Related substances Dissolve a quantity of the mixed contents in mobile phase A to produce a solution of 2 mg of amoxicillin per ml, filter, using the successive filtrate as the test solution. Carry out the method for Related substances described under Amoxicillin. In the chromatogram obtained with the test solution; the area of any peak, apart from the principal peak, is not greater than twice the area of the principal peak in the chromatogram obtained with the reference solution (2 percent); the sum of the areas of all the peaks, apart from the principal peak, is not greater than five times the area of the principal peak in the chromatogram obtained with the reference solution (5%). Disregard any peak with an area less than 0.05 times that of the principal peak in the chromatogram obtained with the reference solution.

Dissolution Carry out the dissolution test (Appendix X C, method 1), using 900 ml of water as the dissolution medium, adjust the rotational speed of the basket to 100 rpm. Withdraw the solution after exactly 45 minutes and filter. Measure accurately a quantity of the successive filtrate and dilute with water to produce a solution of 130 μ g per ml as the test solution. Measure the absorbances of the test solutions at 272 nm (Appendix IV A). Dissolve a quantity

of the mixed contents obtained from the test for weight variation of contents, equivalent to about average weight of one capsule, in water to produce a solution of 130 μ g of amoxicillin per ml as the reference solution. Measure the absorbance of the reference solutions at 272 nm (Appendix IV A). Calculate the dissolution of $C_{16}H_{19}N_3O_5S$ from each capsule. Not less than 80% of the labelled amount is dissolved.

Water Not more than 16.0% (Appendix VIII M, method 1 A).

Other requirements Comply with the general requirements for capsules (Appendix I E).

Assay Dissolve an accurately weighed quantity of the mixed contents obtained from the test for weight variation of contents, equivalent to about 0.125 g of amoxicillin, in phosphate buffer solution (pH 5.0) to produce a solution of 0.5 mg per ml, filter. Carry out the Assay described under Amoxicillin.

Category As described under Amoxicillin.

Strength Calculated as $C_{16}H_{19}N_3O_5S$
(1) 0.125 g (2) 0.25 g

Storage Preserve in tightly closed containers, protected from light.

Amoxicillin Tablets

Amoxicillin Tablets contain not less than 90.0% and not more than 110.0% of the labelled amount of amoxicillin ($C_{16}H_{19}N_3O_5S$).

Description White or almost white tablets.

Identification The retention time of principal peak in the substance being examined in the chromatogram obtained in the Assay is identical with that of the principal peak of amoxicillin CRS in the reference solution correspondingly.

Related substances Dissolve a quantity of powdered tablets in mobile phase A to produce a solution of 2 mg of amoxicillin per ml, filter, using the successive filtrate as the test solution. Carry out the method for Related substances described under Amoxicillin. In the chromatogram obtained with the test solution; the area of any peak, apart from the principal peak, is not greater than twice the area of the principal peak in the chromatogram obtained with the reference solution (2 percent); the sum of the areas of all the peaks, apart from the principal peak, is not greater than five times the area of the principal peak in the chromatogram obtained with the reference solution (5 percent). Disregard and peak with an area less than 0.05 times that of the principal peak in the chromatogram obtained with the reference solution.

Dissolution Carry out the dissolution test (Appendix X C, method 2), using 900 ml of water as the dissolution medium, adjust the rotational speed of the paddle to 75 rpm. Withdraw the solution after exactly 30 minutes and filter, measure accurately a quantity of the successive filtrate and dilute with water to produce a solution of 130 μ g per ml as the test solution. Measure the absorbance of the test solutions at 272 nm (Appendix IV A). Powder 10 tablets and weigh accurately a quantity of the powder equivalent to about average weight of one tablet. Dissolve in water to produce a solution of 130 μ g per ml as the reference solution. Measure the absorbances of the reference solutions at 272 nm (Appendix IV A). Calculate the dissolution of $C_{16}H_{19}N_3O_5S$ from each tablet. Not less than 80% of the labelled amount

is dissolved.

Other requirements Comply with the general requirements for tablets (Appendix I A).

Assay Weigh accurately and powder 10 tablets. Weigh accurately a quantity of the powder equivalent to about 0.125 g of amoxicillin and dissolve in phosphate buffer solution (pH 5.0) to produce a solution of 0.5 mg per ml, filter. Carry out the Assay described under Amoxicillin.

Category As described under Amoxicillin.

Strength Calculated as $C_{16}H_{19}N_3O_5S$ (1) 0.125 g
(2) 0.25 g

Storage Preserve in tightly closed containers, protected from light.

Amoxicillin and Clavulanate Potassium Tablets

Amoxicillin and Clavulanate Potassium Tablets is a mixed preparation of amoxicillin and clavulanate potassium. (The ratio of the labelled content of amoxicillin and clavulanic acid is 2 : 1 or 4 : 1 or 7 : 1). It contains not less than 90.0% and not more than 110.0% of the labelled content of amoxicillin ($C_{16}H_{19}N_3O_5S$) and clavulanate ($C_8H_9NO_5$).

Description Film coated tablets with almost white to pale yellow core; taste, slightly bitter; hygroscopic.

Identification The retention time of principal peaks of amoxicillin and clavulanate in the substance being examined in the chromatogram obtained in the Assay are identical with that of principal peaks of amoxicillin CRS and clavulanate CRS in the chromatogram of the reference solution correspondingly.

Dissolution Carry out the dissolution test (Appendix X C method 2), using 900 ml of water as the dissolution medium, adjust the rotational speed of the paddle to 75 rpm. Withdraw the solution after exactly 30 minutes, filter, take the successive filtrate as the test solution. Dissolve an accurately weighed quantity of amoxicillin CRS and clavulanic acid CRS in water to produce a mixture solution as the reference solution, the concentration is equivalent to the test solution. Carry out the method described under Assay, calculate the dissolution of amoxicillin and clavulanic acid from each tablet respectively. Not less than 80% of the labelled amount is dissolved.

Related substances Dissolve an accurately weighed quantity of the powdered tablets equivalent to the average weight of one tablet in mobile phase A to produce a solution of 2 mg of amoxicillin per ml, filter, take the successive filtrate as the test solution; dissolve an accurately weighed quantity of amoxicillin CRS in mobile phase A to produce a solution of 40 μ g per ml as the reference solution. Carry out the method for high performance liquid chromatography (Appendix V D), using a column packed with octadecylsilane bonded silica gel. The 0.01 mol/L potassium dihydrogen phosphate solution (pH 6.0) as mobile phase A; the mobile phase B is 0.01 mol/L potassium dihydrogen phosphate solution (pH 6.0)-acetonitrile (20 : 80). The flow rate is 1 ml per min and elute with linear gradient as the following table, detection wavelength is 254 nm. The retention time of amoxicillin is about 10 minutes. The number of the theoretical plates of the column is not less than 2000,

calculated with reference to the peak of amoxicillin. Inject 20 μ l of the reference solution into the column, adjust the attenuation so that the principal peak height in the chromatogram is 20%-25% of full scale of the chart. Inject separately 20 μ l each of the test solution and the reference solution and record the chromatogram. In the chromatogram obtained with the test solution, calculate the contents of impurities of which retention time is longer than that of amoxicillin: the area of any peak, apart from the principal peak, is not more than 2.0%; the sum of the areas of all the peaks, apart from the principal peak, is not more than 5.0%, calculated with reference to the labelled amount of amoxicillin.

Time(min)	Mobile phase A(%)	Mobile phase B(%)
0	95	5
0.5	95	5
30.5	59	41
32	95	5
40	95	5

Water Carry out the method for Determination of Water (Appendix VIII M, method 1, A), using a quantity of fine powder. The content of water is not more than 7.5% (for strength of $C_{16}H_{19}N_3O_5S$ 250 mg or less than 250 mg); not more than 10.0% (for strength of $C_{16}H_{19}N_3O_5S$ from 250 mg to 500 mg); not more than 11.0% (for strength of $C_{16}H_{19}N_3O_5S$ more than 500 mg).

Assay Carry out the method for high performance liquid chromatography (Appendix V D), using a column packed with octadecylsilane bonded silica gel and a mixture of 0.01 mol/L potassium dihydrogen phosphate solution (adjust the pH value with 2 mol/L sodium hydroxide solution to 6.0)-acetonitrile (96 : 4) as the mobile phase. Detection wavelength is 220 nm and the number of the theoretical plates of the column is not less than 2000 calculated with reference to the peak of amoxicillin. The resolution factor between the peaks of amoxicillin and clavulanic acid is not less than 3.5.

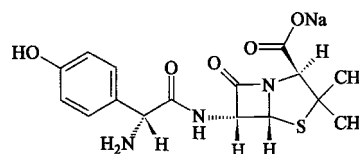
Procedure Powder finely 10 tablets, dissolve an accurately weighed quantity of the powdered tablets (equivalent to about the average weight of one tablet) in water to produce a solution of 1.0 mg of amoxicillin per ml, filter. Inject 10 μ l of the successive filtrate into the column and record the chromatogram. Dissolve an accurately weighed quantity of amoxicillin CRS and clavulanic acid CRS in water to produce a mixture solution as the reference solution, the concentration is equivalent to the test solution. Repeat the operation and calculate the contents of $C_{16}H_{19}N_3O_5S$ and $C_8H_9NO_5$ with respect to the peak areas obtained in the chromatogram by the external standard method respectively.

Category β -lactam antibiotic, penicillins.

Strength (1) 0.375 g ($C_{16}H_{19}N_3O_5S$ 0.25 g; $C_8H_9NO_5$ 0.125 g)
 (2) ① 0.625 g ($C_{16}H_{19}N_3O_5S$ 0.5 g; $C_8H_9NO_5$ 0.125 g)
 ② 0.3125 g ($C_{16}H_{19}N_3O_5S$ 0.25 g; $C_8H_9NO_5$ 0.0625 g)
 (3) ① 0.457 g ($C_{16}H_{19}N_3O_5S$ 0.4 g; $C_8H_9NO_5$ 0.057 g)
 ② 1.0 g ($C_{16}H_{19}N_3O_5S$ 0.875 g; $C_8H_9NO_5$ 0.125 g)

Storage Preserve in tightly closed containers, stored in a dry, cool and dark place.

Amoxicillin Sodium



$C_{16}H_{18}N_3NaO_5S$ 387.40

[34642-77-8]

Amoxicillin Sodium is sodium (2*S*,5*R*,6*R*)-6-[[[(2*R*)-2-amino-2-(4-hydroxy-phenyl) acetyl] amino] 3,3-dimethyl-7-oxo-4-thia-1-azabicyclo [3.2.0] heptane-2-carboxylate. It contains not less than 80.0% of $C_{16}H_{19}N_3O_5S$, calculated on the anhydrous basis.

Description A white or almost white powder or crystals; odourless or slight odour; taste, slightly bitter; hygroscopic. Freely soluble in water; sparingly soluble in ethanol; insoluble in ether.

Specific optical rotation +240° to +290°, in a solution of 2.5 mg per ml in water (Appendix VI E).

Identification (1) The retention time of principal peak of amoxicillin in the substance being examined in the chromatogram obtained in the Assay is identical with that of principal peak of amoxicillin CRS in the chromatogram of the reference solution correspondingly.

(2) Yields the flame reaction of sodium salts (Appendix III)

Alkalinity An aqueous solution of 0.1 g per ml, pH 8.0-10.0 (Appendix VI H).

Clarity and colour of solution To 5 portions each of 0.6 g add 5 ml of water respectively, the solutions are clear and colourless; any opalescence produced is not more pronounced than that of reference suspension I (Appendix IX B); any colour produced is not more intense than that of reference solution Y₇ or YG₇ (Appendix IX A method 1).

Related substances Dissolve a quantity of the substance being examined, accurately weighed, in mobile phase A to produce a solution of 2 mg per ml as the test solution; dissolve an accurately weighed quantity of amoxicillin CRS in mobile phase A to produce a solution of 20 μ g per ml as the reference solution. Carry out the method for high performance liquid chromatography (Appendix V D), using a column packed with octadecylsilane bonded silica gel. A mixture of 0.05 mol/L phosphate buffer solution (0.05 mol/L potassium dihydrogen phosphate solution, adjust the pH with 2 mol/L sodium hydroxide solution to 5.0)-acetonitrile (99 : 1) as mobile phase A; the mobile phase B is 0.05 mol/L phosphate buffer solution (pH 5.0)-acetonitrile (80 : 20). The flow rate is 1 ml per min and detection wavelength is 254 nm. Start the elution isocratically with a mobile phase ratio A : B of 92 : 8, immediately after elution of the amoxicillin peak start the following linear gradient.

Time(min)	Mobile phase A(%)	Mobile phase B(%)
0	92	8
25	0	100
40	0	100
41	92	8
55	92	8

The number of the theoretical plates of the column is not less than 2000 calculated with reference to the peak of amoxicillin. Inject 20 μ l of the reference solution into the column, adjust the attenuation so that the principal peak height in the chromatogram is 20%-25% of full scale of the chart. Inject separately 20 μ l each of the test solution and the reference solution and record the chromatogram. In the chromatogram obtained with the test solution; the area of any peak, apart from the principal peak, is not greater than three times the area of the principal peak in the chromatogram obtained with the reference solution (3 percent); the sum of the areas of all the peaks, apart from the principal peak, is not greater than nine times the area of the principal peak in the chromatogram obtained with the reference solution (9 percent). Disregard any peak with an area less than 0.05 times that of the principal peak in the chromatogram obtained with the reference solution.

Water Not more than 4.0% (Appendix VIII M, method 1 A).

Bacterial endotoxin Carry out the test for bacterial endotoxin (Appendix XI E): not more than 0.15 EU per mg of amoxicillin.

Sterility Dissolve a quantity in a suitable solvent, then transfer to not less than 500 ml of 0.9% sterile sodium chloride solution, the solution complies with the test for sterility (Appendix XI H, membrane filtration method).

Assay Carry out the method for high performance liquid chromatography (Appendix V D), using a column packed with octadecylsilane bonded silica gel and a mixture of 0.05 mol/L potassium dihydrogen phosphate solution (adjust the pH with 2 mol/L potassium hydroxide solution to 5.0)-acetonitrile (97.5 : 2.5) as the mobile phase. The flow rate is 1 ml per min. Detection wavelength is 254 nm and the number of the theoretical plates of the column is not less than 2000 calculated with reference to the peak of amoxicillin.

Procedure Dissolve an accurately weighed quantity in mobile phase and dilute to produce a solution of 0.5 mg per ml. Inject 20 μ l of the resulting solution into the column. Repeat the operation, using amoxicillin CRS instead of the substance being examined. Calculate the content of $C_{16}H_{19}N_3O_5S$ with respect to the peak area obtained in the chromatogram by the external standard method.

Category β -lactam antibiotic, penicillins.

Storage Preserve in hermetically sealed containers, stored in a dry place.

Preparation Amoxicillin Sodium for Injection

Amoxicillin Sodium for Injection

Amoxicillin Sodium for Injection is a sterile powder of amoxicillin sodium. It contains not less than 80.0% of amoxicillin ($C_{16}H_{19}N_3O_5S$), calculated on the anhydrous basis. It contains not less than 90.0% and not more than 110.0% of the labelled amount of amoxicillin ($C_{16}H_{19}N_3O_5S$), calculated with reference to the average weight of contents.

Description A white or almost white powder or crystals.

Identification Comply with tests for Identification described under Amoxicillin Sodium.

Alkalinity An aqueous solution of 0.1 g per ml, pH 8.0-10.0 (Appendix VI H).

Clarity and colour of solution Dissolve each of 5 containers

in water to produce solutions of 0.1 g per ml according to the labelled amount, the solutions are clear and colourless; any opalescence produced is not more pronounced than that of reference suspension I (Appendix IX B); any colour produced is not more intense than that of reference solution Y_8 or YG_8 (Appendix IX A method 1).

Water Not more than 4.5% (Appendix VIII M, method 1 A).

Related substances, Bacterial endotoxin and Sterility Comply with the corresponding requirements described under Amoxicillin Sodium.

Other requirements Complies with the general requirements for injection (Appendix I B).

Assay Carry out the Assay described under Amoxicillin Sodium, using an accurately weighed quantity of the mixed contents obtained in the test for weight variation of contents.

Category As described under Amoxicillin Sodium.

Strength 0.5 g ($C_{16}H_{19}N_3O_5S$)

Storage Preserve in tightly closed containers, protected from light.

Amoxicillin Sodium and Clavulanate Potassium for Injection

Amoxicillin Sodium and Clavulanate Potassium for Injection is a sterile mixture of amoxicillin sodium and clavulanate potassium (5 : 1). It contains not less than 66.0% of Amoxicillin ($C_{16}H_{19}N_3O_5S$) and 13.2% of Clavulanate ($C_8H_9NO_5$) respectively per mg, calculated on the anhydrous basis; It contains not less than 90.0 % and not more than 110.0 % of the labelled amount of amoxicillin ($C_{16}H_{19}N_3O_5S$) and clavulanate ($C_8H_9NO_5$), calculated with reference to the average weight of contents.

Description A white or almost white powder.

Identification The retention time of principal peaks of amoxicillin and clavulanic acid in the substance being examined in the chromatogram obtained in the Assay are identical with that of principal peaks of amoxicillin CRS and clavulanic acid CRS in the chromatogram of the reference solution correspondingly.

Alkalinity An aqueous solution of 100 mg per ml, pH 8.0-10.0 (Appendix VI H).

Clarity and colour of solution Dissolve each of 5 containers in 20 ml of water, the solutions are clear and colourless; any opalescence produced is not more pronounced than that of reference suspension II (Appendix IX B); any colour produced is not more intense than that of reference solution Y_6 or YG_6 (Appendix IX A, method 1).

Related substances Dissolve an accurately weighed quantity of the mixed contents obtained from the test for weight variation of contents in mobile phase A to produce a solution of 2 mg per ml, filter, take the successive filtrate as the test solution; dissolve an accurately weighed quantity of amoxicillin CRS in mobile phase A to produce a solution of 40 μ g per ml as the reference solution. Carry out the method for high performance liquid chromatography (Appendix V D), using a column packed with octadecylsilane bonded silica gel. The 0.01 mol/L potassium dihydrogen phosphate

solution (pH 6.0) as mobile phase A; the mobile phase B is 0.01 mol/L potassium dihydrogen phosphate solution (pH 6.0)-acetonitrile (20 : 80). The flow rate is 1 ml per min and elute with linear gradient as the following table, detection wavelength is 254 nm. The retention time of amoxicillin is about 10 minutes. The number of the theoretical plates of the column is not less than 2000 calculated with reference to the peak of amoxicillin. Inject 20 μ l of the reference solution into the column, adjust the attenuation so that the principal peak height in the chromatogram is 20%-25% of full scale of the chart. Inject separately 20 μ l each of the test solution and the reference solution and record the chromatogram. In the chromatogram obtained with the test solution, calculate the contents of impurities of which retention time is longer than that of amoxicillin; the area of any peak, apart from the principal peak, is not more than 2.0%; the sum of the areas of all the peaks, apart from the principal peak, is not more than 5.0%, calculated with reference to the labelled amount of amoxicillin.

Time (min)	Mobile phase A (%)	Mobile phase B (%)
0	95	5
0.5	95	5
30.5	59	41
32	95	5
40	95	5

Water Not more than 4.0 % (Appendix VIII M, method 1 A).

Bacterial endotoxin Carry out the test for bacterial endotoxin (Appendix XI E): not more than 0.25 EU per mg.

Sterility Dissolve a quantity in a suitable solvent, then transfer to not less than 500 ml of 0.9 % sterile sodium chloride solution, the solution complies with the test for sterility (Appendix XI H, membrane filtration method).

Other requirements Complies with the general requirements for injection (Appendix I B).

Assay Carry out the method for high performance liquid chromatography (Appendix V D), using a column packed with octadecylsilane bonded silica gel and a mixture of 0.01 mol/L potassium dihydrogen phosphate solution (adjust the pH with 2 mol/L sodium hydroxide solution to 6.0)-acetonitrile (96 : 4) as the mobile phase. Detection wavelength is 220 nm and the number of the theoretical plates of the column is not less than 2000 calculated with reference to the peak of amoxicillin.

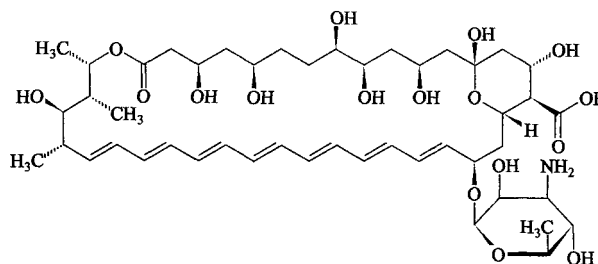
Procedure Dissolve an accurately weighed quantity of the mixed contents obtained from the test for weight variation of contents (equivalent to the content of 1 vial) in water to produce a solution of 1.0 mg of amoxicillin and 0.2 mg of clavulanic acid per ml. Inject 10 μ l of the resulting solution into the column and record the chromatogram. Dissolve an accurately weighed quantity of amoxicillin CRS and clavulanic acid CRS in water to produce a solution of 1.0 mg of amoxicillin and 0.2 mg of clavulanic acid per ml. Repeat the operation and calculate the contents of $C_{16}H_{19}N_3O_5S$ and $C_8H_9NO_5$ with respect to the peak areas obtained in the chromatogram by the external standard method respectively.

Category β -lactam antibiotic, penicillins.

Strength 1.2 g ($C_{16}H_{19}N_3O_5S$ 1 g; $C_8H_9NO_5$ 0.2 g)

Storage Preserve in well closed containers, stored in a dry, cool and dark place.

Amphotericin B



$C_{47}H_{73}NO_{17}$ 924.09

[1397-89-3]

Amphotericin B has a potency of not less than 850 amphotericin B Units per mg, calculated on the dried basis.

Description A yellow to orange yellow powder; odourless or almost odourless; tasteless; hygroscopic; inactivated easily on exposure to sunlight.

Soluble in dimethylsulfoxide; slightly soluble in dimethylformamide; very slightly soluble in methanol; insoluble in water, dehydrated ethanol, chloroform or ether.

Identification (1) Dilute the solution obtained from the test for Amphotericin A with methanol to produce a solution of 5 μ g per ml. It exhibits three maxima at about $362\text{ nm} \pm 2\text{ nm}$, $381\text{ nm} \pm 2\text{ nm}$ and $405\text{ nm} \pm 2\text{ nm}$. The ratio of absorbance at 362 nm to that at 381 nm and the ratio of absorbance at 381 nm to that at 405 nm, is about 0.6 and 0.9 respectively (Appendix IV A).

(2) The infrared absorption spectrum (Appendix IV C) is concordant with the reference spectrum of amphotericin B (Appendix XVI).

Acidity A suspension of 3% in water, pH 4.0-6.0 (Appendix VI H).

Amphotericin A Dissolve a quantity in a small amount of dimethylsulfoxide, add methanol to produce a solution of 100 μ g per ml. The absorbance at 305 nm is not greater than 0.40 (Appendix IV A).

Loss on drying When dried in vacuum over phosphorus pentoxide to constant weight at 60°C , loses not more than 5.0% of its weight (Appendix VIII L).

Assay Dissolve an accurately weighed quantity in dimethylsulfoxide, add dimethylformamide to produce a solution of 100 Units per ml, dilute with phosphate BS (pH 10.5) to produce the final solution of 1.4 Units and 0.7 Units per ml respectively. The concentration of dimethylformamide in the final solutions is 8%. Carry out the Microbiological Assay of Antibiotics (Appendix XI A) using 15 ml of inoculated medium instead of base and seed layers. 1000 amphotericin B units are equivalent to 1 mg of $C_{47}H_{73}NO_{17}$.

Category Antifungal.

Storage Preserve in hermetically sealed containers, protected from light and stored in a cold place.

Preparation Amphotericin B for Injection

Amphotericin B for Injection

Amphotericin B for Injection is a sterile lyophilized

mixture of Amphotericin B, sodium deoxycholate and suitable amount of phosphate buffer. It contains not less than 90.0% and not more than 110.0% of the labelled potency of amphotericin B ($C_{47}H_{73}NO_{17}$), calculated with reference to the average weight of contents.

Description A yellow to orange yellow powder.

Identification Dissolve a quantity in a small quantity of water and dilute with methanol to produce a solution containing 5 μ g of amphotericin B per ml. It complies with test (1) for Identification described under Amphotericin B.

Alkalinity Dissolve the content of one container in 5 ml of water, pH 7.2-8.0 (Appendix VI H).

Clarity of Solution Add water to each of 5 containers to produce solutions containing 5 mg of Amphotericin B per ml, the solutions are clear; any opalescence produced is not more pronounced than that of reference suspension 1 (Appendix IX B).

Loss on drying When dried in vacuum over phosphorus pentoxide to constant weight at 60°C, loses not more than 8.0% of its weight (Appendix VIII L).

Bacterial endotoxin Carry out the test for bacterial endotoxin (Appendix XI E); not more than 5.0 EU per 1000 amphotericin B units; not more than 0.9 EU per 1000 amphotericin B units for intrathecal injection.

Sterility Dissolve a quantity in a suitable solvent, then transfer to not less than 500 ml of 0.9% sterile sodium chloride solution, the solution complies with the test for sterility (Appendix XI H, membrane filtration method).

Other requirements Complies with the general requirements for injection (Appendix I B).

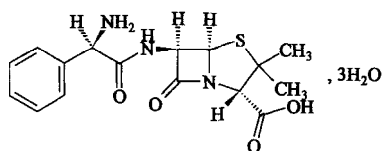
Assay Carry out the Assay described under Amphotericin B, using an accurately weighed quantity of the mixed contents obtained from the test for weight variation of contents.

Category As described under Amphotericin B.

Strength (1) 5 mg (5000 Units) (2) 25 mg (25000 Units) (3) 50 mg (50000 Units)

Storage Preserve in well closed containers, protected from light and stored in a cold place.

Ampicillin



$C_{16}H_{19}N_3O_4S \cdot 3H_2O$ 403.45

Ampicillin is 6-[D (-)-2-amino-2-phenylacetamido] penicillanic acid trihydrate. It contains not less than 96.0% of Ampicillin ($C_{16}H_{19}N_3O_4S$), calculated on the anhydrous basis.

Description A white, crystalline powder; taste, slightly bitter.

Slightly soluble in water; insoluble in chloroform, ethanol, ether and involatile oils, soluble in dilute solutions of acids or alkali.

Specific optical rotation Dissolve a quantity in water to produce a solution of 2.5 mg per ml by heating on a 60°C water bath and cool, the optical rotation is +280° to +305°, calculated with reference to the anhydrous substance (Appendix VI E).

Identification The infrared absorption spectrum (Appendix IV C) is concordant with the reference spectrum of Ampicillin (Appendix XVI).

Acidity Dissolve a quantity in water to produce a solution of 2.5 mg per ml by heating on a 60°C water bath and cool. pH is 3.5-5.5 (Appendix VI H).

Clarity of solution Dissolve five portions each of 0.6 g in 5 ml of hydrochloric acid solution (1 mol/L) and dissolve another five portions each of 0.6 g in 5 ml of ammonia hydroxide solution (2 mol/L), observe immediately, the solutions are clear, any opalescence produced is not more pronounced than that of reference suspension II (Appendix IX B).

N, N-dimethyl phenylamine Carry out the method for gas chromatography (Appendix V E), using a column packed with 3% silica as the stationary phase, and maintain the column temperature at 120°C. The resolution factor between the peaks of N, N-dimethylphenylamine and the internal standard substance complies with the related requirements.

Internal standard solution Dissolve a quantity of naphthalene, accurately weighed, in hexane to produce a solution of about 50 μ g per ml.

Reference standard solution To 50 mg N, N-dimethylphenylamine, accurately weighed, add 2 ml of hydrochloric acid and 20 ml of water, mix well, dilute with water to 50 ml. Measured accurately 5 ml to 250 ml volumetric flask, dilute to volume with water, mix well.

Procedure To 1.0 g of the substance being examined, accurately weighed, add 5 ml of sodium hydroxide solution (1 mol/L) and 1 ml of internal standard solution accurately measured. Shake thoroughly, allow it to stand. Inject 2 μ l of upper layer into the column, record the peak areas correspondingly obtained in the chromatogram. Repeat the operation, using 1 ml of reference standard solution, accurately measured. Calculate the content of N, N-dimethylphenylamine by the internal standard method. Not more than 0.0020%.

Related substance Dissolve an accurately weighed quantity in mobile phase A to produce a solution of 3 mg per ml as test solution. Measured accurately 1 ml to an 100 ml volumetric flask, dilute with mobile phase A to volume and mix well, as the reference solution. Carry out the method as described under Assay. A mixture of 12% acetic acid solution-0.2 mol/L dihydrogen phosphate potassium solution-acetonitrile-water (0.5 : 50 : 400 : 550) as the mobile phase B, and elute with linear gradient as the following table. The retention time of ampicillin is about 8-10 min. Inject 20 μ l of the reference solution into the column. Adjust the attenuation so that the principal peak height in the chromatogram is 20% of the full scale of the chart. Inject 20 μ l separately of the test solution and the reference solution into the column and record the chromatograms. Single peak area other than the principle peak is not more than the peak area of ampicillin in the reference solution (1.0%). The total peak areas other than the principle peak are not more than three times the area of ampicillin in the reference solution (3.0%). (disregard any peak with an area less than 0.05 times the area of the principal peak in the chromatogram obtained with reference

solution).

Time (min)	Mobile phase A (per cent V/V)	Mobile phase B (per cent V/V)
0	85	15
10	85	15
40	0	100
50	0	100
51	85	15
60	85	15

Water 12.0%-15.0% (Appendix VIII M, method 1 A).

Residue on ignition Not more than 0.5%, using 1.0 g (Appendix VIII N).

Heavy metals Carry out the limit test for heavy metals (Appendix VIII H, method 2), using the residue obtained in the test for Residue on ignition; not more than 0.0020%.

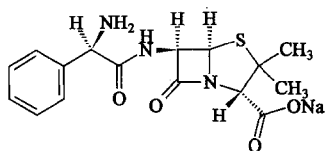
Assay Carry out the method for high performance liquid chromatography (Appendix V D) using a column packed with octadecylsilane bonded silica gel, a mixture of mobile phase A-mobile phase B (described under Related substance) (85 : 15), as the mobile phase. The flow rate is 1.0 ml per minute. Detection wavelength is 254 nm. Dissolve an accurately weighed quantity of ampicillin CRS and cefradine CRS in mobile phase A to produce a mixed solution of 0.3 mg ampicillin per ml and 0.02 mg cefradine per ml. Inject 20 μ l of the solution into the column and record the chromatogram. The resolution factor between the peak of ampicillin and that of the cefradine is not less than 3.0.

Procedure Dissolve an accurately weighed quantity in mobile phase A to produce a solution of 1.0 mg per ml, mix well as the test solution. Inject 20 μ l of the test solution into the column and record the chromatogram. Dissolve an accurately weighed quantity of ampicillin CRS measured as the reference solution. Repeat the operation. Calculate the content of $C_{16}H_{19}N_3O_4S$ with respect to the peak area obtained in the chromatogram by the external standard method.

Category β -lactam antibiotic, penicillins.

Storage Preserve in hermetically sealed containers, stored in a cool place and protected from light.

Ampicillin Sodium



$C_{16}H_{18}N_3NaO_4S$ 371.39

[69-52-3]

Ampicillin Sodium is sodium (2*S*,5*R*,6*R*)-3,3-dimethyl-6[(*R*)-(2-amino-2-phenylacetamido)]-7-oxo-4-thia-1-azabicyclo [3.2.0] heptane-2-carboxylate. It contains not less than 85.0% of Ampicillin ($C_{16}H_{19}N_3O_4S$), calculated on the anhydrous basis.

Description A white or almost white, crystalline or amorphous powder; odourless or odour slight; taste, slightly bitter; hygroscopic.

Freely soluble in water; sparingly soluble in ethanol; inso-

luble in ether.

Identification (1) The retention time of principal peak of the substance being examined in the chromatogram obtained in the Assay is identical with that the principal peak of ampicillin RS in the chromatogram of the reference solution correspondingly.

(2) Dissolve 0.25 g in 5 ml of water and add 0.5 ml of acetic acid solution (2 mol/L), mix well. Allow to stand in an ice bath for 10 minutes then filter with a sintered glass filter. Wash the precipitate with 2-3 ml of a mixture of acetone-water (9 : 1) and dry at 60°C for 30 minutes. The infrared spectrum of the dried precipitate (Appendix IV C) is concordant with the reference spectrum of ampicillin trihydrate (Appendix XVI).

(3) Yields the flame reaction of sodium salts (Appendix III).

Alkalinity Dissolve a quantity in water to produce a solution of 0.1 g per ml, pH 8.0-10.0 (Appendix VI H).

Clarity and colour of solution To 5 portions each of 0.6 g add 5 ml of water respectively, the solutions are clear and colourless; any opalescence produced is not more pronounced than that of reference suspension 1 (Appendix IX B); any colour produced is not more intense than that of reference solution YG₅ (Appendix IX A, method 1).

Related substance Dissolve an accurately weighed quantity in mobile phase A to produce a solution of 3 mg per ml as the test solution. Measured accurately 1 ml to an 100 ml volumetric flask, add mobile phase A to volume and mix well, as the reference solution. Carry out the method as described under Ampicillin; Dissolve about 0.2 g of the substance being examined in 1.0 ml water, heat on a 60°C water bath for one hour. Measured 0.5 ml to an 50 ml volumetric flask, add mobile phase A to volume, inject 20 μ l of the solution and record the chromatogram. Adjust the retention time of ampicillin to about 8-10 min, the bigger peak with a retention time of 2.8 relative to ampicillin is dimer ampicillin. The peak area of dimer ampicillin is not greater than 4.5 times the area of ampicillin in the reference solution (4.5%). Other single peak area other than the principle peak is not greater than twice the area of ampicillin in the reference solution (2.0%). The total peak areas other than the principle peak are not greater than five times the area of ampicillin in the reference solution (5.0%). (Disregard any peak with an area less than 0.05 times the area of the principal peak in the chromatogram obtained with reference solution).

Dichloromethane Dilute 1.0 g of dichloromethane, accurately weighed, with water to 500 ml as the internal standard solution; Dilute 1.0 g of dichloromethane, accurately weighed, with water to 500 ml and mix well. To 1 ml of the internal standard solution, add accurately 1 ml of internal standard solution, dilute with water to 10 ml as the reference solution. To about 1.0 g, accurately weighed, add accurately 1 ml of internal standard solution and dilute with water to 10 ml, mix well, as the test solution. Carry out the method for gas chromatography (Appendix V E), using a column packed with 10% macrogol 1000 as the stationary phase, maintain the temperature of the column at 60°C, that of the injection port at 100°C and that of the FID detector at 150°C. Inject separately 20 μ l of the test solution and the reference solution and record the chromatograms. The content of dichloromethane is not more than 0.2%, calculated with respect to the peak area in the chromatogram by external standard method.

Water Not more than 2.0% (Appendix VIII M, method 1 A).

Pyrogens Complies with the test for pyrogens (Appendix XI D), using 1 ml of a solution of 25 mg per ml in sterile

Water for Injection per kg of the rabbit's weight.

Sterility Dissolve a quantity in a suitable solvent, then transfer to not less than 500 ml of 0.9% sterile sodium solution, the solution complies with the test for sterility (Appendix XI H, membrane filtration method).

Assay Dissolve a quantity, accurately weighed, in mobile phase A to produce a solution of about 1 mg per ml as the test solution. Carry out the Assay described under Ampicillin.

Category β -lactam antibiotic, penicillins.

Storage Preserve in hermetically sealed containers, stored in a dry place.

Preparation Ampicillin Sodium for Injection

Ampicillin Sodium for Injection

Ampicillin Sodium for Injection is a sterile powder of ampicillin sodium. It contains not less than 85.0% of $C_{16}H_{19}N_3O_4S$, calculated on the anhydrous basis. It contains not less than 95.0% and not more than 105.0% of the labelled amount of Ampicillin ($C_{16}H_{19}N_3O_4S$), calculated with reference to the average weight of contents.

Description A white or almost white, crystalline or amorphous powder.

Identification Complies with the tests for Identification described under Ampicillin Sodium.

Clarity and colour of solution To each of 5 containers, add water to produce solution of 0.1 g per ml, the solutions are clear and colourless; any opalescence produced is not more pronounced than that of reference suspension I (Appendix IX B); any colour produced is not more intense than that of reference solution YG₅ (Appendix IX A, method 1).

Related substance Carry out the Related substance described under Ampicillin Sodium.

Water Not more than 2.5% (Appendix VIII M, method 1 A).

Alkalinity, Pyrogens and sterility Complies with the requirements described under Ampicillin Sodium.

Other requirements Complies with the general requirements for injection (Appendix I B).

Assay Carry out the Assay described under Ampicillin Sodium, using an accurately weighed quantity of the mixed contents obtained from the test for weight variation of contents.

Category As described under Ampicillin Sodium.

Strength Calculated as $C_{16}H_{19}N_3O_4S$
(1) 0.5 g (2) 1.0 g (3) 2.0 g

Storage Preserve in tightly closed containers, stored in a dry place.

Ampicillin Sodium and Sulbactam Sodium for Injection

Ampicillin Sodium and Sulbactam Sodium for Injection is a sterile powder of ampicillin sodium

and sulbactam sodium. [the labelled amounts representing proportions of ampicillin ($C_{16}H_{19}N_3O_4S$) to sulbactam ($C_8H_{11}NO_5S$) of 2 : 1] It contains not less than 56.3% of ampicillin ($C_{16}H_{19}N_3O_4S$) and 28.0% of sulbactam ($C_8H_{11}NO_5S$) respectively per mg, calculated on the anhydrous basis; It contains not less than 90.0% and not more than 110.0% of the labelled amount of ampicillin ($C_{16}H_{19}N_3O_4S$) and sulbactam ($C_8H_{11}NO_5S$), calculated with the reference to the average weight of contents.

Description A white or almost white powder or crystalline powder.

Identification (1) The retention time of two principal peaks in the substance being examined in the chromatogram obtained in the Assay are identical with that of two principal peaks in the chromatogram of the reference solution correspondingly.

(2) Yields the flame reaction of sodium salts (Appendix III).

Alkalinity An aqueous solution of 10 mg of ampicillin and 5 mg of sulbactam per ml, pH 8.0-10.0 (Appendix VI H).

Clarity and colour of solution To each of 5 containers add water to produce solutions of 0.15 g per ml according to the labelled amount, the solution is clear and colourless; any opalescence produced is not more pronounced than that of reference suspension I (Appendix IX B); any colour produced is not more intense than that of reference solution Y₅ or YG₅ (Appendix IX A method 1).

Related substances Dissolve a quantity of the substance being examined, accurately weighed, in mobile phase to produce a test solution containing 3 mg of ampicillin and 1.5 mg of sulbactam per ml. Transfer 1 ml of test solution, measured accurately in a 100 ml volumetric flask, dilute with mobile phase to volume and mix well as reference solution. Carry out the method as described under Assay. Inject 10 μ l of the reference solution into the column. Adjust the attenuation so that the ampicillin peak height in the chromatogram is about 20%-25% of full scale of the chart. Inject accurately 10 μ l of test solution and reference solution respectively into column and record the chromatogram for five times the retention time of the ampicillin peak. The area of any peak other than the principal peak is not greater than one and a half times the sum area of the ampicillin peak and sulbactam peak in the chromatogram obtained with the reference solution (1.5%). The sum of the areas of all peaks other than the principal peak is not greater than two and a half times the sum areas of the ampicillin peak and sulbactam peak in the chromatogram obtained with the reference solution (2.5%). (Disregard any peak with an area less than 0.05 times the sum area of the ampicillin peak and sulbactam peak in the chromatogram obtained with reference solution.)

Water Not more than 2.0% (Appendix VIII M method 1 A).

Bacterial endotoxin Carry out the test for bacterial endotoxin (Appendix XI E); less than 0.10 EU per mg (containing 0.67 mg of ampicillin and 0.33 mg of sulbactam).

Sterility Dissolve a quantity in a suitable solvent, transfer to not less than 500 ml of sterile 0.9% sodium chloride solution, the solution complies with the test for sterility (Appendix XI H, membrane filtration method).

Other requirements Complies with the general requirements for injections (Appendix I B).

Assay Carry out the method for high performance liquid chromatography (Appendix V D), using a column packed with octadecylsilane bonded silica gel and a mixture of 0.02 mol/L sodium dihydrogen phosphate solution (dissolve 2.76 g of sodium dihydrogen phosphate in 950 ml of water, adjust pH value to 4.0 ± 0.1 , dilute to 1000 ml with water and mix well)-acetonitrile (92 : 8) as the mobile phase. The flow rate is about 1 ml per minute. Detection wavelength is 230 nm. The retention time of ampicillin should be over 6 minutes. Dissolve 6 mg of ampicillin CRS and 3 mg of sulbactam CRS respectively in 10 ml of 0.01 mol/L sodium hydroxide solution, allow to stand for 30 minutes, adjust the pH value to 4.0 ± 0.1 with 1 mol/L phosphoric acid solution. Transfer 5 ml of two solution respectively to a 25 ml volumetric flask, add 5 mg of ampicillin CRS and 2.5 mg of sulbactam CRS, dilute to volume with mobile phase and mix well. Inject 10 μ l of the resulting solution into column and record the chromatogram. The resolution factor between the peaks of sulbactam and ampicillin alkaline degradation product complies with the related requirements. The number of theoretical plates of the column calculated with ampicillin is not less than 5000. The elute order is sulbactam alkaline degradation product, sulbactam, ampicillin alkaline degradation product and ampicillin.

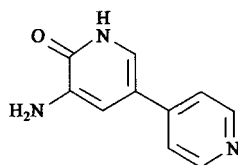
Procedure Dissolve an accurately weighed quantity of the mixed contents, obtained in the test for weight variation of contents in mobile phase to produce a test solution containing 0.6 mg of ampicillin and 0.3 mg of sulbactam per ml. Dissolve an accurately weighed quantity of ampicillin CRS and sulbactam CRS in mobile phase to produce a reference solution of 0.6 mg of ampicillin and 0.3 mg of sulbactam per ml respectively. Inject separately 10 μ l each of the resulting solutions into the column and record the chromatogram. Calculate the content of $C_{16}H_{19}N_3O_4S$ and $C_8H_{11}NO_5S$ with respect to the peak area obtained in the chromatogram by the external standard method respectively.

Category β -Lactam Antibiotic.

Strength (1) 0.75 g ($C_{16}H_{19}N_3O_4S$ 0.5 g; $C_8H_{11}NO_5S$ 0.25 g)
(2) 1.50 g ($C_{16}H_{19}N_3O_4S$ 1.0 g; $C_8H_{11}NO_5S$ 0.5 g)

Storage Preserve in well closed containers, stored in a dry, cool and dark place.

Amrinone



$C_{10}H_9N_3O$ 187.20

[60719-84-8]

Amrinone is 5-Amino-[3,4'-bipyridin]-6 (1H)-one. It contains not less than 98.5% of $C_{10}H_9N_3O$, calculated on the dried basis.

Description Pale yellow or pale yellowish brown needle crystals or a crystalline powder; odourless; tasteless; gradually darkening on exposure to light. Slightly soluble in methanol; very slightly soluble in ethanol; practically insoluble in water; soluble in lactic acid.

Identification (1) Dissolve about 5 mg in 5 ml of 0.1 mol/L

L hydrochloric acid solution, add 1 ml of trinitrophenol TS, a yellow precipitate is produced.

(2) The light absorption of a solution of 5 μ g per ml in 0.1 mol/L hydrochloric acid solution exhibits a maximum at 317 nm (Appendix IV A).

(3) The infrared absorption spectrum (Appendix IV C) is concordant with the reference spectrum of amrinone (Appendix XVI).

Related substances Carry out the method for high performance liquid chromatography (Appendix V D), using a column packed with octadecylsilane bonded silica gel and a mixture of methanol-acetonitrile-0.01 mol/L potassium dihydrogen phosphate solution (adjust to pH 6.2 ± 0.05 with 1 mol/L potassium hydroxide solution)(100 : 50 : 850) as the mobile phase. Detection wavelength is 274 nm and the number of the theoretical plates of the column is not less than 2000, calculated with reference to the peak of amrinone. The resolution factor among the peaks complies with related requirements. Sonicate to dissolve about 25 mg, accurately weighed, in 2 ml of 0.1 mol/L hydrochloric acid solution in a 50 ml volumetric flask, allow to cool, dilute with the mobile phase to volume and mix well as the test solution. Accurately measure 1 ml of the test solution into a 100 ml volumetric flask, dilute to volume with mobile phase and mix well as the reference solution. Inject 20 μ l of the reference solution. Adjust the attenuation so that the principal peak height in the chromatogram is 10%-25% of the full scale of the chart. Inject separately 20 μ l of each of the test solution and the reference solution into the column and record the chromatogram for five times the retention time of the principal peak. The sum of the areas of all peaks other than the principal peak is not greater than the area of the principal peak in the chromatogram obtained with the reference solution.

Loss on drying When dried to constant weight at 105°C , loses not more than 0.5% of its weight (Appendix VIII L).

Residue on ignition Not more than 0.2% (Appendix VIII N), using 1.0 g.

Heavy metals Carry out the limit test for heavy metals (Appendix VIII H, method 2), using the residue obtained in the test for Residue on ignition; not more than 0.001%.

Sterility Complies with the test for sterility (Appendix XI H).

Assay Dissolve about 0.35 g, accurately weighed, in 70 ml of hydrochloric acid solution (20 \rightarrow 70). Carry out the method for potentiometric titration (Appendix VII A), titrate with sodium nitrite (0.1 mol/L) VS. Each ml of sodium nitrite (0.1 mol/L) VS is equivalent to 18.72 mg of $C_{10}H_9N_3O$.

Category Cardiotonic.

Storage Preserve in tightly closed containers, protected from light.

Preparation Amrinone for Injection

Amrinone for Injection

Amrinone for injection is a sterile powder or crystals. It contains not less than 90.0% and not more than 110.0% of the labelled amount of Amrinone ($C_{10}H_9N_3O$).

Description Pale yellow or pale yellowish brown needle crystals or a crystalline powder.

Identification Complies with tests (1) and (2) for Identification described under Amrinone.

Acidity Dissolve the content of 1 container in 1 ampoule of Solvent for Amrinone for Injection, add water to produce a solution of 5 mg per ml, pH 3.2-4.0 (Appendix VI H).

Clarity of solution Dissolve the content of 1 container in 1 ampoule of Solvent for Amrinone for Injection, the reconstituted solution is clear (Appendix IX B).

Related substances Weigh accurately a quantity of the mixed contents obtained in the test for weight variation of contents, proceed as describe for related substances under Amrinone. The sum of the areas of all peaks other than the principal peak is not greater than the area of the principal peak in the chromatogram obtained with the reference solution.

Loss on drying When dried to constant weight at 105°C, loses not more than 0.5% of its weight (Appendix VIII L).

Sterility Dissolve the contents of 1 container in 1 ampoule of Solvent for Amrinone for Injection, the reconstituted solution complies with the test for sterility (Appendix XI H, membrane filtration method).

Pyrogens Dissolve the contents of 2 containers in 2 ampoules of Solvent for Amrinone for Injection separately, add Sodium Chloride Injection to produce a solution of 1.5 mg per ml. Complies with the test for pyrogens (Appendix XI D), using 5 ml per kg of rabbit's weight.

Other requirements Complies with the general requirements for injections (Appendix I B).

Assay Weigh accurately a quantity of the mixed contents obtained in the test for weight variation of contents equivalent to about 25 mg amrinone into a 100 ml volumetric flask, add a quantity of 0.1 mol/L hydrochloride acid solution, shake to dissolve amrinone, dilute with 0.1 mol/L hydrochloride acid solution to volume and mix well. Transfer 2 ml, accurately measured, to a 100 ml volumetric flask, dilute with 0.1 mol/L hydrochloride acid solution to volume and mix well. Dissolve a quantity of amrinone CRS, accurately weighed, in 0.1 mol/L hydrochloride acid solution to produce a solution 5 µg per ml. Measure the absorbance of the two solutions at 317 nm (Appendix IV A), calculate the content of $C_{10}H_9N_3O$.

Category As described under amrinone.

Strength 50 mg

Storage Preserve in well closed containers, protected from light.

Note: Solvent for Amrinone for Injection

Solvent for Amrinone for Injection is a sterile solution of lactic acid. It contains not less than 90.0% and not more than 110.0% of the labelled amount of lactic acid ($C_3H_6O_3$).

Description A colourless clear liquid.

Identification When warmed with potassium permanganate TS, yields acetaldehyde, recognisable by its odour.

pH 2.2-2.5 (Appendix VI H).

Sterility Complies with the test for sterility (Appendix XI H, membrane filtration method).

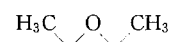
Other requirements Complies with the general requirements for injections (Appendix I B).

Assay Accurately measure 50 ml, add 10 ml of water and mix well. Add 25 ml of sodium hydroxide (1 mol/L) VS, accurately measured, boil for 5 minutes, add 2 drops of phenolphthalein IS, titrate while hot with sulfuric acid (0.5 mol/L) VS until the solution becomes colourless. Perform a blank determination and make any necessary correction. Each ml of sodium hydroxide (1 mol/L) VS is equivalent to 90.08 mg of $C_3H_6O_3$.

Strength 5 ml : 80 mg

Storage Preserve in well closed container.

Anaesthetic Ether



$C_4H_{10}O$ 74.12

[60-29-7]

Anaesthetic Ether may contain a suitable stabilizer.

Description A colourless, clear, very mobile liquid; odour, characteristic; taste, burning and slightly sweet. Highly volatile and flammable; mixture of its vapour with air is explosive on exposure to fire; deteriorated slowly on exposure to air and light.

Miscible freely with ethanol, chloroform, benzene, petroleum ether, fatty oils or volatile oils; soluble in water.

Relative density 0.713-0.718 (Appendix VI A, hydrostatic method).

Boiling range 33.5-35.5°C (Appendix VI B), it distils within a range of 1°C (Do not distil if the substance to be examined does not comply with the test for peroxides).

Acidity To 10 ml of water add 2 drops of bromothymol blue IS. Add sodium hydroxide (0.02 mol/L) VS dropwise and shake until a blue colour is developed; then add 25 ml of the substance being examined, stopper and shake well, add 0.30 ml of sodium hydroxide (0.02 mol/L) VS, shake well, the blue colour does not disappear in the aqueous layer.

Aldehyde Transfer 50 ml to a 100 ml distilling flask, distil on a water bath below 40°C, until only 1-2 ml remains. Measure 10 ml of the distillate into a stoppered conical flask containing 100 ml of water, add 1 ml of 0.1% sodium bisulfite solution, insert the stopper and shake vigorously for 10 seconds. Allow it to stand in a cool and dark place for 30 minutes, add 2 ml of starch IS, titrate with iodine (0.01 mol/L) VS until the solution becomes slight blue. Maintain the temperature of the solution below 18°C, add 2 g of sodium bicarbonate, shake well, until the blue colour disappears, add 1.0 ml of dilute iodine solution [dilute 9 ml of iodine (0.01 mol/L) VS with water to 40 ml], the blue colour reappears in aqueous layer.

Peroxide Place 5 ml in a stoppered colour comparison tube of less than 15 ml in capacity, add 8 ml of freshly prepared potassium iodide and starch solution (dissolve 10 g of potassium iodide in water and dilute to 95 ml, add 5 ml of starch IS and mix). Insert the stopper, shake vigorously for 1 minute and allow to stand in the dark for 30 minutes; no colour is produced in either of the layers.

Foreign odour Transfer 10 ml to an evaporating dish, allow to evaporate spontaneously to dryness, no foreign odour is perceptible.

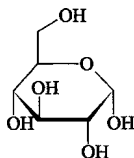
Non-volatile matter This test should be done after ensure that the substance being examined complies with the test for peroxides. Pour 50 ml in a tared evaporating dish,

evaporate to dryness by air or on gentle warming, then dried to constant weight at 105°C, the residue weighs not more than 1 mg.

Category General anaesthetics by inhalation.

Storage Preserve in hermetically containers, Almost full-filled, protected from light, and fire, stored in a cool place. After stored for 2 years, it must be reexamined and proved to be in compliance with all requirements.

Anhydrous Glucose



$C_6H_{12}O_6$ 180.16

[228-44-6]

Anhydrous Glucose is D-(+)-glucopyranose.

Description Colourless crystals or a white crystalline powder; odourless; taste, sweet.

Freely soluble in water; slightly soluble in ethanol.

Specific optical rotation Dissolve about 10 g, weighed accurately, with a quantity of water and 2.0 ml of ammonia TS in a 50 ml volumetric flask and dilute with water to volume. Mix well and allow to stand for 60 minutes. The specific optical rotation of the resulting solution is +52.6°—+53.2° at 25°C (Appendix VI E).

Identification (1) Dissolve about 0.2 g in 5 ml of water, add dropwise to hot alkaline cupric tartrate TS; a red precipitate of cuprous oxide is formed.

(2) The infrared absorption spectrum (Appendix IV C) is concordant with the reference spectrum of anhydrous glucose (Appendix XVI).

Acidity Dissolve 2.0 g in 20 ml of water, add 3 drops of phenolphthalein IS and 0.20 ml of sodium hydroxide (0.02 mol/L) VS; a pink colour is produced.

Clarity and colour of solution Dissolve 5.0 g in hot water, cool, dilute to 10 ml with water; the solution is clear and colourless. Any opalescence produced is not more pronounced than that of reference suspension I (Appendix IX B). Any colour produced is not more pronounced than that of a solution prepared by diluting 1.0 ml of a reference solution (mix 3 ml of standard cobaltous chloride CS and 3 ml of standard potassium dichromate CS with 6 ml of standard copper sulfate CS and add sufficient water to produce 50 ml) with water to 10 ml.

Clarity of ethanolic solution To 1.0 g add 20 ml of ethanol and reflux on a water bath for about 40 minutes; the solution is clear.

Chloride Carry out the limit test for chlorides (Appendix VIII A), using 0.60 g. Any opalescence produced is not more pronounced than that of a reference using 6.0 ml of sodium chloride standard solution (0.01%).

Sulfate Carry out the limit test for sulfates (Appendix VIII B), using 2.0 g. Any opalescence produced is not more pronounced than that of a reference using 2.0 ml of potassium sulfate standard solution (0.01%).

Sulfites and soluble starch Dissolve 1.0 g in 10 ml of water, add 1 drop of iodine TS; a yellow colour is produced.

Loss on drying When dried to constant weight at 105°C, loses not more than 1.0% of its weight (Appendix VIII L).

Residue on ignition Not more than 0.1% (Appendix VIII N).

Protein Dissolve 1.0 g in 10 ml of water, add 3 ml of sulfosalicylic acid solution (1→5), no tribidity or precipitate is produced.

Barium Dissolve 2.0 g in 20 ml of water, and divide the solution into two equal portions. To one portion add 1 ml of dilute sulfuric acid and to the other add 1 ml of water, mix well, allow to stand for 15 minutes, both portions are equally clear.

Calcium Dissolve 1.0 g in 10 ml of water, add 1 ml of ammonia TS and 5 ml of ammonium oxalate TS, mix well and allow to stand for 1 hour. Any opalescence produced is not more pronounced than that of a reference using 1.0 ml of calcium standard solution (weigh accurately 0.1250 g of calcium carbonate to 500 ml volumetric flask, add 5 ml of water and 0.5 ml of hydrochloric acid to dissolve and dilute with water to volume, mix well; each ml is equivalent to 0.10 mg of Ca) (0.01%).

Iron Dissolve 2.0 g in 20 ml of water, add 3 drops of nitric acid, boil gently for 5 minutes. Allow to cool, dilute to 45 ml with water, add 3 ml of ammonium thiocyanate solution (30→100) and mix well. Any colour produced is not more intense than that of a reference solution prepared in the same manner using 2.0 ml of iron standard solution (0.001%).

Heavy metals Dissolve 5.0 g in 23 ml of water, add 2 ml of sodium acetate BS (pH 3.5), carry out the limit test for heavy metals (Appendix VIII H, method 1); not more than 0.0004%.

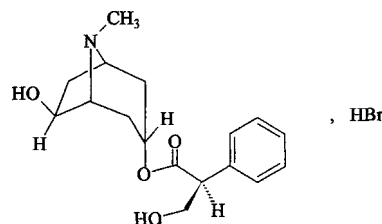
Arsenic Dissolve 2.0 g in 5 ml of water, add 5 ml of dilute sulfuric acid and 0.5 ml of bromine-potassium bromide TS. Heat on a water bath for about 20 minutes, maintain the presence of excess of bromine. Add a quantity of bromine-potassium bromide TS if necessary, replace the evaporated water constantly. Cool, then add 5 ml of hydrochloric acid and dilute with water to 28 ml. The solution complies with the limit test for arsenic (Appendix VIII J, method 1) (0.0001%).

Category Nutrient.

Storage Preserve in tightly closed containers.

Preparation (1) Compound Sodium Lactate and Glucose Injection
(2) Glucose Injection
(3) Glucose and Sodium Chloride Injection

Anisodamine Hydrobromide



$C_{17}H_{23}NO_4 \cdot HBr$ 386.29

Anisodamine Hydrobromide is the hydrobromide of an alkaloid [6β-hydroxy-1αH, 5αH-tropane-3α-ol

(±) tropiate] isolated from the root of *Scopolia tangutica* Maxim. (Solanaceae). It contains not less than 98.5% of $C_{17}H_{23}NO_4 \cdot HBr$, calculated on the dried basis.

Description White crystals or a crystalline powder; odourless. Very soluble in water; freely soluble in ethanol; slightly soluble in acetone.

Melting range 176-181°C (Appendix VI C).

Specific optical rotation -9.0° to -11.5° , in a solution of 0.1 g per ml in water (Appendix VI E).

Identification (1) The infrared absorption spectrum (Appendix IV C) is concordant with the reference spectrum of anisodamine hydrobromide (Appendix XVI).

(2) Yields the reactions characteristic of tropane alkaloids (Appendix III).

(3) The aqueous solution yields the reactions characteristic of bromides (Appendix III).

Acidity Dissolve 0.50 g in 15 ml of water, add 1 drop of methyl red IS, if a red colour produced, becomes yellow on the addition of 0.3 ml of sodium hydroxide (0.02 mol/L) VS.

Other alkaloids Carry out the method for thin-layer chromatography (Appendix V B), using neutral aluminium oxide (activity grade II-III) as the coating substance and a mixture of chloroform-dehydrated ethanol (95 : 5) as the mobile phase. Apply separately to the plate 10 μ l each of two solutions in methanol containing (1) 10 mg per ml of anisodamine hydrobromide CRS, (2) 10 mg per ml of the substance being examined. After developing and removal of the plate, spray with a mixture of dilute potassium iodobismuthate TS-potassium iodide TS (1 : 1). No spot in the chromatogram obtained with solution (2) is observed other than the spot similar in position and colour to that of the principal spot in the chromatogram obtained with solution (1).

Loss on drying When dried to constant weight at 120°C, loses not more than 1.0% of its weight (Appendix VIII L).

Assay Dissolve about 0.2 g, accurately weighed, in 20 ml of glacial acetic acid, heat gently if necessary, add 5 ml of mercuric acetate TS and 1 drop of crystal violet IS. Titrate with perchloric acid (0.1 mol/L) VS until the solution becomes pure blue. Perform a blank determination and make any necessary correction. Each ml of perchloric acid (0.1 mol/L) VS is equivalent to 38.63 mg of $C_{17}H_{23}NO_4 \cdot HBr$.

Category Anticholinergic agent.

Storage Preserve in tightly closed containers, protected from light.

Preparation (1) Anisodamine Hydrobromide Injection
(2) Anisodamine Hydrobromide Tablets

Anisodamine Hydrobromide Injection

Anisodamine Hydrobromide Injection is a sterile solution of anisodamine hydrobromide in Water for Injection. It contains not less than 90.0% and not more than 110.0% of the labelled amount of anisodamine hydrobromide ($C_{17}H_{23}NO_4 \cdot HBr$).

Description A clear, colourless liquid.

Identification (1) Carry out the test for Other alkaloids described under Anisodamine Hydrobromide, using the residue obtained on evaporating 1 ml of the injection to dryness. The colour and position of the principal spot

obtained with solution (2) are identical to those of the principal spot obtained with solution (1).

(2) Evaporate 1 ml to dryness on a water bath, the residue yields the reactions characteristic of tropane alkaloids (Appendix III).

(3) Yields the reactions characteristic of bromides (Appendix III).

pH value 3.5-5.5 (Appendix VI H).

Other requirements Complies with the general requirements for injections (Appendix I B).

Assay Dilute an accurately measured quantity of the injection with water to produce a solution of about 70 μ g per ml, as test solution. Dilute an accurately weighed quantity of anisodamine hydrobromide CRS with water to produce a solution of about 70 μ g per ml, as reference solution. Accurately measure 3 ml of each of test solution and reference solution, to two separators with 15 ml of chloroform separately, add 6.0 ml of bromocresol green solution [dissolve 50 mg of bromocresol green and 1.021 g of potassium hydrogen phthalate in 1.6 ml of 0.2 mol/L hydrochloric acid solution, dilute with water to 100 ml, shake well and filter, if necessary] respectively, shake for 3 minutes and allow it to stand until separation takes place. Separate the chloroform layer and measure its absorbance at 420 nm (Appendix IV A). Calculate the content of $C_{17}H_{23}NO_4 \cdot HBr$.

Category As described under Anisodamine Hydrobromide.

Strength (1) 1 ml : 10 mg (2) 1 ml : 20 mg

Storage Preserve in well closed containers, protected from light.

Anisodamine Hydrobromide Tablets

Anisodamine Hydrobromide Tablets contain not less than 95.0% and not more than 115.0% of the labelled amount of anisodamine hydrobromide ($C_{17}H_{23}NO_4 \cdot HBr$).

Description White tablets

Identification (1) Stir a quantity of the powdered tablets equivalent to 10 mg of anisodamine hydrobromide with 5 ml of ethanol, filter and evaporate the filtrate to dryness on a water bath. The residue yields the reactions characteristic of tropane alkaloids (Appendix III).

(2) Stir a quantity of the powder with water and filter. The filtrate yields the reactions characteristic of bromides (Appendix III).

Other requirements Comply with the general requirements for tablets (Appendix I A).

Assay Weigh accurately and powder 20 tablets. Weigh accurately a quantity of the powder, equivalent to 7 mg of anisodamine hydrobromide, to a 100 ml volumetric flask, add water to dissolve the anisodamine hydrobromide, dilute to volume, shake well and filter, using the filtrate as the test solution. Dissolve an accurately weighed quantity of anisodamine hydrobromide CRS with water to produce a solution containing about 70 μ g of anisodamine hydrobromide, as the reference solution. To 3 ml of each of the test solution and the reference solution, accurately measured, with 15 ml of chloroform separately in separators, add 6.0 ml of bromocresol green solution [dissolve 50 mg of bromocresol green and 1.021 g of potassium hydrogen phthalate in 1.6 ml of (0.2 mol/L) hydrochloric acid solution, dilute with water to 100 ml, shake well and filter, if necessary] respectively, shake for 3

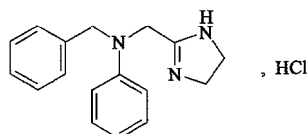
minutes and allow it to stand until separation takes place. Separate the chloroform layer and measure its absorbance at 420 nm (Appendix IV A). Calculate the content of $C_{17}H_{23}NO_4 \cdot HBr$.

Category As described under Anisodamine Hydrobromide.

Strength 5 mg

Storage Preserve in tightly closed containers, protected from light.

Antazoline Hydrochloride



$C_{17}H_{19}N_3 \cdot HCl$ 301.8 [154-68-7] (phosphate)

Antazoline Hydrochloride is 4, 5-dihydro-*N*-phenyl-*N*-(phenylmethyl)-1*H*-imidazole-2-methanamine hydrochloride. It contains not less than 98.0% of $C_{17}H_{19}N_3 \cdot HCl$, calculated on the dried basis.

Description A white or almost white crystalline powder; odourless or almost odourless; taste, bitter. Soluble in ethanol; sparingly soluble in water; slightly soluble in chloroform; practically insoluble in ether.

Melting range 238-243°C, with decomposition (Appendix VI C).

Identification (1) To about 50 mg add 5 ml of water and 0.5 ml nitric acid, a red colour is produced and turns to dark green immediately.

(2) The light absorption of a solution of 20 µg per ml in hydrochloric acid (0.1 mol/L) exhibits two maxima at 241 nm and 291 nm; the absorbance are about 1.0 and 0.13, respectively (Appendix IV A).

(3) The infrared absorption spectrum (Appendix IV C) is concordant with the reference spectrum of antazoline hydrochloride (Appendix XVI).

(4) The aqueous solution yields the reactions characteristic of chlorides (Appendix III).

Acidity Dissolve 1.0 g in 100 ml of water, pH 5.0-6.5 (Appendix VI H).

Loss on drying When dried to constant weight at 105°C, loses not more than 1.0% of its weight (Appendix VIII L).

Residue on ignition Not more than 0.1% (Appendix VIII N).

Assay To about 0.2 g, accurately weighted, add 20 ml of glacial acetic acid and 5 ml of mercuric acetate TS. Carry out the method for potentiometric titration (Appendix VII A), titrate with perchloric acid (0.1 mol/L) VS. Perform a blank determination and make any necessary correction. Each ml of 0.1 mol/L VS is equivalent to 30.18 mg of $C_{17}H_{19}N_3 \cdot HCl$.

Category Antihistaminic.

Storage Preserve in tightly closed containers, protected from light.

Preparation Antazoline Hydrochloride Tablets

Antazoline Hydrochloride Tablets

Antazoline Hydrochloride Tablets contain not less than 93.0% and not more than 107.0% of the labelled amount of antazoline hydrochloride ($C_{17}H_{19}N_3 \cdot HCl$).

Description White tablets.

Identification (1) Shake a quantity of the powdered tablets equivalent to about 50 mg of antazoline hydrochloride with 5 ml of water to dissolve antazoline hydrochloride, add 1 ml of sodium hydroxide TS and shake. Extract with 25 ml of chloroform, evaporate the chloroform layer to dryness on a water bath. Dissolve the residue in 0.2 ml of hydrochloric acid, add 5 ml of water and 0.5 ml of nitric acid, a red colour is produced and turns to dark green rapidly.

(2) The light absorption of the solution obtained in the Assay exhibits two maxima at 241 nm and 291 nm (Appendix IV A).

(3) Shake a quantity of the powdered tablets with water and filter, the filtrate yields the reactions characteristic of chlorides (Appendix III).

Other requirements Comply with the general requirements for tablets (Appendix I A).

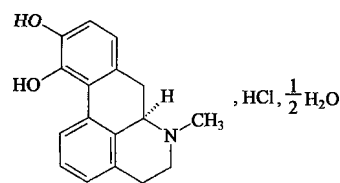
Assay Weigh accurately and powder 20 tablets. Accurately weigh a quantity of the powdered tablets equivalent to about 0.1 g of antazoline hydrochloride to a 200 ml volumetric flask, add 160 ml of 0.1 mol/L hydrochloric acid solution, shake, warm to dissolve the antazoline hydrochloride, allow to cool, dilute with 0.1 mol/L hydrochloric acid solution to volume, mix well and filter. Transfer 2 ml of the filtrate, accurately measured, to a 100 ml volumetric flask, dilute with 0.1 mol/L hydrochloric acid solution to volume. Measure the absorbance of the resulting solution at 241 nm (Appendix IV A). Repeat the operation, using a solution of 10 µg per ml of antazoline hydrochloride CRS in 0.1 mol/L hydrochloric acid solution. Calculate the content of $C_{17}H_{19}N_3 \cdot HCl$.

Category As described under Antazoline Hydrochloride.

Strength 0.1 g

Storage Preserve in tightly closed containers, protected from light.

Apomorphine Hydrochloride



$C_{17}H_{17}NO_2 \cdot HCl \cdot \frac{1}{2}H_2O$ 312.80 [1372-20-7]

Apomorphine Hydrochloride is (*R*)-5,6,6α,7-tetrahydro-6-methyl-4*H*-dibenzo[*de,g*]quinoline-10,11-diol hydrochloride hemihydrate. It contains not less than 98.0% of $C_{17}H_{17}NO_2 \cdot HCl$, calculated on the dried basis.

Description White or greyish white lustrous crystals or a crystalline powder; odourless; it changes to green on exposure to air or light.

Soluble in hot water; sparingly soluble in water or ethanol; very slightly soluble in chloroform or ether.

Identification (1) To 10 mg add 1 ml of nitric acid, a solution with dark purple colour is produced.

(2) Dissolve 50 mg in 5 ml of water, add 1 ml of sodium bicarbonate TS, a white or greenish white precipitate is produced; which becomes emerald-green gradually on adding 3 drops of iodine TS and shaking vigorously. Shake the mixture vigorously with 5 ml ether and allow to stand, the ether layer becomes ruby-red, while the water layer remains green in colour.

(3) The infrared absorption spectrum (Appendix IV C) is concordant with the reference spectrum of apomorphine hydrochloride (Appendix XVI).

(4) The aqueous solution yields the reaction characteristic of chlorides (Appendix III).

Acidity Dissolve 0.10 g in 10 ml of water, pH 3.0-4.0 (Appendix VI H).

Colour of solution A solution of 0.10 g in 10 ml of freshly boiled and cooled water is not more intensely coloured than the reference solution [Dissolve 5 mg in 100 ml of freshly boiled and cooled water. To 1 ml of the solution in a test tube add 6 ml of freshly boiled and cooled water, 1 ml of sodium bicarbonate TS and 0.5 ml of iodine solution (0.05 mol/L); allow to stand for 30 seconds, add 0.6 ml of sodium thiosulfate solution (0.1 mol/L) and dilute to 10 ml with freshly boiled and cooled water].

Related substances Carry out the method for high performance liquid chromatography (Appendix V D), using a column packed with octadecylsilane bonded silica gel and a mixture of acetonitrile-0.04 mol/L potassium dihydrogen phosphate solution (adjust the pH Value to 3.0 with phosphonic acid.) (20 : 80) as the mobile phase. Detection wavelength is at 212 nm, and the number of theoretical plates of the column is not less than 3000, calculated with reference to the peak of apomorphine hydrochloride. Add a quantity equivalent to about 20 mg of anhydrous apomorphine hydrochloride to 100 ml volumetric flask, dilute with mobile phase to the volume, mix well, use as the test solution. Measure accurately 1 ml of above solution to 100 ml volumetric flask and dilute with mobile phase to the volume as the reference solution. Inject 20 μ l of the reference solution into the column, accurately measured, adjust the attenuation so that the principal peak height in the chromatogram is 10%-20% of the full scale of the chart. Inject separately 20 μ l each of the test and reference solution, both accurately measured, into the column and record the chromatogram for twice the retention time of the principal peak. The sum of peak areas due to impurities is not greater than twice the area of the principal peak of the reference solution.

Loss on drying When dried to constant weight at 105°C, loses not more than 5.0% of its weight (Appendix VIII L).

Residue on ignition Not more than 0.1% (Appendix VIII N).

Assay Dissolve about 0.25 g, accurately weighed, in 20 ml of glacial acetic acid and 6 ml of mercuric acetate TS, add 1 drop of crystal violet IS and titrate with perchloric acid (0.1 mol/L) VS until the colour changes to green. Perform a blank determination and make any necessary correction. Each ml of perchloric acid (0.1 mol/L) VS is equivalent to 30.38 mg of $C_{17}H_{17}NO_2 \cdot HCl$.

Category Vomiting agent.

Storage Preserve in tightly closed containers, protected from light.

Preparation Apomorphine Hydrochloride Injection

Apomorphine Hydrochloride Injection

Apomorphine Hydrochloride Injection is a sterile solution of apomorphine hydrochloride in Water for Injection. It contains not less than 93.0% and not more than 107.0% of the labelled amount of apomorphine hydrochloride ($C_{17}H_{17}NO_2 \cdot HCl \cdot \frac{1}{2}H_2O$). It may contain suitable stabilizers.

Description A clear, colourless to pale yellowish-green liquid; turning to green on exposure to light.

Identification (1) To 1 ml add 1 ml of sodium bicarbonate TS, a white or greenish-white precipitate is produced; add iodine TS dropwise slowly and shake, the precipitate becomes emerald-green; add 2 ml of ether, shake vigorously and allow the mixture to stand, the ether layer becomes ruby-red, while the water layer remains green in colour.

(2) Yields the reactions characteristic of chlorides (Appendix III).

pH value 2.5-4.0 (Appendix VI H).

Colour Not more intense than reference solution YG₃ (Appendix IX A, method 1).

Other requirements Complies with the general requirements for injection (Appendix I B).

Assay Measure accurately a volume equivalent to about 50 mg of apomorphine hydrochloride into a separator, dilute with freshly boiled and cooled water to 25 ml. Add 0.5 g of sodium bicarbonate, shake and extract with 25 ml of peroxide-free ether and then with four 15 ml portions of peroxide-free ether. Combine the ether extracts and wash 3 times with 5 ml each of water. Combine the washings and extract with 5 ml of peroxide-free ether. Combine the ether extracts, add 20 ml of hydrochloric acid (0.02 mol/L) VS, accurately measured, shake vigorously and allow to stand. Separate the acid layer and wash the ether layer with 5 ml each of water for 2 times. Combine the washings and the acid extract, add 1-2 drops of methyl red IS, titrate with sodium hydroxide (0.02 mol/L) VS. Each ml of hydrochloric acid (0.02 mol/L) VS is equivalent to 6.256 mg of $C_{17}H_{17}NO_2 \cdot HCl \cdot \frac{1}{2}H_2O$.

Category As described under Apomorphine Hydrochloride.

Strength 1 ml : 5 mg

Storage Preserve in well closed containers, protected from light.

Aprotinin

Aprotinin is the proteolytic enzymes inhibitor obtained by extraction and purification from bovine pancreas or lung. It contains not less than 3.0 Units per mg, calculated on the dried basis.

Description A white to slightly yellow powder.

Freely soluble in water or 0.9% sodium chloride solution; insoluble in ethanol, acetone or ether.

Identification Dissolve a quantity of the substance being examined and trypsin in water to produce solutions of 1 mg

per ml respectively. Transfer 10 μ l of each solution to a separate depression on a white spot plate, mix well, add 0.2 ml of methyl *n*-tosyl-L-arginate hydrochloride TS. Allow it to stand for a few minutes, no purple colour is produced. Treat 10 μ l of trypsin solution in the same manner, a purple colour is produced.

Acidity An aqueous solution of 5 mg per ml, pH 5.0-7.0 (Appendix VI H).

Clarity of solution An aqueous solution of 2 mg per ml is clear.

Absorbance The light absorption of a solution of 3.0 units per ml in water exhibits a maximum at 277 nm and the absorbance is not more than 0.8 (Appendix IV A).

Water Not more than 6.0% (Appendix VIII M, method 1 A).

Proteins impurities of higher molecular mass Dissolve a quantity of the substance being examined in 3 mol/L acetic acid solution to produce a solution of 300 units per ml. Carry out the method for column chromatography (Appendix V C), using a column (80-100 cm \times 2.5 cm) packed with about 50 g of glucosan gel G-50 (type of ultra-fine) and 3 mol/L acetic acid solution as the eluent with a flow rate 22-25 ml per hour. Detection wavelength is 277 nm. Inject 1.0 ml of the resulting solution into the column. The sum of the areas of all the peaks eluting before the principal peak is not more than 3.0% of the total area of the peaks.

Pyrogens Complies with the test for pyrogens (Appendix XI D), using 1 ml of a solution of 15 Units per ml in sterile Water for Injection or Sodium Chloride Injection per kg of the rabbit's weight.

Undue toxicity Complies with the test for Undue toxicity (Appendix XI C), using a solution of 4 Units per ml in sterile Water for Injection or Sodium Chloride Injection, injected intravenously.

Depressor substances Complies with the test for depressor substances (Appendix XI G), using 1.5 Units per kg of the cat's weight.

Assay Substrate solution Dissolve 171.3 mg of ethyl *N*-benzoyl-L-arginate hydrochloride in water and dilute to 25 ml. Freshly prepared before use.

Trypsin CRS solution Dissolve a quantity of Trypsin CRS, accurately weighed, in hydrochloric acid solution (0.001 mol/L) to produce a solution of about 0.8 Units per ml (equivalent to about 1 mg per ml). Freshly prepared before use, stored in an ice bath.

Dilute trypsin CRS solution Dilute 1 ml of trypsin CRS solution, accurately measured, with borax-calcium chloride BS (pH 8.0) to 20 ml, stand at room temperature for 10 minutes, stored in an ice bath.

Test solution To a quantity, accurately weighed, add borax-calcium chloride BS (pH 8.0) to produce a solution of about 1.67 Units per ml (equivalent to about 0.6 mg per ml). Dilute 0.5 ml of the solution and 2 ml of trypsin CRS solution, both accurately measured, with borax-calcium chloride BS (pH 8.0) to 20 ml. Allow it to react for 10 minutes, stored in an ice bath (use within two hours).

Procedure Transfer 9.0 ml of borax-calcium chloride BS (pH 8.0) and 1.0 ml of the substrate solution to a 25 ml beaker, kept at $25^{\circ}\text{C} \pm 0.5^{\circ}\text{C}$ for 3-5 minutes in a water bath. Adjust to pH 8.0 by the addition of sodium hydroxide solution (0.1 mol/L) dropwise with stirring, add 1 ml of the test solution (kept at 25°C for 3-5 minutes) and start a timer immediately. Titrate the liberated acid with sodium hydroxide (0.1 mol/L) VS by a 1 ml microburette to keep the solution maintaining at pH 7.9-8.1. Read the consumed

volume of sodium hydroxide (0.1 mol/L) VS at pH 8.0 in an interval of 1 minute for a period of 6 minutes. Repeat the operation using 1 ml of dilute trypsin CRS solution as reference test. Plot a graph with time as abscissa and the consumed volume of sodium hydroxide solution in ml as ordinate, a linear line is obtained. The two lines should coincide almostly. Calculate the volume in ml of sodium hydroxide (0.1 mol/L) VS consumed per minute and the activity from the following expression:

$$\text{Activity in Units of aprotinin per mg} = \frac{(2 n_1 - n_2) 4000 f}{W}$$

where 4000 is coefficient;

W is the quantity in mg of aprotinin at the concentration of about 1.67 Units per ml;

n_1 is the volume in ml of sodium hydroxide (0.1 mol/L) VS consumed per minute by the dilute trypsin CRS solution;

n_2 is the volume in ml of sodium hydroxide (0.1 mol/L) VS consumed per minute by the test solution;

2 means the quantity of trypsin in test solution is twice as much as reference test;

f is the correction factor of sodium hydroxide (0.1 mol/L) VS.

Definition of Activity in Units 1 aprotinin activity Unit (E. P. U) represents its inhibitory action on the activity of 1 trypsin Unit (1 trypsin Unit represents the activity to hydrolyse 1 μ mol of ethyl *N*-benzoyl-L-arginate per second). The activity of aprotinin is determined by measuring its inhibitory action on a solution of trypsin of known activity. The activity unit of the aprotinin is calculated from the difference between the initial activity and the residual activity of the trypsin.

Category Proteolytic enzyme inhibitor.

Storage Preserve in hermetically sealed containers, protected from light.

Preparation Aprotinin for Injection

Aprotinin for Injection

Aprotinin for Injection is sterile, lyophilized aprotinin. It contains not less than 85.0% of the labelled amount of aprotinin.

Description A white or almost white lyophilized mass or powder.

Freely soluble in water.

Identification A solution of 3 Units per ml in water complies with tests for Identification described under Aprotinin.

Acidity Dissolve the content of 1 container with 2 ml of water, pH 5.0-7.0 (Appendix VI H).

Colour of solution A solution of 6 Units per ml in water is colourless; any colour produced is not more intense than that of the reference solution Y₂ (Appendix IX A).

Water Not more than 7.0% (Appendix VIII M, method 1 A).

Pyrogens, Depressor substances Complies with the corresponding tests described under Aprotinin.

Other requirements Complies with the general requirements for injections (Appendix I B).

Assay Dissolve the contents of 3 containers separately with 2 ml of borax-calcium chloride BS (pH 8.0). Combine the

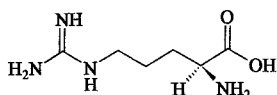
solutions and mix well. Dilute a quantity, accurately measured, equivalent to about 33.4 Units of aprotinin with borax-calcium chloride BS (pH 8.0) to 20 ml. Dilute 0.5 ml of the solution and 2 ml of trypsin CRS solution, both accurately measured, to 20 ml. Allow the reaction to proceed for 10 minutes and carry out Assay described under Aprotinin immediately, calculate the content of aprotinin.

Category As described under Aprotinin.

Strength (1) 28 Units (2) 56 Units (3) 278 Units

Storage Preserve in hermetically sealed containers, protected from light and stored in a cool place.

Arginine



$C_6H_{14}N_4O_2$ 174.20

Arginine is L-2-Amino-5-guanidopentanoic acid. It contains not less than 99.0% of $C_6H_{14}N_4O_2$, calculated on the dried basis.

Description A white crystals or crystalline powder; almost odourless; taste, characteristic. Freely soluble in water, very slightly soluble in ethanol.

Specific optical rotation +26.9° to +27.9°, in a solution of 80 mg per ml in 6 mol/L hydrochloric acid solution (Appendix VI E).

Identification The infrared absorption spectrum (Appendix IV C) is concordant with the reference spectrum of arginine (Appendix X VI).

Alkalinity Dissolve 2.5 g in 25 ml of water, pH 10.5-12.0 (Appendix VI H).

Transmittance of solution Dissolve 1.0 g in 10 ml of water, measure the transmittance at 430 nm (Appendix IV A), not less than 98.0%.

Chloride Carry out the limit test for chloride (Appendix VIII A), using 0.3 g. Any opalescence produced is not more pronounced than that of a reference solution, using 6.0 ml of sodium chloride standard solution (0.02%).

Sulfates Carry out the limit test for sulfates (Appendix VIII B), using 1.0 g. Any opalescence produced is not more pronounced than that of a reference solution using 2.0 ml of potassium sulfate standard solution (0.02%).

Ammonium Carry out the limit test for ammonium (Appendix VIII K), using 0.10 g. Any opalescence produced is not more pronounced than that of a reference solution using 2.0 ml of ammonium chloride standard solution (0.02%).

Proteins Dissolve 1 g in 10 ml of water, add 5 drops of 20% trifluoroacetic acid, no precipitate is produced.

Other amino acids Dissolve a quantity of arginine in water to produce a solution of 100 mg per ml as test solution, measured accurately 0.4 ml of the test solution into a 100 ml volumetric flask, dilute with water to the volume, mix well, use the solution as reference solution. Carry out the thin-layer chromatography (Appendix V B), using silica gel G as the coating substance and a mixture of n-propanol and concentrated ammonia solution (66 : 37) as the mobile phase. Apply separately to the plate 1 µl each of above two solutions, after developing and removal of the plate, dry it

in air, then heat at 90°C for 10 minutes, cool and spray with a solution of 1% ninhydrin in n-propanol, heat at 90°C until the colour changes and examine immediately. The spots apart from the principal spot in the chromatogram obtained with the test solution is not more intense than the principal spot obtained with the reference solution (0.4%).

Loss on drying When dried to constant weight at 105°C for 3 hours, loses not more than 0.2% of its weight (Appendix VIII L).

Residue on ignition Not more than 0.1% (Appendix VIII N).

Iron Carry out the limit test for iron (Appendix VIII G). Using 1.0 g. Any colour produced is not more intense than that of a reference solution using 1.0 ml of iron standard solution (0.001%).

Heavy metals Dissolve 1.0 g in 23 ml of water and 2 ml of acetate BS (pH 3.5). Carry out the limit test for heavy metals (Appendix VIII H, method 1); not more than 0.001%.

Arsenic Dissolve 2.0 g in 23 ml of water, add 5 ml of hydrochloric acid. Carry out the limit test for arsenic (Appendix VIII J, method 1); not more than 0.001%.

Pyrogens Complies with the test for pyrogens (Appendix XI D), using 10 ml of a solution of 50 mg per ml in sodium chloride for injection per kg of rabbit's weight.

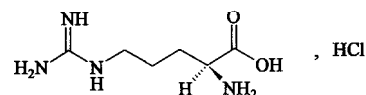
Assay Dissolve about 80 mg, accurately weighed, in 3 ml of anhydrous formic acid, add 50 ml of glacial acetic acid. Carry out the method for potentiometric titration (Appendix VII A). Titration with perchloric acid (0.1 mol/L) VS, perform a blank determination and make any necessary correction. Each ml of perchloric acid (0.1 mol/L) VS is equivalent to 8.710 mg of $C_6H_{14}N_4O_2$.

Category Amino acid.

Storage Preserve in well closed containers.

Preparation Arginine Hydrochloride Injection

Arginine Hydrochloride



$C_6H_{14}N_4O_2 \cdot HCl$ 210.66

Arginine Hydrochloride is L-2-amino-5-guanidopentanoic acid hydrochloride. It contains not less than 98.5% of $C_6H_{14}N_4O_2 \cdot HCl$, calculated on the dried basis.

Description A white, crystalline powder; the aqueous solution exhibits acid reaction.

Freely soluble in water; very slightly soluble in ethanol.

Specific optical rotation +21.5°-+23.5°, in a solution of 80 mg per ml in hydrochloric acid solution (6 mol/L) (Appendix VI E).

Identification The infrared absorption spectrum (Appendix IV C) is concordant with the reference spectrum of arginine hydrochloride (Appendix XVI).

Transmittance of solution Dissolve 1 g in 10 ml of water, measure the transmittance at 430 nm (Appendix IV A); not less than 98.0%.

Sulfates Carry out the limit test for sulfates (Appendix VIII B), using 0.5 g. Any opalescence produced is not more pronounced than that of a reference solution using 1.0 ml of potassium sulfate standard solution (0.02%).

Phosphates To 0.4 g add 0.3 g of magnesium nitrate and 5 ml of water in a crucible, evaporate to dryness on a water bath and then ignite gently until incineration is complete. Add 5 ml of water and 3 ml of sulfuric acid solution (1→4) to the residue and heat gently for 5 minutes. Add 10 ml of hot water, filter and wash the residue with a quantity of hot water. Combine the filtrate and the washings in a 25 ml Neesler cylinder and dilute to volume with water. Add 1 ml of ammonium molybdate solution [dissolve 0.5 g of ammonium molybdate in 10 ml of sulfuric acid solution (3→100)] and 1 ml of phosphorus TS. Heat the solution at 60°C for 10 minutes, a blue colour produced is not more intense than that of a reference solution prepared in the same manner using 0.8 ml of phosphate standard solution (dissolve 0.143 g of potassium dihydrogen phosphate, accurately weighed, in water to produce 1000 ml) (0.02%).

Ammonium Carry out the limit test for ammonium (Appendix VIII K), using 0.1 g. Any colour produced is not more intense than that of a reference solution using 2.0 ml of ammonium chloride standard solution (0.02%).

Protein Dissolve 1 g in 10 ml of water, add 5 drops of 20% trichloroacetic acid solution, no precipitate is produced.

Other amino acid Carry out the method for thin-layer chromatography (Appendix V B), using silica gel G as the coating substance and a mixture of *n*-propanol-concentrated ammonia solution (2 : 1) as the mobile phase. Apply to the plate 1 µl of a 10 mg per ml solution in water. After developing and removal of the plate, dry it in air, then heat at 105°C for 10 minutes and allow to cool. Spray with a 1% solution of ninhydrin in methanol containing 3% (ml/ml) of acetic acid, heat at 105°C until the colour is produced and examine immediately. No spot other than the principal spot is observed.

Loss on drying When dried to constant weight at 105 °C for 3 hours, loses not more than 0.20% of its weight (Appendix VIII L).

Residue on ignition Not more than 0.1% (Appendix VIII N).

Iron Carry out the limit test for iron (Appendix VIII G), using 2.0 g. Any colour produced is not more intense than that of a reference solution, using 2.0 ml of iron standard solution (0.001%).

Heavy metals Dissolve 2.0 g in 23 ml of water and 2 ml of acetate BS (pH 3.5). Carry out the limit test for heavy metals (Appendix VIII H, method 1); not more than 0.0010%.

Arsenic Dissolve 2.0 g in 23 ml of water, add 5 ml of hydrochloric acid. Carry out the limit test for arsenic (Appendix VIII J, method 1); not more than 0.0001%.

Pyrogens Complies with the test for pyrogens (Appendix XI D), using 10 ml of a solution of 50 mg per ml in sterile Water for Injection per kg of rabbit's weight (for injection).

Chlorine content Dissolve about 0.35 g, accurately weighed, in 20 ml of water, add 2 ml of dilute acetic acid TS and 8-10 drops of bromophenol blue IS. Titrate with silver nitrate (0.1 mol/L) VS until the colour changes to bluishviolet. Each ml of silver nitrate (0.1 mol/L) VS is equivalent to 3.545 mg of Cl. The chlorine content is not less than 16.5% and not more than 17.1%, calculated on the dried basis.

Assay Dissolve about 0.1 g, accurately weighed, in 10 ml of glacial acetic acid and 5 ml of mercuric acetate TS by warming gently. Cool, carry out the method for potentiometric titration (Appendix VII A), titrate with

perchloric acid (0.1 mol/L) VS. Perform a blank determination and make any necessary correction. Each ml of perchloric acid (0.1 mol/L) VS is equivalent to 10.53 mg of $C_6H_{14}N_4O_2 \cdot HCl$.

Category Amino acid.

Storage Preserve in tightly closed containers.

Preparation (1) Arginine Hydrochloride Injection
(2) Arginine Hydrochloride Tablets

Arginine Hydrochloride Injection

Arginine Hydrochloride Injection is a sterile solution of Arginine Hydrochloride in Water for Injections. It contains not less than 95.0% and not more than 105.0% of the labelled amount of arginine hydrochloride ($C_6H_{14}N_4O_2 \cdot HCl$).

Description A colourless, clear liquid.

Identification To a quantity, add 2 mg of ninhydrin and heat, a bluish-violet colour is produced.

pH value 3.0-5.0 (Appendix VI H).

Pyrogens Complies with the test for pyrogens (Appendix XI D), using 5 ml per kg of the rabbit's weight injected slowly.

Other requirements Complies with the general requirements for injection (Appendix I B).

Assay Dilute 10 ml, accurately measured, in a 100 ml volumetric flask, to volume with hydrochloric acid solution (6→10), mix well. Carry out the method for Determination of Optical Rotation (Appendix VI E) and multiply by 4.444 to obtain the amount (g) of $C_6H_{14}N_4O_2 \cdot HCl$ in 10 ml of the substance being examined.

Category As described under Arginine Hydrochloride.

Strength 20 ml : 5 g

Storage Preserve in well closed containers.

Arginine Hydrochloride Tablets

Arginine hydrochloride tablets contain not less than 90.0% and not more than 110.0% of the labelled amount of arginine hydrochloride ($C_6H_{14}N_4O_2 \cdot HCl$).

Description White tablets.

Identification (1) Dissolve a quantity of the powdered tablets, containing 0.25 g of arginine hydrochloride in 5 ml of water, stir and filter. Add 0.5 ml each of α -naphthol solution (dissolve 0.5 g of α -naphthol in 10 ml of 10% sodium hydroxide) and sodium hypobromite solution (dilute 0.2 ml of bromine with 10 ml of 10% sodium hydroxide) into 1 ml of the successive filtrate, a red colour is produced immediately.

(2) Dissolve a quantity of the powdered tablets in water to produce a solution of 10 mg per ml as test solution, prepare a reference solution of 0.1 mg of arginine hydrochloride CRS per ml. Carry out the thin-layer chromatography (Appendix V B), using silica gel G as the coating substance and a mixture of *n*-propanol-concentrated ammonia water (2 : 1) as the mobile phase. Apply separately to the plate 1 µl each of above two solutions, after developing and removal of the plate, dry it in air, heat at 105°C for 10 minutes, cool and spray with 0.5% ninhydrin in acetone, heat at 105°C until

the colour changes and examine immediately. The colour and position of the principal spot in the chromatogram obtained with the test solution corresponds to the principal spot obtained in the reference solution.

(3) The retention time of principal peak of the arginine hydrochloride in the substance being examined in the chromatogram obtained in the Assay is identical with that of the principal peak of arginine hydrochloride CRS in the chromatogram of the reference solution.

(4) The filtrate obtained in the test (1) yields the reactions characteristic of chlorides (Appendix III).

(2) or (3) may be used alternatively.

Other requirements Comply with the general requirements for tablets (Appendix I A).

Assay Carry out the method for high performance liquid chromatography (Appendix V D). Using a column packed with octadecylsilane bonded silica gel and a mixture of 0.05 mol/L acetate BS (pH 6.4)-50% acetonitrile solution (65 : 35) as the mobile phase. Detection wavelength is 362 nm. The number of theoretical plates of the column is not less than 3000, calculated with reference to the peak of arginine hydrochloride. The resolution factor between the peaks of arginine hydrochloride and internal standard substance complies with the related requirements.

Internal standard solution Dissolve a quantity of lactamic acid in water to produce a solution of 0.5 mg per ml, mix well.

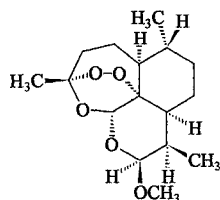
Procedure Weigh accurately and powder finely 20 tablets, weigh accurately a quantity of the powdered tablets equivalent to about 100 mg of arginine hydrochloride to a 100 ml volumetric flask, dilute with water to the volume, mix well, filter and transfer 1 ml each of the filtrate and internal standard solution into a 10 ml volumetric flask, add 1 ml of 0.5 mol/L sodium bicarbonate solution and 150 μ l of 1% 2, 4-dinitrofluorobenzene in acetonitrile, mix well. Allow to stand in a dark place and heat on water bath at $60 \pm 2^\circ\text{C}$ for 60 minutes, cool and dilute with phosphate BS (pH 7.0) to the volume as test solution, mix well. Inject 10 μ l of the test solution into the column and record the chromatogram. Dissolve a quantity of arginine CRS in water to produce a solution of 0.8 mg per ml as reference solution, transfer 1 ml each of the reference solution and internal standard solution into a 10 ml volumetric flask, proceed as described above beginning at the words "add 1 ml of 0.5 mol/L sodium bicarbonate solution..." Repeat the operation, calculate content of $\text{C}_6\text{H}_{14}\text{N}_4\text{O}_2$ with respect to the peak area obtained in the chromatogram by external standard method, the content of $\text{C}_6\text{H}_{14}\text{N}_4\text{O}_2 \cdot \text{HCl}$ is calculated by multiply the result with 1.209.

Category As described under Arginine Hydrochloride.

Strength 0.25 g

Storage Preserve in tightly closed containers and stored in a dry place.

Artemether



Artemether is (3*R*, 5*aS*, 6*R*, 8*aS*, 9*R*, 10*S*, 12*R*, 12*aR*)-decahydro-10-methoxy-3, 6, 9-trimethyl-3, 12-epoxy-12*H*-pyrano [4, 3-*j*]-1, 2-benzodioxepin. It contains not less than 98.0% and not more than 102.0% of $\text{C}_{16}\text{H}_{26}\text{O}_5$, calculated on the dried basis.

Description White crystals or crystalline powder; odourless; taste, slightly bitter.

Very soluble in acetone or chloroform; soluble in ethanol or ethyl acetate; practically insoluble in water.

Melting range $86-90^\circ\text{C}$ (Appendix VI C).

Specific optical rotation $+168^\circ$ to $+173^\circ$, calculated on the dried basis, in a solution of 10 mg per ml in dehydrated ethanol (Appendix VI E).

Identification (1) Dissolve about 30 mg in 1 ml of dehydrated ethanol, add 0.1 g of potassium iodide, shake and heat on hot water; a pale yellow colour is produced.

(2) Dissolve about 30 mg in 6 ml of dehydrated ethanol, place several drops on a white porcelain plate, add 1 drop of 1% anisaldehyde solution in sulfuric acid; a peachblow colour is produced.

(3) Use the solution obtained under related substances as test solution. Prepare a reference solution of 10 mg of artemether CRS per ml in chloroform. Carry out the test described under Related substances, beginning at the words "Carry out the method for thin-layer chromatography..." The colour and position of the principal spot in the chromatogram obtained with the test solution corresponds to those of the principal spot obtained with the reference solution.

(4) The infrared absorption spectrum (Appendix IV C) is concordant with the reference spectrum of artemether CRS (Appendix XVI).

Related substances Carry out the method for thin-layer chromatography (Appendix V B), using silica gel G as the coating substance and a mixture of benzene-ethyl acetate (9 : 1) as the mobile phase. Apply to the plate 5 μ l of the solution in chloroform containing 10 mg per ml of the substance being examined, after developing and removal of the plate, dry it in air and expose it to iodine vapour. No spot other than the principal spot appears.

Chlorides To 0.25 g, add 25 ml of water, shake and filter. Using the filtrate, carry out the limit test for chlorides (Appendix VIII A). Any opalescence produced is not more pronounced than that of a reference solution using 2.5 ml of sodium chloride standard solution (0.01%).

Loss on drying When dried in vacuum over phosphorous pentoxide to constant weight, loses not more than 0.5% of its weight (Appendix VIII L).

Residue on ignition Not more than 0.1% (Appendix VIII N).

Assay Carry out the method for high performance liquid chromatography (Appendix V D), using a column packed with octadecylsilane bonded silica gel and a mixture of water-acetonitrile (45 : 55) as the mobile phase. Detection wavelength is 210 nm and the number of the theoretical plates of the column is not less than 2000, calculated with reference to the peak of artemether.

Procedure Transfer about 0.1 g, accurately weighed, to a 10 ml volumetric flask, dissolve and dilute to volume with mobile phase, and mix well. Inject 20 μ l, accurately measured, into the column, record the chromatogram. Repeat the operation, using an accurately weighed quantity of artemether CRS, instead of the substance being examined. Calculate the content of $\text{C}_{16}\text{H}_{26}\text{O}_5$ with respect to the peak area obtained in the chromatogram by the external standard method.

Category Antimalarial.

Storage Preserve in tightly closed containers, stored in a cool place and protected from light.

Preparation Artemether Capsules

Artemether Capsules

Artemether Capsules contain not less than 90.0% and not more than 110.0% of the labelled amount of artemether ($C_{16}H_{26}O_5$).

Identification (1) Dissolve a quantity of the contents of the capsules equivalent to about 80 mg of artemether in 10 ml of dehydrated ethanol, filter and the filtrate complies with tests (1), (2) for Identification described under Artemether.

(2) Dissolve a quantity of the contents of the capsules in chloroform to produce a solution of 10 mg per ml, filter and the filtrate complies with test (3) for Identification described under Artemether.

Dissolution Carry out the dissolution test (Appendix X C, method 2), using 500 ml of water (for strength 40 mg) or 1000 ml of water (for strength 100 mg) as the dissolution medium, adjust the rotational speed of the paddle to 100 rpm. Withdraw the solution after exactly 60 minutes and filter. Measure accurately 5 ml of the successive filtrate into a 25 ml volumetric flask, dilute to volume with 1.0 mol/L hydrochloric acid solution in dehydrated ethanol, and mix well as the test solution. Weigh accurately about 16 mg of artemether CRS, into a 100 ml volumetric flask, add dehydrated ethanol to dissolve and dilute to volume. Measure accurately 5 ml into a 50 ml volumetric flask, add 5 ml of water and dilute to volume with 1.0 mol/L hydrochloric acid solution in dehydrated ethanol, and mix well as the reference solution. Immerse the two resulting solutions in a water bath at $70^\circ\text{C} \pm 1^\circ\text{C}$ for 90 minutes, cool to room temperature, measure the absorbance of the two solutions at 254 nm (Appendix IV A), using 1.0 mol/L hydrochloric acid solution in dehydrated ethanol as the blank. Calculate the dissolution of $C_{16}H_{26}O_5$ from each capsule. Not less than 65% of the labelled amount is dissolved.

Other requirements Comply with the general requirements for capsules (Appendix I E).

Assay Carry out the method for high performance liquid chromatography (Appendix V D), using a column packed with octadecylsilane bonded silica gel and a mixture of water-acetonitrile (45 : 55) as the mobile phase. Detection wavelength is 210 nm and the number of the theoretical plates of the column is not less than 2000, calculated with reference to the peak of artemether.

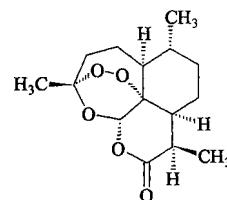
Procedure Triturate a quantity of the mixed contents obtained from the test for weight variation of contents. Weigh accurately a quantity of the powder equivalent to about 100 mg of artemether into a 25 ml volumetric flask, add a quantity of mobile phase, ultrasonic for 10 minutes to dissolve the artemether, cool and dilute to volume with mobile phase, mix well, filter, inject accurately measured 20 μl of successive filtrate into the column. Dissolve an accurately weighed quantity of artemether CRS, in mobile phase to produce a solution of 4 mg per ml. Repeat the operation. Calculate the content of $C_{16}H_{26}O_5$ with respect to the peak area obtained in the chromatogram by the external standard method.

Category as described under Artemether.

Strength (1) 40 mg (2) 100 mg

Storage Preserve in tightly closed containers, stored in a cool place and protected from light.

Artemisinin



$C_{15}H_{22}O_5$ 282.34

[63968-64-9]

Artemisinin is (3*R*,5*αS*,6*R*,8*αS*,9*R*,12*S*,12*αR*)-octahydro-3,6,9-trimethyl-3,12-epoxy-12*H*-pyrano [4,3-*j*]-1,2-benzodioxepin-10 (3*H*)-one. It contains not less than 99.0% of $C_{15}H_{22}O_5$, calculated on the dried basis.

Description Colourless needle crystals; taste, bitter.

Freely soluble in acetone, ethyl acetate, chloroform or, benzene; soluble in methanol, ethanol, dilute ethanol, ether and petroleum ether; practically insoluble in water; Freely soluble in glacial acetic acid.

Melting point 150-153°C (Appendix VI C).

Specific optical rotation +75° to +78°, in a solution of 10 mg per ml in dehydrated ethanol (Appendix VI E).

Identification (1) Dissolve about 5 mg in 0.5 ml of dehydrated ethanol, add 0.4 ml of potassium iodide TS, 2.5 ml of dilute sulfuric acid and 4 drops of starch IS, a violet colour is produced immediately.

(2) Dissolve about 5 mg in 0.5 ml of dehydrated ethanol, add 0.5 ml of hydroxylamine hydrochloride TS and 0.25 ml of sodium hydroxide TS, heat in a water bath to boil gently, cool, add 2 drops of hydrochloric acid and 1 drop of ferric chloride TS, a deep violet-red colour is immediately produced.

(3) The colour and position of the principal spot in the chromatogram obtained under the test for Related substances with the test solution corresponds to that of the principal spot obtained with the reference solution.

(4) The infrared absorption spectrum (Appendix IV C) is concordant with the reference spectrum of artemisinin (Appendix XVI).

Related substances Dissolve the artemisinin CRS and the substance being examined in chloroform to produce the reference solution and test solution each of 10 mg per ml, respectively. Carry out the method for thin-layer chromatography (Appendix V B), using silica gel G as the coating substance and a mixture of petroleum ether (60-90°C) - ether (6 : 4) as the mobile phase. Apply separately to the plate 3 μl each of the two solutions. After developing and removal of the plate, dry it in air and spray with methanolic solution of anisaldehyde (add slowly 10 ml of glacial acetic acid and 5 ml of concentrate sulfuric acid to 55 ml of methanol, cool to room temperature, pour into 30 ml of methanol containing 0.5 ml of anisaldehyde, mix well and protected from light). Heat the plate at 110°C for 3-5 minutes. The colour and position of the principal spot in the chromatogram obtained with test solution corresponds to that of the principal spot obtained with the reference solution and no other spot is detected.

Loss on drying When dried to constant weight at 80°C,

loses not more than 0.5% of its weight (Appendix VIII L).

Residue on ignition Not more than 0.1% (Appendix VIII N).

Assay Dissolve an accurately weighed quantity in ethanol to produce a solution of about 50 µg per ml. Measure accurately 10 ml to a 50 ml volumetric flask, dilute with 0.2% sodium hydroxide solution to volume, mix well, warm in 50°C ± 1°C water bath for 30 minutes, cool to room temperature. Perform a blank determination with 10 ml of ethanol and make any necessary correction. Measure the absorbance of the solution at 292 nm (Appendix IV A). Repeat the operation, using an accurately weighed quantity of artemisinin CRS instead of the substance being examined. Calculate the content of C₁₅H₂₂O₅.

Category Antimalarial.

Storage Preserve in tightly closed containers, protected from light.

Artesunate Tablets

Artesunate tablets contain not less than 90.0% and not more than 110.0% of the labelled amount of artesunate (C₁₉H₂₈O₈).

Description White tablets.

Identification Dissolve a quantity of powdered tablets equivalent to about 0.1 g of artesunate in 2 ml of chloroform, filter. Carry out the following tests with the filtrate.

(1) Place 2-3 drops of filtrate on a white porcelain plate. Add 1 drop of 2% anisaldehyde sulfuric acid solution after the chloroform volatilized, a red colour is produced.

(2) Take 4-5 drops of the filtrate, volatilize the chloroform, add 1 ml of 7% hydroxylamine hydrochloride in 80% ethanol, add 3 ml of ethanolic potassium hydroxide TS, heat in a water bath to boil, cool, acidify with dilute hydrochloric acid and add 1 drop of ferric chloride TS, a purple colour is produced immediately.

Dissolution Carry out dissolution test (Appendix X C, method 2), using water as the dissolution medium, adjust the rotational speed of the paddle to 100 rpm. Withdraw a quantity of the solution after exactly 30 minutes, filter. Measure accurately 20 ml of successive filtrate in a 25 ml volumetric flask, add 2.5 ml of sodium hydroxide solution (1 mol/L), dilute with water to volume, mix well. Weigh accurately 10 mg (50 mg strength) or 20 mg (100 mg strength) of artesunate CRS in a 250 ml volumetric flask, add 200 ml of water and 25 ml of sodium hydroxide solution (1 mol/L), dilute with water to volume, mix well. Warm the two solutions in water bath at 50°C ± 1°C for 45 minutes, cool to room temperature rapidly. Measure the absorbance at 289 nm (Appendix IV A), calculate the dissolution of C₁₉H₂₈O₈ from each tablet. Not less than 60% of the labelled amount is dissolved.

Related substances Dissolve a quantity of the powdered tablets in chloroform to produce a solution of 5 mg per ml and allow to stand as the test solution. Dissolve an accurately weighed quantity of dihydroartemisinin CRS in chloroform to produce a solution of 0.1 mg per ml as the reference solution. Carry out the method for thin-layer chromatography (Appendix V B), using silica gel G as the coating substance and petroleum (60-90°C) -ethyl acetate-glacial acetic acid (48 : 36 : 1) as the mobile phase. Apply separately to the plate 10 µl each of the solutions. After developing and removal of the plate, dry it in air and spray with 2% anisaldehyde solution in sulfuric acid. Any spot, other than the principal spot in the chromatogram obtained

with the test solution is not more intense than the principal spot obtained with the reference solution.

Other requirements Comply with the general requirements for tablets (Appendix I A).

Assay Weigh accurately and powder 20 tablets. To an accurately weighed quantity of the powder equivalent to about 0.5 g of artesunate in a 200 ml conical flask add accurately 50 ml of neutral ethanol (neutral to phenolphthalein IS), shake thoroughly and filter. Measure accurately 25 ml of successive filtrate to a 100 ml conical flask, add 2 drops of phenolphthalein IS, titrate with sodium hydroxide (0.05 mol/L) VS. Each ml of sodium hydroxide (0.05 mol/L) VS is equivalent to 19.22 mg of C₁₉H₂₈O₈.

Category Antimalarial.

Strength (1) 50 mg (2) 100 mg

Storage Preserve in tightly closed containers, protected from light.

Asparaginase

Asparaginase is an enzyme with action of amide hydrolysis obtained from *E. coli* ASI 357 or *Erwinia carotovora*. It has a potency of not less than 250 Asparaginase Units per mg of protein, Calculated on the dried basis.

Description A white crystalline powder; odourless; tasteless. Freely soluble in water; insoluble in ethanol or ether.

Identification (1) Dissolve 5 mg in 1 ml of water, add 5 ml of 20% sodium hydroxide solution, mix well, add 1 drop of 1% cupric sulfate solution, mix well, a blue violet colour is produced.

(2) Dissolve a quantity in 0.1 mol/L phosphate BS (pH 6.7) to produce a solution of 200 units per ml as the test solution; prepare the reference solution in the same manner using asparaginase CRS instead of the substance being examined.

Carry out the method for size-exclusion chromatography (Appendix V H), using a column packed with hydrophilic gel for chromatography and 0.1 mol/L phosphate BS (pH 6.7) as the mobile phase. The flow rate is 0.6 ml per minute and the detection wavelength is 280 nm. Inject separately 20 µl of each of the test solution and the reference solution into the column, record the chromatogram. The retention time of the principal peak of the test solution is identical with that of the reference solution.

Acidity or alkalinity Dissolve a quantity in water to produce a solution of 10 mg per ml, pH 6.5-7.5 (Appendix VI H).

Clarity and colour of solution A solution of 5 mg per ml in water is clear and colourless.

Purity Inject 20 µl of the test solution described under identification (2) into the column, record the chromatogram. The area of the principal peak is not less than 90.0% of the total areas.

Loss on drying When dried at 105°C for 3 hours, loses not more than 5.0% of its weight (Appendix VIII L), using 0.1 g.

Heavy metals Carry out the limit test for heavy metals (Appendix VIII H, method 1), using 0.5 g; not more than 0.002%.

Undue toxicity Dissolve a quantity in Sodium Chloride Injection to produce a solution of 44000 Units per ml. Inject 0.5 ml of the solution into a tail vein of each of 5 healthy

male mice weighing $20 \text{ g} \pm 1 \text{ g}$. None of the mice shows short of breathing or twitching within 30 minutes.

Pyrogens Complies with the test for pyrogens (Appendix XI D), using 1 ml of a solution of 200 Units per ml in Sodium Chloride Injection per kg of rabbit's weight.

Depressor substances Complies with the test for depressor substances (Appendix XI G), using 10000 Units per kg of the cat's weight.

Assay Enzyme activity *Reference solution* Dissolve an accurately weighed quantity of ammonium sulfate previously dried to constant weight at 105°C in water to produce a 0.001 mol/L solution.

Test solution Dissolve about 0.1 g, accurately weighed, in 0.1 mol/L phosphate BS (Adjust the pH value of 0.1 mol/L disodium hydrogen phosphate solution with 0.1 mol/L sodium dihydrogen solution to 8.0) to produce a solution of 5 units per ml.

Procedure To each of three test tubes ($14 \text{ cm} \times 1.2 \text{ cm}$) add accurately 1.9 ml of 0.33% asparagine solution in the phosphate BS described above, warm in a 37°C water bath for 3 minutes, add accurately 0.5 ml of the 25% trichloroacetic acid solution to one tube (t_0), 0.1 ml of the test solution to each of the other tubes (t) respectively, place the tubes in a 37°C water bath for exact 15 minutes. Add 0.1 ml of the test solution to tube and to each tube add 0.5 ml of 25% trichloroacetic acid solution, mix well, as a blank reaction solution (t_0) and reaction solution (t). Measure accurately 0.5 ml of each of t_0 , t and the reference solution separately to each tube, each solution using two tubes, add 7.0 ml of water and 10 ml of mercuric potassium iodide solution (dissolve 23 g of mercuric iodide and 16 g of potassium iodide in water and add to 100 ml, mix with the equal volume of 20% sodium hydroxide solution before using), mix well. To another tube add 7.5 ml of water and 1.0 ml of mercuric potassium iodide solution, as a blank reference solution, allow to stand for 15 minutes, measure the absorbance (A_0 , A_t and A_s) at 450 nm (Appendix IV A) respectively, calculate the average value as follows:

$$\text{Potency} = \frac{(A_t - A_0) \times 5 \times \text{dilution factor} \times F}{A_s \times W}$$

(Unit/mg)

Where 5 is reaction constant;

F is correction factor of concentration of reference solution.

W is the weight of substance being examined (mg)

1 micromol of ammonia is produced per minute when asparagine is decomposed at $37^\circ\text{C} \pm 1^\circ\text{C}$ by 1 Unit of asparaginase.

Content of protein Carry out the method for determination of nitrogen (Appendix VII D, method 2), using about 20 mg, accurately weighed, multiply the result by 6.25 to calculate the content of protein per mg of the substance being examined.

Enzyme Activity Calculate the Enzyme activity from the expression

$$\frac{\text{Enzyme Activity}}{\text{Activity}} = \frac{\text{potency of asparaginase per mg of the substance being examined (Unit)}}{\text{the content of protein per mg of the substance being examined (mg)}}$$

Category Antineoplastic.

Storage Preserve in tightly closed containers, stored in a cold place and protected from light.

Preparation Asparaginase for Injection

Asparaginase for Injection

Asparaginase for Injection is a sterile, lyophilized preparation of asparaginase with a quantity of stabilizing agent and excipient. It contains not less than 85.0% and not more than 115.0% of the labelled potency of asparaginase.

Description A white lyophilized mass or powder.

Identification (1) A solution of 1000 Units per ml in water complies with test (1) for Identification described under Asparaginase.

(2) Complies with test (2) for Identification described under Asparaginase.

Acidity or alkalinity Dissolve each container in 10 ml of water, pH 6.5-7.5 (Appendix VI H).

Purity Carry out the test for Purity described under Asparaginase; not less than 90.0%.

Loss on drying When dried to constant weight at 105°C , loses not more than 5.0% of its weight (Appendix VIII C), using 0.1 g.

Pyrogens Complies with the test for Pyrogens described under Asparaginase, using 2 containers.

Sterility To each container add 2 ml of Water for Injection, the solution complies with the test for sterility (Appendix XI H).

Other requirements Complies with the general requirements for injection except that minor fibrous insoluble matter and slight opalescence is permitted for Clarity (Appendix I B).

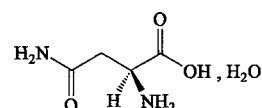
Assay Dissolve each of three containers in 0.1 mol/L phosphate BS (pH 8.0) respectively to produce a solution of about 5 Units per ml. Carry out the Assay described under Asparaginase. The potency per container complies with the related requirement. If one of them fails, repeat the assay using the other three containers, all of them comply with the requirement.

Category As described under Asparaginase.

Strength 10 000 Units

Storage Preserve in tightly closed containers, stored in a cool place and protected from light.

Asparagine



$\text{C}_4\text{H}_8\text{N}_2\text{O}_3 \cdot \text{H}_2\text{O}$ 150.13

[5794-13-8]

Asparagine is the monohydrate of Asparagine. It contains not less than 98.0% of $\text{C}_4\text{H}_8\text{N}_2\text{O}_3$, calculated on the dried basis.

Description White crystals or crystalline powder; odourless. Freely soluble in hot water, practically insoluble in methanol, ethanol or ether; freely soluble in dilute hydrochloric acid or sodium hydroxide TS.

Specific optical rotation $+31^\circ$ to $+35^\circ$, in a solution of 20

mg per ml in 3 mol/L hydrochloric acid solution (Appendix VI E).

Identification (1) Dissolve 1 g in 5 ml of 10% sodium hydroxide solution and heat gently until boiling, vapour is produced which changes the colour of a wet strip of red litmus TP to blue with an odour of ammonia.

(2) Dissolve 1 mg in 5 ml of water, add about 5 mg of ninhydrin and heat. A purple colour is produced.

Transmittance of solution Dissolve 0.4 g in 20 ml of water, the transmittance at 430 nm is not less than 98.0% (Appendix IV A).

Chloride Carry out the limit test for chloride (Appendix VIII A), using 1.0 g. Any opalescence produced is not more pronounced than that of a reference solution using 5.0 ml of sodium chloride standard solution (0.005%).

Sulfate Carry out the limit test for sulfate (Appendix VIII B). Dissolve 2.0 g in 25 ml of water, heat and cool. Any opalescence produced is not more pronounced than that of a reference solution using 1.0 ml of potassium sulfate standard solution (0.005%).

Free amino acid Carry out the method for thin-layer chromatography (Appendix V B), using silica gel G as the coating substance and a mixture of phenol-water (3 : 1) as the mobile phase. Dissolve a quantity of the substance being examined in a small volume of 50% formic acid solution and dilute with water to produce a test solution containing 2 mg per ml. Dissolve a quantity of aspartic acid CRS in a small volume of 50% formic acid solution and dilute with water to produce a reference solution containing 0.05 mg per ml. Apply separately to the plate 5 μ l each of above two solutions. After development and removal of the plate, dry it in air. Spray with a solution of 1% ninhydrin in a mixture of 3 volumes of acetic acid and 97 volumes of methanol, heat at 80°C. The principal spot in the chromatogram obtained with the test solution is not more intense than the principal spot obtained with the reference solution (2.5%).

Loss on drying When dried at 105°C for 3 hours, loses not less than 11.5%, and not more than 12.5% of its weight (Appendix VIII L).

Residue on ignition Not more than 0.1% (Appendix VIII N).

Iron Carry out the limit test for iron (Appendix VIII G), dissolve 1.0 g in 25 ml of water. Any colour produced is not more intense than that of a reference solution using 1.0 ml of iron standard solution (0.001%).

Ammonium Carry out the limit test for ammonium (Appendix VIII K), using 0.02 g. Any opalescence produced is not more intense than that of a reference solution using 2.0 ml of ammonium chloride standard solution (0.1%).

Heavy metals Dissolve 1.0 g in 23 ml of water by heating, add 2 ml of acetate BS (pH 3.5). Carry out the limit test for heavy metals (Appendix VIII H, method 1); not more than 0.001%.

Arsenic Dissolve 2.0 g in a mixture of 23 ml of water and 5 ml of hydrochloric acid. Carry out the limit test for arsenic (Appendix VIII J, method 1); not more than 0.0001%.

Assay Weigh accurately about 0.15 g, carry out the method for determination of nitrogen (Appendix VII D, method 1). Each ml of sulfuric acid (0.05 mol/L) VS is equivalent to 6.606 mg of $C_4H_8N_2O_3$.

Category Amino acid.

Storage Preserve in tightly closed containers, stored in a cool place and protected from light.

Preparation Asparagine Tablets

Asparagine Tablets

Asparagine tablets contain not less than 90.0% and not more than 110.0% of the labelled amount of Asparagine ($C_4H_8N_2O_3$).

Description White tablets.

Identification A quantity of the powdered tablets complies with the tests for identification described under Asparagine.

Other requirements Comply with the general requirements for tablets (Appendix I A).

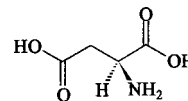
Assay Weigh accurately and powder finely 10 tablets. Accurately weigh a quantity of the powdered tablets equivalent to about 0.15 g of Asparagine. Carry out the Assay described under Asparagine.

Category As described under Asparagine.

Strength 0.25 g (calculated as $C_4H_8N_2O_3$)

Storage Preserve in tightly closed containers, stored in a cool place and protected from light.

Aspartic Acid



$C_4H_7NO_4$ 133.10

Aspartic acid is L-2-aminobutanedioic acid. It contains not less than 98.5% of $C_4H_7NO_4$, calculated on the dried basis.

Description White crystals or a crystalline powder; odourless; taste, slightly sour. Soluble in hot water; slightly soluble in water; insoluble in ethanol; soluble in dilute hydrochloric acid solution or sodium hydroxide solution.

Specific optical rotation +24.0° to +26.0°, in a solution of about 80 mg per ml in 6 mol/L hydrochloric acid solution (Appendix VI E).

Identification The infrared absorption spectrum (Appendix IV C) is concordant with the reference spectrum of aspartic acid (Appendix XVI).

Acidity Dissolve 0.10 g in 20 ml of water, pH 2.0-4.0 (Appendix VI H).

Transmittance of solution Dissolve 1.0 g in 10 ml of 1 mol/L hydrochloric acid solution, the transmittance at 430 nm is not less than 98.0% (Appendix IV A).

Chloride Carry out the limit test for chloride (Appendix VIII A), using 0.30 g. Any opalescence produced is not more pronounced than that of a reference solution using 6.0 ml of sodium chloride standard solution (0.02%).

Sulfate Carry out the limit test for sulfate (Appendix VIII B), using 0.70 g. Any opalescence produced is not more pronounced than that of a reference solution using 1.4 ml of potassium sulfate standard solution (0.02%).

Ammonium Carry out the limit test for ammonium (Appendix VIII K), using 0.10 g. Any colour produced is not more intense than that of a reference solution using 2.0 ml of ammonium chloride standard solution (0.02%).

Other amino acids Carry out the method for thin-layer chromatography (Appendix V B), using silica gel G as the coating substance and *n*-butanol -water-glacial acetic acid (2 : 2 : 1) as the mobile phase. Apply separately to the plate 5 µl of each of two solutions of the substance being examined in water containing (1) 10 mg per ml, (2) 0.05 mg per ml. After developing and removal of the plate, dry it in air and spray with a solution of ninhydrin in acetone (1 → 50), heat at 90°C until the colour is produced and examine immediately. Any spots, other than the principal spot in the chromatogram obtained with solution (1) is not more intense than the principal spot obtained with solution (2).

Loss on drying When dried at 105°C for 3 hours, loses not more than 0.2% of its weight (Appendix VIII L).

Residue on ignition Not more than 0.1% (Appendix VIII N), using 1.0 g.

Iron Carry out the limit test for iron (Appendix VIII G), using 1.0 g. Any colour produced is not more intense than that of a reference solution using 1.0 ml of iron standard solution (0.001%).

Heavy metals Carry out the limit test for heavy metals (Appendix VIII H, method 2), using the residue obtained in the test for Residue on ignition; not more than 0.001%.

Arsenic Dissolve 2.0 g in 23 ml of water, add 5 ml of hydrochloric acid, carry out the limit test for arsenic (Appendix VIII J, method 1); not more than 0.0001%.

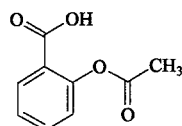
Pyrogens Complies with the test for pyrogens (Appendix XI D), using 10 ml of a solution of 10 mg per ml in Sodium Chloride Injection per kg of the rabbit's weight (for parenteral administration).

Assay Dissolve about 0.1 g, accurately weighed, in 2 ml of anhydrous formic acid, add 30 ml of glacial acetic acid. Carry out the method for potentiometric titration (Appendix VII A), titrate with perchloric acid (0.1 mol/L) VS. Perform a blank determination and make any necessary correction. Each ml of perchloric acid (0.1 mol/L) VS is equivalent to 13.31 mg of $C_9H_7NO_4$.

Category Amino Acid.

Storage Preserve in tightly closed containers.

Aspirin



$C_9H_8O_4$ 180.16

[50-78-2]

Aspirin is 2-(acetyloxy) benzoic acid. It contains not less than 99.5% of $C_9H_8O_4$.

Description White crystals or a white crystalline powder; odourless or with a faint acetic acid odour; taste, faintly sour; gradually hydrolyses in contact with moisture to form salicylic acid and acetic acid; aqueous solution yields an acidic reaction.

Freely soluble in ethanol; soluble in chloroform or ether; slightly soluble in water or anhydrous ether; soluble in

solutions of sodium hydroxide or sodium carbonate with decomposition.

Identification (1) To about 0.1 g add 10 ml of water, boil and cool. Add 1 drop of ferric chloride TS; a violet colour is produced.

(2) To about 0.5 g add 10 ml of sodium carbonate TS, boil for 2 minutes and cool. Add excessive dilute sulfuric acid; a white precipitate is produced and an odour of acetic acid is perceptible.

(3) The infrared absorption spectrum (Appendix IV C) is concordant with the reference spectrum of aspirin (Appendix XVI).

Clarity of solution A solution of 0.50 g in 10 ml of sodium carbonate TS preheated previously to about 45°C is clear.

Salicylic acid Dissolve 0.10 g in 1 ml of ethanol, add cold water to produce 50 ml, add immediately 1 ml of freshly prepared dilute ferric ammonium sulfate solution [to 1 ml of hydrochloric acid solution (9 → 100) add 2 ml of ferric ammonium sulfate IS and add water to produce 100 ml] and mix well; any colour produced within 30 seconds is not more intense than that of a reference solution (dissolve 0.1 g of salicylic acid, accurately weighed, in water, add 1 ml of glacial acetic acid, mix well, add water to produce 1000 ml and mix well. Measure accurately 1 ml, add 1 ml of ethanol, 48 ml of water and 1 ml of freshly prepared dilute ferric ammonium sulfate solution and mix well) (0.1%).

Readily carbonizable substances Carry out the limit test for readily carbonizable substances (Appendix VIII O), using 0.5 g; any colour produced is not more intense than that of a reference preparation (mix 0.25 ml of standard cobalt chloride CS, 0.25 ml of standard potassium dichromate CS, and 0.40 ml of standard copper sulfate CS, with water to produce 5 ml).

Residue on ignition Not more than 0.1% (Appendix VIII N).

Heavy metals Dissolve 1.0 g in 23 ml of ethanol, add 2 ml of acetate BS (pH 3.5) carry out the limit test for heavy metals (Appendix VIII H, method 1); not more than 0.001%.

Assay Dissolve about 0.4 g, accurately weighed, in 20 ml of neutral ethanol (neutral to phenolphthalein IS) and add 3 drops of phenolphthalein IS. Titrate with sodium hydroxide (0.1 mol/L) VS. Each ml of sodium hydroxide (0.1 mol/L) VS is equivalent to 18.02 mg of $C_9H_8O_4$.

Category Antipyretic, anti-inflammatory and analgesic agent, anticoagulant.

Storage Preserve in tightly closed containers, stored in a dry place.

Preparation (1) Aspirin Enteric Capsules
(2) Aspirin Effervescent Tablets
(3) Aspirin Enteric-coated Tablets
(4) Aspirin Suppositories
(5) Aspirin Tablets

Aspirin, Heavy Magnesium Carbonate and Dihydroxyaluminium Aminoacetate Tablets

Aspirin, Heavy Magnesium Carbonate and Dihydroxyaluminium Aminoacetate Tablets contain not less than 95.0% and not more than 105.0% of the labelled amount of aspirin ($C_9H_8O_4$); contain not less than 35.0% and not more than 45.0% of

the labelled amount of heavy magnesium carbonate, calculated with reference to magnesium oxide (MgO); contain not less than 33.0% and not more than 43.0% of the labelled amount of dihydroxyaluminium aminoacetate, calculated with reference to aluminium oxide (Al_2O_3).

Formula	Aspirin	330 g
	Heavy magnesium carbonate	100 g
	Dihydroxyaluminium aminoacetate	50 g
	Tartaric acid	3.3 g
	Excipients	a quantity
	To make	1000 tablets

Description White and yellow double-layer tablets

Identification (1) Boil a quantity of the powder of the white layer equivalent to about 0.1 g of aspirin with 10 ml of water, cool and add 1 drop of ferric chloride TS; a violet colour is produced.

(2) To a quantity of the powder of the yellow layer equivalent to about 0.1 g of heavy magnesium carbonate, add 10 ml of dilute hydrochloric acid; effervescence begins. Gently warm until dissolved. Add sodium hydroxide TS to make the solution alkaline; a white gelatinous precipitate is produced. Filter and divide the precipitate into two portions. To one portion add excessive sodium hydroxide TS, the precipitate is insoluble; to another portion add 3 drops of iodine TS, the precipitate becomes reddish-brown.

(3) Dissolve a quantity of the powder of the yellow layer equivalent to about 0.05 g of dihydroxyaluminium aminoacetate in 5 ml of dilute hydrochloric acid by gentle warming, add dropwise ammonia TS until a white gelatinous precipitate is produced, add a few drops of 1% sodium alizarinsulfonate; the precipitate becomes cherry red.

Free salicylic acid To a quantity of the powder of the white layer equivalent to about 0.1 g of aspirin, add 3 ml of anhydrous chloroform, constantly stir for 2 minutes and filter through a filter paper moistened with anhydrous chloroform. Wash the residue with two portions of anhydrous chloroform, each of 1 ml. Combine the washings and filtrate, evaporate to dryness in the air flow at room temperature. Dissolve the residue in 4 ml of anhydrous ethanol. Transfer the solution to a 100 ml volumetric flask, wash the container with a small amount of 5% ethanol solution, transfer the washings to the same volumetric flask, dilute with 5% ethanol solution to volume and mix well. To 50 ml of the solution, add immediately 1 ml of freshly prepared dilute ferric ammonium sulfate solution (to 1 ml of hydrochloric acid solution (9 → 100), add 2 ml of ferric ammonium sulfate IS and add water to produce 100 ml) and mix well. Any colour produced within 30 seconds is not more intense than that of a reference solution (dissolve 0.1 g of salicylic acid, accurately weighed, in water in a 1000 ml volumetric flask, add 1 ml of glacial acetic acid mix well, dilute with water to volume and mix well. To 1.5 ml of the solution, accurately measured, add 2 ml of anhydrous ethanol and add 5% ethanol solution to produce 50 ml, add 1 ml of the above freshly prepared dilute ferric ammonium sulfate solution and mix well) (0.3%).

Dissolution Carry out the dissolution test (Appendix X, C, method 1), using hydrochloric acid solution 1000 ml (dilute 24 ml of dilute hydrochloric acid with water to 1000 ml) as the dissolution medium, adjust the rotational speed of the basket to 100 rpm. Withdraw 10 ml of the solution after exactly 30 minutes and filter. Transfer 3 ml of the successive filtrate, accurately measured, to a 50 ml volumetric flask, add 5 ml of 0.4% sodium hydroxide solution, boil in a water bath for 5 minutes, cool, add 2.5 ml of dilute sulfuric acid

solution, dilute with water to volume and mix well. Measure the absorbance of the resulting solution at 303 nm (Appendix IV A), calculate the dissolution of $\text{C}_7\text{H}_6\text{O}_3$ from each tablet, taking 265 as the value of A (1%, 1 cm), and multiplying the result by 1.304. Not less than 80% of the labelled amount is dissolved.

Other requirements Comply with the general requirements for tablets (Appendix I A)

Assay *Aspirin* Weigh accurately and powder 10 tablets. Weigh accurately a quantity of the powdered tablets equivalent to about 0.1 g of aspirin into a 50 ml volumetric flask, add a quantity of anhydrous ethanol, shake for 15 minutes to dissolve aspirin, dilute to volume with anhydrous ethanol and mix well. Filter, transfer 1 ml of the successive filtrate, accurately measured, to a 25 ml volumetric flask, add anhydrous ethanol to volume and mix well. Dissolve an accurately weighed quantity of aspirin CRS in anhydrous ethanol to produce a solution of about 80 µg per ml. Measure the absorbances of the resulting solutions at 276 nm (Appendix IV A). Calculate the content.

Magnesium Oxide To an accurately weighed quantity of the powdered tablets equivalent to about 0.1 g of heavy magnesium carbonate in a beaker, add 5 ml of hydrochloric acid and 25 ml of water, boil to dissolve heavy magnesium carbonate, cool to room temperature with constant stirring. Filter, wash the residue and the container with 25 ml of water in several portions. Combine the washings and filtrate, add 1 drop of methyl red IS, add ammonia TS dropwise until the colour changes from red to yellow, continue to boil for 5 minutes. Filter while hot, wash the residue and the container with 30 ml of 2% ammonium chloride solution. Combine the washings and filtrate, cool, add 5 ml of triethanolamine solution (1 → 2) and 10 ml of ammonia-ammonium chloride BS (pH 10.0), add a small amount of eriochrome black T indicator after cooling in an ice bath for 10 minutes, rapidly titrate with disodium edeate (0.05 mol/L) VS towards the end point, continue the titration until the colour changes from claret to bluish purple. Each ml of disodium edeate (0.05 mol/L) VS is equivalent to 2.015 mg of MgO .

Aluminium Oxide Weigh accurately a quantity of the above powdered tablets equivalent to about 0.05 g of dihydroxyaluminium aminoacetate into a small beaker, add 6 ml of hydrochloric acid solution (1 → 2), warm gently to dissolve the dihydroxyaluminium aminoacetate, add 20 ml of water, boil and cool to room temperature with constant stirring. Filter, wash the residue and the container with 25 ml of water in several portions. Combine the washings and filtrate, add ammonia TS dropwise until a precipitate is just produced. Add hydrochloric acid dropwise until the precipitate is just dissolved. Add 10 ml of ammonium acetate BS (pH 6.0), add 25 ml of disodium edeate (0.05 mol/L) VS, accurately measured, boil for 10 minutes, add 1 ml of xylenol orange IS, titrate with zinc (0.05 mol/L) VS until the colour changes from yellow to red. Perform a blank determination and make any necessary correction. Each ml of disodium edeate (0.05 mol/L) VS is equivalent to 2.549 mg of Al_2O_3 .

Category Analgesic; antipyretic; nonsteroidal anti-inflammatory.

Storage Preserve in tightly closed containers, stored in a dry place and protected from light.

Aspirin Effervescent Tablets

Aspirin Effervescent Tablets contain not less than

90.0% and not more than 110.0% of the labelled amount of aspirin ($C_9H_8O_4$).

Description White tablets.

Identification (1) Add 10 ml of water to a quantity of the powdered tablets equivalent to about 0.1 g of aspirin, heat to boil, allow to cool and add a drop of ferric chloride TS; a violet colour is produced.

(2) The retention time of the principal peak of aspirin in the test solution in the chromatogram obtained in the Assay is identical with that of the principal peak of aspirin CRS in the chromatogram of the reference solution.

Salicylic acid Carry out the method for high performance liquid chromatography described under Assay, the detection wavelength is 300 nm. Inject 10 μ l of the test solution obtained in Assay into the column, record the chromatogram. Dissolve a quantity of salicylic acid CRS in a mixture of acetonitrile-methanol-formic acid (40 : 59 : 1) to produce a solution of 15 μ g per ml. Repeat the operation described above, and calculate the content of salicylic acid with respect to the peak area obtained in the chromatogram by the external standard method. The content of salicylic acid is not more than 3.0% of the labelled amount of aspirin.

Other requirement Comply with the general requirements for tablets (Appendix I A), except test for friability.

Assay Carry out the method for high performance liquid chromatography (Appendix V D), using a column packed with octadecylsilane bonded silica gel and a mixture of acetonitrile-methanol-0.01 mol/L potassium dihydrogen phosphate solution-triethylamine (10 : 50 : 40 : 0.11, adjust pH to 3.3-3.4 with phosphoric acid) as the mobile phase. Detection wavelength is 280 nm, the number of theoretical plates of the column is not less than 2000, calculated with reference to the peak of aspirin. The resolution factor between the peaks of aspirin and salicylic acid complies with the related requirements.

Procedure Weigh accurately and powder 10 tablets. Weigh accurately a quantity of the powder equivalent to about 25 mg of aspirin in a 100 ml conical flask, add accurately 50 ml of a mixture of acetonitrile-methanol-formic acid (40 : 59 : 1), shake thoroughly for 10 minutes to dissolve aspirin, filter quickly. Inject 10 μ l of the successive filtrate into the column, record the chromatogram. Dissolve a quantity of aspirin CRS in a mixture of acetonitrile-methanol-formic acid (40 : 59 : 1) to produce a solution of 0.5 mg per ml. Repeat the operation, and calculate the content of $C_9H_8O_4$ with respect to the peak area obtained in the chromatogram by the external standard method.

Category As described under Aspirin.

Strength (1) 0.1 g (2) 0.5 g

Storage Preserve in tightly closed containers, stored in a dry place.

Aspirin Enteric Capsules

Aspirin Enteric Capsules contain not less than 93.0% and not more than 107.0% of the labelled amount of aspirin ($C_9H_8O_4$).

Description Capsules containing white granules.

Identification (1) Add 10 ml of water to a quantity of the contents equivalent to about 0.1 g of aspirin, heat to boil, allow to cool and add a drop of ferric chloride TS; a violet colour is produced.

(2) The retention time of the principal peak of aspirin in the test solution in the chromatogram obtained in the Assay is identical with that of the principal peak of aspirin CRS in the chromatogram of the reference solution correspondingly.

Salicylic acid Carry out the method for high performance liquid chromatography described under Assay, the detection wavelength is 300 nm. Weigh accurately a quantity of the contents obtained on the Assay, equivalent to about 0.1 g of aspirin, in a 100 volumetric flask, dilute with 1% glacial acetic acid solution in anhydrous methanol to volume, mix well, filter and inject 20 μ l of the successive filtrate into the column, record the chromatogram. Dissolve a quantity of salicylic acid CRS with 1% glacial acetic acid solution in anhydrous methanol to produce a solution of 30 μ g per ml. Repeat the operation mentioned above, and calculate the content of salicylic acid with respect to the peak area obtained in the chromatogram by the external standard method. The content of salicylic acid is not more than 3.0% of the labelled amount of aspirin.

Drug release (1) *The amount released in acid solution* Comply with the requirements for Drug Release Test [Appendix X D, method 2 (2)], using the apparatus of the dissolution test method I and 500 ml of 0.1 mol/L hydrochloric acid solution as the dissolution medium. Adjust the rotational speed of the basket to 100 rpm. Withdraw the solution after exactly 2 hours, and filter. Inject 20 μ l of the successive filtrate into the column, record the chromatogram. Dissolve a quantity of aspirin CRS in 0.1 mol/L hydrochloric acid solution to produce a solution of 20 μ g per ml. Repeat the operation, and calculate the content of $C_9H_8O_4$ released from each capsule in acid solution.

(2) *The amount released in buffer solution* Drain above 0.1 mol/L hydrochloric acid solution from each of 6 vessels and add immediately 1000 ml of phosphate BS (pH 6.8) at $37^\circ\text{C} \pm 0.5^\circ\text{C}$. Continue to operate the apparatus, withdraw the solution after exactly 45 minutes, and filter. Inject 20 μ l of the successive filtrate into the column, record the chromatogram. Dissolve a quantity of aspirin CRS in phosphate BS (pH 6.8) to produce a solution of 0.1 mg per ml. Repeat the operation, and calculate the content of $C_9H_8O_4$ released from each capsule in the buffer solution.

Other requirement Comply with the general requirements for capsules (Appendix I E).

Assay Carry out the method for high performance liquid chromatography (Appendix V D), using a column packed with octadecylsilane bonded silica gel and a mixture of 1% glacial acetic acid solution-methanol (50 : 50) as the mobile phase. Detection wavelength is 280 nm, the number of theoretical plates of the column is not less than 1500, calculated with reference to the peak of aspirin. The resolution factor between the peaks of aspirin and salicylic acid complies with the related requirements.

procedure Dissolve an accurately weighed quantity (equivalent to about 0.1 g of aspirin) of mixed contents obtained in the test for weight variation with 1% glacial acetic acid solution in anhydrous methanol in a 100 ml volumetric flask and dilute to volume, mix well, and filter. Transfer 5 ml of successive filtrate into a 100 volumetric flask and dilute with 1% glacial acetic acid solution in anhydrous methanol to volume, mix well. Inject 20 μ l of the successive filtrate into the column, record the chromatogram. Dissolve a quantity of aspirin CRS with 1% glacial acetic acid solution in anhydrous methanol to produce a solution of 50 μ g per ml. Repeat the operation, and calculate the content of $C_9H_8O_4$ with respect to the peak area obtained in the chromatogram by the external standard method.

Category As described under Aspirin.

Strength 0.1 g

Storage Preserve in tightly closed containers, stored in a dry place.

Aspirin Enteric-coated Tablets

Aspirin Enteric-coated Tablets contain not less than 95.0% and not more than 105.0% of the labelled amount of aspirin ($C_9H_8O_4$).

Description Enteric-coated tablets, with white core.

Identification To a quantity of the powdered tablets equivalent to about 0.1 g of aspirin add 10 ml of water, boil, cool and add 1 drop of ferric chloride TS; a violet colour is produced.

Salicylic acid Triturate 5 tablets with 30 ml of ethanol in portions and transfer the mixture to a 100 ml volumetric flask, shake thoroughly, dilute with water to volume, mix well, filter immediately. Measure accurately 2 ml of the successive filtrate in a Nessler cylinder, add water to produce 50 ml, then add immediately 3 ml of freshly prepared dilute ferric ammonium sulfate solution [to 1 ml of 1 mol/L hydrochloric acid solution, add 2 ml of ferric ammonium sulfate IS and add water to produce 100 ml], and mix well; any colour produced within 30 seconds is not more intense than that of a reference solution (To 4.5 ml of 0.01% salicylic acid solution, accurately measured, add 3 ml of ethanol, 1 ml of 0.05% tartaric acid solution, dilute with water to produce 50 ml, add 3 ml of freshly prepared dilute ferric ammonium sulfate solution and mix well) (1.5%).

Drug release Comply with the drug release test [Appendix X D, method 2 (1)], using the apparatus of the dissolution test method I and 750 ml of 0.1 mol/L hydrochloric acid as the dissolution medium. Adjust the rotational speed of the basket to 100 rpm. Withdraw 10 ml of the solvent after exactly 120 minutes, filter, use the successive filtrate as the test solution (1). Then add 250 ml of 37°C 0.2 mol/L sodium phosphate solution, mix well, adjust the pH to 6.8 ± 0.05 with 2 mol/L hydrochloric acid solution or 2 mol/L sodium hydroxide solution. Withdraw 10 ml of the buffer solution after exactly 45 minutes and filter, use the successive filtrate as the test solution (2). Measure the absorbance of the test solution (1) at 280 nm, using 0.1 mol/L hydrochloric acid solution as the blank; the absorbance is not more than 0.25. Weigh accurately 21 mg of aspirin CRS in a 100 ml volumetric flask, add a quantity of sodium phosphate BS (0.05 mol/L) (measure 250 ml of 0.2 mol/L sodium phosphate solution and 750 ml of 0.1 mol/L hydrochloric acid solution, mix well, adjust to pH 6.8 ± 0.05) to dissolve and dilute to volume, as the reference solution. Measure the absorbance of the test solution (2) and the reference solution at 265 nm, using sodium phosphate BS (0.05 mol/L) as the blank. Calculate the amount of $C_9H_8O_4$ released from each tablet; not less than 70% of the labelled amount is released.

Other requirement Comply with the general requirements for tablets (Appendix I A).

Assay Weigh accurately and powder 10 tablets, triturate with divided portions of 70 ml neutral ethanol and transfer to a 100 ml volumetric flask, shake thoroughly, wash the mortar several times with sufficient water, combine the washings to the flask, dilute with water to volume, mix well and filter. Measure accurately 10 ml of the successive

filtrate equivalent to about 0.3 g of aspirin into a conical flask, add 20 ml of neutral ethanol (neutral to phenolphthalein IS), shake well. Add 3 drops of phenolphthalein IS and sodium hydroxide (0.1 mol/L) VS dropwise until the solution becomes pink. Add 40 ml of sodium hydroxide (0.1 mol/L) VS, accurately measured, heat on a water bath for 15 minutes with shaking, cool immediately to room temperature and titrate with sulfuric acid (0.05 mol/L) VS. Perform a blank determination and make any necessary correction. Each ml of sodium hydroxide (0.1 mol/L) VS is equivalent to 18.02 mg of $C_9H_8O_4$.

Category As described under Aspirin.

Strength 0.3 g

Storage Preserve in tightly closed containers, stored in a dry place.

Aspirin Suppositories

Aspirin suppositories contain not less than 90.0% and not more than 110.0% of the labelled amount of aspirin ($C_9H_8O_4$).

Description Creamy-white or slightly yellow suppositories.

Identification Warm to dissolve a quantity equivalent to about 0.6 g of aspirin with 20 ml of ethanol, cool in an ice bath for 5 minutes and stir constantly, filter, evaporate the filtrate on a water bath to dryness. The residue complies with the tests (1), (2) for Identification described under Aspirin.

Salicylic acid Carry out the method for high performance liquid chromatography described under Assay, the wave length of the detector is 300 nm. Dissolve a quantity of salicylic acid CRS with ethanol to produce a solution of 15 µg per ml as the reference solution. Inject 10 µl of the solution into the column and record the chromatogram. Inject 10 µl of diluted solution of the successive filtrate obtained from the Assay (diluted with ethanol to produce a solution of 0.5 mg per ml) into the column; calculate the content of salicylic acid with respect to peak area obtained in the chromatogram by external standard method. The salicylic acid is not more than 3.0% of the labelled amount of aspirin.

Other requirements Comply with the general requirements for suppositories (Appendix I D).

Assay Carry out the method for high performance liquid chromatography (Appendix V D), using a column packed with octadecylsilane bonded silica gel and a mixture of methanol-0.1% diethylamine solution glacial acetic acid (40 : 60 : 4) as the mobile phase. The detection wavelength is 280 nm and the number of theoretical plates of the column is not less than 2000, calculated with reference to the peak of aspirin and the resolution factors between the peaks of aspirin, salicylic acid and internal standard comply with the related requirements.

Internal Standard Solution Dissolve a quantity of caffeine with ethanol to produce a solution of 4 mg per ml as the internal standard.

Procedure Melt 5 suppositories in a small beaker, accurately weighed, on a 40-50°C water bath, cool to room temperature with stirring, weigh accurately a quantity (equivalent to about 0.15 g of aspirin) in a 50 ml volumetric flask, add 5 ml of the internal standard solution accurately measured and a quantity of ethanol, warm on a 40-50°C water bath, shake thoroughly to dissolve aspirin, dilute with ethanol to volume and then set in an ice bath for 1 hour,

filter immediately; measure accurately 2 ml of the successive filtrate to a 50 ml volumetric flask, dilute with ethanol to volume, mix well. Inject 10 μ l into the column, record the chromatogram. Dissolve about 0.15 g of aspirin CRS, accurately weighed, in a 50 ml volumetric flask, add 5 ml of the internal standard and dilute with ethanol to volume, mix well. Measure accurately 2 ml of the solution in a 50 ml volumetric flask, dilute with ethanol to volume, mix well. Repeat the operation. Calculate the content of $C_9H_8O_4$ with respect to the peak area obtained in the chromatogram by internal standard method.

Category As described under Aspirin.

Strength (1) 0.1 g (2) 0.3 g (3) 0.45 g (4) 0.5 g

Storage Preserve in tightly closed containers, stored in a cool and dry place.

Aspirin Tablets

Aspirin Tablets contain not less than 95.0% and not more than 105.0% of the labelled amount of aspirin ($C_9H_8O_4$).

Description White tablets, deteriorated on exposure to moisture.

Identification (1) To a quantity of the powdered tablets equivalent to about 0.1 g of Aspirin add 10 ml of water, boil, cool and add 1 drop of ferric chloride TS; a violet colour is produced.

(2) To a quantity of the powdered tablets equivalent to about 0.5 g of Aspirin add 10 ml of sodium carbonate TS, shake and allow to stand for 5 minutes. Filter, boil the filtrate for 2 minutes, cool and add a few drops of sulfuric acid; a white precipitate is produced and an odour of acetic acid is perceptible.

Salicylic acid To a quantity of the powdered tablets equivalent to about 0.1 g of Aspirin add 3 ml of anhydrous chloroform, stir continuously for 2 minutes and filter with a filter paper moistened with anhydrous chloroform. Wash the residue twice with each of 1 ml of anhydrous chloroform, combine the filtrate and washings, evaporate to dryness at room temperature. Dissolve the residue in 4 ml of dehydrated ethanol and transfer to a 100 ml volumetric flask. Wash the container with 5% ethanol and combine the washings to the volumetric flask, dilute with 5% ethanol to volume and mix well. Measure 50 ml of the solution and add immediately 1 ml of freshly prepared dilute ferric ammonium sulfate solution [to 1 ml of hydrochloric acid solution (9→100) add 2 ml of ferric ammonium sulfate IS and add water to produce 100 ml], mix well; any colour produced within 30 seconds is not more intense than that of a reference solution (dissolve 0.1 g of salicylic acid, accurately weighed, in water in a 1000 ml volumetric flask, add 1 ml of glacial acetic acid, mix well, add water to volume and mix well; measure accurately 1.5 ml, add 2 ml of dehydrated ethanol and sufficient 5% ethanol to produce 50 ml, add 1 ml of freshly prepared ferric ammonium sulfate solution, and mix well) (0.3%).

Dissolution Carry out the dissolution test (Appendix X C, method 1), using hydrochloric acid solution 1000 ml (dilute 24 ml of dilute hydrochloric acid with water to 1000 ml) as the dissolution medium, adjust the rotational speed of the basket to 100 rpm. Withdraw 10 ml of the solution after exactly 30 minutes and filter. Transfer 3 ml of the successive filtrate, accurately measured, to a 50 ml volumetric flask, add 5 ml of 0.4% sodium hydroxide

solution, boil in a water bath for 5 minutes and cool. Add 2.5 ml of dilute sulfuric acid, dilute with water to volume and mix well. Measure the absorbance at 303 nm (Appendix IV A). Calculate the dissolution of $C_9H_8O_4$ from each tablet, taking 265 as the value of A (1%, 1 cm) for $C_7H_6O_3$ and multiply the result by 1.304. Not less than 80% of the labelled amount is dissolved.

Other requirements Comply with the general requirements for tablets (Appendix I B).

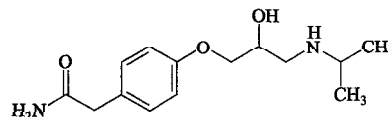
Assay Weigh accurately and powder 10 tablets. Weigh accurately a quantity of the powder equivalent to about 0.3 g of Aspirin in a conical flask, add 20 ml of neutral ethanol (neutral to phenolphthalein IS), shake thoroughly. Add 3 drops of phenolphthalein IS and add dropwise sodium hydroxide (0.1 mol/L) VS until the solution becomes pink. Add 40 ml of sodium hydroxide (0.1 mol/L) VS, accurately measured, heat on a water bath for 15 minutes with shaking, cool immediately to room temperature and titrate with sulfuric acid (0.05 mol/L) VS. Perform a blank determination and make any necessary correction. Each ml of sodium hydroxide (0.1 mol/L) VS is equivalent to 18.02 mg of $C_9H_8O_4$.

Category As described under Aspirin.

Strength (1) 0.3 g (2) 0.5 g

Storage Preserve in tightly closed containers, stored in a dry place.

Atenolol



$C_{14}H_{22}N_2O_3$ 266.34

[29122-68-7]

Atenolol is 4-[3-[(1-methylethyl) amino-2-hydroxy] propoxy] benzeneacetamide. It contains not less than 98.0% of $C_{14}H_{22}N_2O_3$, calculated on the dried basis.

Description A white powder; odourless or slightly odour. Soluble in ethanol; slightly soluble in chloroform or water; practically insoluble in ether.

Melting point 151-155°C (Appendix VI C).

Identification (1) The light absorption of a 10 μ g per ml solution in dehydrated ethanol exhibits maxima at 227 nm, 276 nm and 283 nm (Appendix IV A).

(2) The infrared absorption spectrum (Appendix IV C) is concordant with the reference spectrum of atenolol (Appendix XVI).

Clarity of solution Dissolve 50 mg in 10 ml of water and 5 ml of dilute hydrochloric acid, the solution is clear.

Related substance Carry out the method described under Assay. Dissolve a quantity of the substance being examined with the mobile phase by ultrasonic, dilute with the mobile phase to produce a solution of 0.1 mg per ml as the test solution; Dilute 1 ml of test solution, accurately measured, with the mobile phase to 100 ml and mix well as the reference solution. Inject 20 μ l of the reference solution into the column, adjust the attenuation so that the principal peak height in the chromatogram is 20% of full scale of the chart; Inject separately accurately measured 20 μ l each of the test

solution and the reference solution into the column, record the chromatogram for three times the retention time of the principal peak. The sum of the areas of all peaks other than the principal peak are not greater than the area of the principal peak in the chromatogram obtained with the reference solution.

Loss on drying When dried to constant weight at 105°C, loses not more than 1.0% of its weight (Appendix VIII L).

Residue on ignition Not more than 0.1% (Appendix VIII N).

Assay Carry out the method for high performance liquid chromatography (Appendix V D), using a column packed with octadecylsilane bonded silica gel and a mixture of 700 ml of phosphate BS (dissolve 6.8 g of potassium dihydrogen phosphate with water and dilute to 1000 ml, adjust the pH to 3.0 with phosphoric acid), 300 ml of methanol and 1.30 g of sodium octanesulfonate as the mobile phase. Detection wavelength is 275 nm and the number of theoretical plates of the column is not less than 2000, calculated with reference to the peak of atenolol. The resolution factor between the peaks of atenolol and internal standard complies with the related requirements.

Internal standard solution Dissolve a quantity of phenacetine with the mobile phase to produce a solution of 80 µg per ml.

Procedure Dissolve an accurately weighed quantity, in the mobile phase with ultrasonic treatment to produce a solution of 0.32 mg per 1 as the test solution. Dilute 5 ml each of the test solution and the internal standard solution, both accurately measured, with the mobile phase to 25 ml, mix well. Inject 20 µl of the resulting solution into the column, record the chromatogram. Repeat the operation, using an accurately weighed quantity of atenolol CRS instead of the substance being examined, calculate the content of $C_{14}H_{22}N_2O_3$ with respect to the peak area obtained in the chromatogram by the internal standard method.

Category β -adrenoreceptor antagonist.

Storage Preserve in tightly closed containers.

Preparation Atenolol Tablets

Atenolol Tablets

Atenolol Tablets contain not less than 90.0% and not more than 110.0% of the labelled amount of atenolol ($C_{14}H_{22}N_2O_3$).

Description White or sugar-coated tablets with white core.

Identification Comply with test (1) for Identification described under Atenolol, using the test solution obtained in the Assay.

Related substance Comply with the test for Related substance described under Atenolol. Dissolve a quantity of powdered tablets equivalent to about 0.10 g of atenolol with the mobile phase by ultrasonic, dilute with the mobile phase to 100 ml and mix well, filter, take the successive filtrate as the test solution.

Dissolution Carry out the dissolution test (Appendix X C, method 2), using hydrochloric acid solution (9 → 1000) 1000 ml as the dissolution medium, adjust the rotational speed of the paddle to 50 rpm. Withdraw 10 ml of the solution after exactly 45 minutes and filter. Dilute a quantity of the successive filtrate with the dissolution medium to produce a solution of about 10 µg per ml. Dissolve an accurately weighed quantity of atenolol CRS in the dissolution

medium to produce a solution of about 10 µg per ml. Measure the absorbance at 224 nm (Appendix IV A), calculate the dissolution of $C_{14}H_{22}N_2O_3$ from each tablet. Not less than 70% of the labelled amount is dissolved.

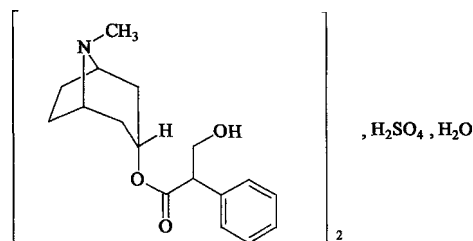
Other requirements Comply with the general requirements for tablets (Appendix I A).

Assay Weigh accurately and powder 10 tablets, with the coating removed if the tablets are sugar coated. Triturate a quantity of the powder equivalent to about 35 mg of atenolol, accurately weighed, in a mortar with a quantity of dehydrated ethanol. Transfer with dehydrated ethanol in portions to a 50 ml volumetric flask, dilute to volume and mix well. Filter. Transfer 5 ml of the successive filtrate, accurately measured, to another 50 ml volumetric flask, dilute with dehydrated ethanol to volume and mix well. Measure the absorbance of the resulting solution and that of a 70 µg per ml solution of atenolol CRS in dehydrated ethanol at 276 nm (Appendix IV A). Calculate the content of $C_{14}H_{22}N_2O_3$.

Category, Storage As described under Atenolol.

Strength (1) 25 mg (2) 50 mg (3) 100 mg

Atropine Sulfate



$(C_{17}H_{23}NO_3)_2 \cdot H_2SO_4 \cdot H_2O$ 694.84 [5908-99-6]

Atropine Sulfate is 8-methyl-8-azabicyclo [3, 2, 1]-oct-3-ol ester of α -(hydroxymethyl) benzeneacetic acid, sulfate (2 : 1), monohydrate. It contains not less than 98.5% of $(C_{17}H_{23}NO_3)_2 \cdot H_2SO_4$, calculated on the dried basis.

Description Colourless crystals or a white crystalline powder; odourless.

Very soluble in water; freely soluble in ethanol.

Melting point Not lower than 189°C, with decomposition, determined after drying at 120°C for 3 hours (Appendix VI C).

Identification (1) The infrared absorption spectrum (Appendix IV C) is concordant with the reference spectrum of atropine sulfate (Appendix XVI).

(2) Yields the reactions characteristic of tropane alkaloids (Appendix III).

(3) The aqueous solution yields the reactions characteristic of sulfates (Appendix III).

Acidity Dissolve 0.50 g in 10 ml of water, add 1 drop of methyl red IS and titrate with sodium hydroxide (0.02 mol/L) VS; not more than 0.15 ml is required to produce a yellow colour.

Hyoscyamine Carry out the determination of optical rotation (Appendix VI E), using a solution of 50 mg per ml, calculated on the dried basis, in water; the optical rotation is not more than -0.40° .

Other alkaloids Dissolve 0.25 g in 1 ml of hydrochloric acid solution (9→1000). Dilute with water to produce 15 ml, add 2 ml of ammonia TS to 5 ml of the solution and mix; no opalescence is produced immediately.

Loss on drying When dried at 120°C for 3 hours, loses not more than 5.0% of its weight (Appendix VIII L).

Residue on ignition Not more than 0.1% (Appendix VIII N).

Assay Dissolve 0.5 g, accurately weighed, in a mixture of 10 ml of glacial acetic acid and 10 ml of acetic anhydride, add 1-2 drops of crystal violet IS and titrate with perchloric acid (0.1 mol/L) VS until the colour changes to pure blue. Perform a blank determination and make any necessary correction. Each ml of perchloric acid (0.1 mol/L) VS is equivalent to 67.68 mg of $(C_{17}H_{23}NO_3)_2 \cdot H_2SO_4$.

Category Anticholinergic.

Storage Preserve in tightly closed containers.

Preparation (1) Atropine Sulfate Injection
(2) Atropine Sulfate Tablets

Atropine Sulfate Injection

Atropine Sulfate Injection is a sterile solution of atropine sulfate in Water for Injection. It contains not less than 90.0% and not more than 110.0% of the labelled amount of atropine sulfate $[(C_{17}H_{23}NO_3)_2 \cdot H_2SO_4 \cdot H_2O]$.

Description A clear, colourless liquid.

Identification (1) Evaporate a quantity equivalent to about 5 mg of atropine sulfate on a water bath to dryness; the residue yields the reactions characteristic of tropane alkaloids (Appendix III).

(2) Yields the reactions characteristic of sulfates (Appendix III).

pH value 3.5-5.5 (Appendix VI H).

Other requirements Complies with the general requirements for injections (Appendix I B).

Assay Measure accurately a quantity equivalent to about 2.5 mg of atropine sulfate to a 50 ml volumetric flask, dilute with water to volume and mix well, using the resulting solution as the Test solution. Weigh accurately 25 mg of atropine sulfate CRS, to a 25 ml volumetric flask, dissolve in water to volume and mix well. Transfer 5 ml of the solution, accurately measured, to a 100 ml volumetric flask, dilute with water to volume, as the reference solution. Transfer separately 2 ml each of the test solution and the reference solution, accurately measured, to two separators each containing 10 ml of chloroform. Add 2.0 ml of bromocresol green solution [dissolve 50 mg of bromocresol green and 1.021 g of potassium hydrogen phthalate in 6.0 ml of sodium hydroxide solution (0.2 mol/L), dilute with water to produce 100 ml, filter if necessary] to each separator, extract for 2 minutes and allow to separate into two layers. Measure the absorbance of the chloroform layers at 420 nm (Appendix IV A), calculate the content of $(C_{17}H_{23}NO_3)_2 \cdot H_2SO_4 \cdot H_2O$ and multiply by 1.027.

Category As described under Atropine Sulfate.

Strength (1) 1 ml : 0.5 mg (2) 1 ml : 1 mg
(3) 1 ml : 2 mg (4) 1 ml : 5 mg
(5) 1 ml : 10 mg (6) 2 ml : 1 mg
(7) 2 ml : 5 mg (8) 2 ml : 10 mg

Storage Preserve in well closed containers.

Atropine Sulfate Tablets

Atropine Sulfate Tablets contain not less than 90.0% and not more than 110.0% of the labelled amount of atropine sulfate $[(C_{17}H_{23}NO_3)_2 \cdot H_2SO_4 \cdot H_2O]$.

Description White tablets.

Identification (1) Transfer a quantity of powdered tablets equivalent to about 1 mg of atropine sulfate into a separator, add 5 ml of ammonia TS and extract with 10 ml of ether. Transfer the ether layer to a porcelain dish and evaporate to dryness. The residue yields the reaction characteristic of tropane alkaloids (Appendix III).

(2) The aqueous solution yields the reactions characteristic of sulfates (Appendix III).

Content uniformity Comply with the requirement (Appendix X E). Transfer 1 tablet to a stoppered test tube, add 6.0 ml of water, accurately measured. Shake thoroughly for 30 minutes and centrifuge. Carry out the method described under the Assay, using the supernatant liquids as the test solution.

Other requirements Comply with the general requirements for tablets (Appendix I A).

Assay Weigh accurately and powder 20 tablets. Transfer a quantity of the powdered tablets equivalent to about 2.5 mg of atropine sulfate, accurately weighed, to a 50 ml volumetric flask, add water and shake to dissolve atropine. Dilute with water to volume and filter. The successive filtrate is used as the test solution. Weigh accurately 25 mg of atropine sulfate CRS, to a 25 ml volumetric flask, dissolve in water to volume and mix well. Transfer 5 ml of the solution, accurately measured, to a 100 ml volumetric flask, dilute with water to volume, as the reference solution.

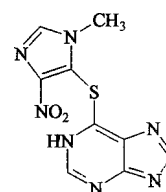
Transfer separately 2 ml each of the test solution and the reference solution, accurately measured, to two separators each containing 10 ml of chloroform. Add 2.0 ml of bromocresol green solution [dissolve 50 mg of bromocresol green and 1.021 g of potassium hydrogen phthalate in 6.0 ml of sodium hydroxide solution (0.2 mol/L), dilute with water to produce 100 ml, filter if necessary] to each separator, extract for 2 minutes and allow to separate into two layers. Measure the absorbance of the chloroform layers at 420 nm (Appendix IV A), calculate the content of $(C_{17}H_{23}NO_3)_2 \cdot H_2SO_4 \cdot H_2O$ and multiply by 1.027.

Category As described under Atropine Sulfate.

Strength 0.3 mg

Storage Preserve in tightly closed containers.

Azathioprine



$C_9H_7N_7O_2S$ 277.27

[466-86-6]

Azathioprine is 6-[(1-methyl-4-nitro-1*H*-imidazol-5-yl)thio]-1*H*-purine. It contains not less than 98.0% of $C_9H_7N_7O_2S$, calculated on the dried basis.

Description A pale yellow powder or crystalline powder; odourless; taste, slightly bitter. Very slightly soluble in ethanol; practically insoluble in water; freely soluble in dilute ammonia solution.

Identification (1) Dissolve about 5 mg in several ml of hydrochloric acid (1→2), add drops of iodine TS, a brown precipitate is produced.

(2) Dissolve about 5 mg with (2 mol/L) hydrochloric acid solution and dilute to 100 ml, mix well. Measure accurately 5 ml, dilute with water to 50 ml. The light absorption of the resulting solution exhibits a maximum at 280 nm (Appendix IV A).

(3) The infrared absorption spectrum (Appendix IV C) is concordant with the reference spectrum of azathioprine (Appendix XVI).

Acidity or alkalinity Shake 0.50 g with 25 ml of water for 15 minutes, filter. To 20 ml of the successive filtrate, add 0.1 ml of methyl red IS. Not more than 0.1 ml of hydrochloric acid (0.02 mol/L) VS or sodium hydroxide (0.02 mol/L) VS is required to change the colour of the solution.

Related substances Dissolve about 25 mg of the substance being examined in 3 ml of dimethylsulfoxide, dilute with mobile phase to produce a solution of about 250 µg per ml (solution 1), measure accurately 1 ml, dilute with mobile phase to 100 ml and mix well (solution 2). Dissolve a quantity of 6-mercaptopurine CRS, accurately weighed, in a quantity of dimethylsulfoxide, dilute with mobile phase to produce a solution of 1.25 µg per ml (solution 3). Carry out the method for high performance liquid chromatography (Appendix V D), using a column packed with octadecylsilane bonded silica gel and a mixture of methanol-0.05% sodium acetate solution (18 : 82) as the mobile phase. Detection wavelength is 300 nm and the number of the theoretical plates of the column is not less than 3000. Inject 20 µl of the solution (2) into the column, adjust the attenuation so that the principal peak height in the chromatogram is 20%-25% of the full scale of the chart. Inject separately 20 µl each of above three solutions into the column, and record the chromatogram for twice the retention time of the principal peak. In the chromatogram obtained with solution (1) the peak area of 6-mercaptopurine is not greater than that of the principle peak in the chromatogram obtained with solution (3), and the sum of the areas of all peaks other than the principal peak is not greater than 1/2 of the area of the principal peak in the chromatogram obtained with solution (2) respectively.

Loss on drying When dried to constant weight at 105°C, loses not more than 0.5% of its weight (Appendix VIII L).

Residue on ignition Not more than 0.1% (Appendix VIII N).

Assay Dissolve about 0.6 g, accurately weighed, with 20 ml of dilute ammonia solution in a 200 ml volumetric flask. Add accurately 50 ml of silver nitrate (0.1 mol/L) VS, dilute with water to volume and mix well. Filter, measure accurately 100 ml of the successive filtrate, add 20 ml of nitric acid (1→2), allow to cool, add 2 ml of ferric ammonium sulfate IS, titrate with ammonium thiocyanate (0.1 mol/L) VS. Perform a blank determination and make any necessary correction. Each ml of silver nitrate (0.1 mol/L) VS is equivalent to 27.73 mg of $C_9H_7N_7O_2S$.

Category Immunosuppressive.

Storage Preserve in tightly closed containers, protected from light.

Preparation Azathioprine Tablets

Azathioprine Tablets

Azathioprine Tablets contain not less than 93.0% and not more than 107.0% of the labelled amount of azathioprine ($C_9H_7N_7O_2S$).

Description Pale yellow tablets.

Identification To a quantity of the powdered tablets equivalent to about 0.2 g of azathioprine, add 40 ml of 50% ethanol. Shake on heating in a water bath and filter. Evaporate the filtrate to dryness. The residue complies with tests (1), (2) for Identification described under Azathioprine.

Dissolution Carry out dissolution test (Appendix X C, method 2), using 900 ml of water as the dissolution medium, adjust the rotational speed of the paddle to 50 rpm. Withdraw 10 ml of the solution after exactly 30 minutes and filter. Dilute the successive filtrate, accurately measured, with water to produce a solution of 10 µg per ml. Dissolve azathioprine CRS in water to produce a solution of 10 µg per ml. Measure the absorbance of the resulting solutions at 280 nm (Appendix IV A). Calculate the dissolution of $C_9H_7N_7O_2S$ from each tablet. Not less than 75% of the labelled amount is dissolved.

Other requirements Comply with the general requirements for tablets (Appendix I A).

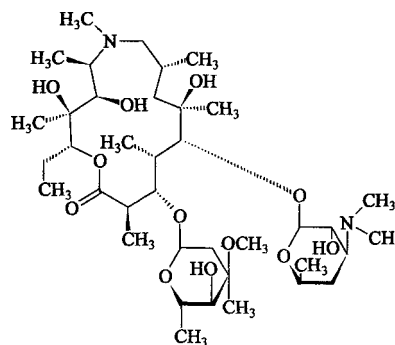
Assay Weigh accurately and powder 20 tablets. Weigh accurately a quantity equivalent to about 0.6 g of azathioprine, carry out the method for Assay described under Azathioprine beginning at the words "to 200 ml volumetric flask". Each ml of silver nitrate (0.1 mol/L) VS is equivalent to 27.73 mg of $C_9H_7N_7O_2S$.

Category As described under Azathioprine.

Strength (1) 50 mg (2) 100 mg

Storage Preserve in tightly closed containers, protected from light.

Azithromycin



$C_{38}H_{72}N_2O_{12}$ 749.00

[83905-01-5]

Azithromycin is (2*R*,3*S*,4*R*,8*R*,10*R*,11*R*,12*S*,13*S*,14*R*)-13-[(2,6-Dideoxy-3-*C*-methyl-3-*C*-methyl-3-*O*-methyl- α -L-ribo-hexopyranosyl)oxy]-2-ethyl-

3,4,10-trihydroxy-3,5,6,8,10,12,14-heptamethyl-11-[[3,4,6-trideoxy-3-(dimethyl-amino)- β -D-xylahexopyranosyl]oxy]-1-oxa-6-azacyclopentadecan-15-one. It has a potency of not less than 945 Azithromycin Units per mg, calculated on the anhydrous basis.

Description A white or almost white crystalline powder; odourless; taste, bitter; slightly hygroscopic.

Freely soluble in methanol, acetone, dehydrate ethanol, chloroform or dilute hydrochloric acid solution; practically insoluble in water.

Specific optical rotation -45° to -49° , in a solution of 20 mg per ml in dehydrate ethanol (Appendix VI E).

Identification (1) Dissolve separately a quantity of the substance being examined and azithromycin CRS in dehydrate ethanol to produce solutions each of 5 mg of azithromycin per ml as the test solution and the reference solution. Carry out the method for Related substances. The colour and position of the principal spot in the chromatogram obtained with the test solution correspond to the principal spot obtained with the reference solution.

(2) The infrared absorption spectrum (Appendix IV C) is concordant with the reference spectrum of azithromycin (Appendix XVI). If any disagreement is found, dissolve a quantity in acetone, mix well, dry it in vacuum and then perform the determination.

Crystallinity Complies with the requirement for Crystallinity (Appendix IX D).

Alkalinity Dissolve about 0.1 g in 25 ml of methanol with shaking, add 25 ml of water, mix well, pH 9.0-11.0 (Appendix VI H).

Related substances Dissolve an accurately weighed quantity in dehydrate ethanol to produce a solution of 20 mg azithromycin per ml as the test solution. Transfer accurately 1.5 ml of the test solution and 30 mg of erythromycin CRS to a 50 ml volumetric flask, transfer separately 1.0 ml and 0.5 ml of the test solution to another two 50 ml volumetric flasks, dilute with dehydrate ethanol to volume respectively as reference solution (1), (2) and (3). Transfer 1.0 ml of the reference solution (3) to 10 ml volumetric flasks, dilute with dehydrate ethanol to volume as reference solution (4). Carry out the method for thin-layer chromatography (Appendix V B), using silica gel G as the coating substance and a mixture of ethyl acetate-n-hexane-diethylamine (10 : 10 : 2) as the mobile phase. Apply separately to the plate 2 μ l each of above five solutions in dehydrated solutions containing (1) 20 mg per ml, (2) 0.6 mg of the substance being examined and 0.6 mg of erythromycin CRS respectively, (3) 0.4 mg per ml of the substance being examined (4) 0.2 mg per ml of the substance being examined and (5) 0.02 mg of the substance being examined. After developing and removal of the plate, dry it in air, spray with an indicator (dissolve 2.5 g of sodium molybdenate and 1 g of cerium sulfate in 10% sulfuric acid solution and dilute to 100 ml), heat at 105°C for a few minutes. The spots of azithromycin and erythromycin in the chromatogram obtained with reference solution (1) must be separated completely. The most intense secondary spot in the chromatogram obtained with test solution is not more intense than the principal spot obtained with reference solution (2) (2%), and any other secondary spots is not more intense than the principal spot obtained with reference solution (3) (1%). Reference solution (4) must appear a clear spot, otherwise repeat the test.

Water Not more than 5.0% (Appendix VIII M, method 1 A).

Residue on ignition Not more than 0.2% (Appendix VIII N), using 1.0 g.

Heavy metals Carry out the limit test for heavy metals (Appendix VIII H, method 2), using the residue obtained in the test for Residue on ignition; not more than 0.0025%.

Assay Dissolve an accurately weighed quantity in ethanol (using 1 ml of ethanol for 2 mg), dilute with sterile water to produce a solution of 1000 Units per ml. Carry out the microbiological assay of antibiotics (Appendix XI A). 1000 Azithromycin Units is equivalent to 1 mg of $\text{C}_{38}\text{H}_{72}\text{N}_2\text{O}_{12}$.

Category Macrolide antibiotic.

Storage Preserve in tightly closed containers, stored in a cool and dry place.

Preparation (1) Azithromycin for Suspension
(2) Azithromycin Capsules
(3) Azithromycin Dispersible Tablets
(4) Azithromycin Granules

Azithromycin Capsules

Azithromycin Capsules contain not less than 90.0% and not more than 110.0% of the labelled amount of azithromycin ($\text{C}_{38}\text{H}_{72}\text{N}_2\text{O}_{12}$).

Description Capsules containing white or almost white crystalline powder.

Identification Dissolve a quality of the contents of the capsules in dehydrate ethanol, filter and evaporate the successive filtrate to dryness on a water bath. The residue complies with test (1) for Identification describe under Azithromycin.

Related substances Comply with the test for Related Substances as described under Azithromycin, using a quality of the contents of the capsules.

Water Not more than 5.0% (Appendix VIII M, method 1 A).

Dissolution Carry out the dissolution test (Appendix X C, method 2), using a phosphate BS (to 6000 ml of 0.1 mol/L disodium hydrogen phosphate solution add 40 ml of hydrochloric acid, adjust the pH value to 6.0, add 0.6 g of pancreatin, mix well after dissolve) 900 ml as the dissolution medium, adjust the rotational speed of the paddle to 100 rpm. Withdraw the solution after exactly 45 minutes and filter. Dilute an accurately measured quantity of the successive filtrate with the same solvent to produce a solution of 55 μg per ml, as test solution. Dissolve an accurately weighed quantity of the mixed contents obtained from the test for weight variation of contents equivalent to about the average weight of one capsule and a empty capsule shell in a volumetric flask, add a quantity of ethanol (using 1 ml of ethanol for 2 mg of the labelled amount of azithromycin) and the dissolution medium, shake for 30 minutes or ultrasonicate for 10 minutes to dissolve azithromycin. Dilute an accurately measured quantity of the successive filtrate with the dissolution medium to produce a solution of 55 μg per ml and filter, using the successive filtrate as the reference solution. Measure accurately 5 ml each of the two solution separately to two tubes with stoppers respectively, add accurately 5 ml of sulfuric acid solution (75 \rightarrow 100), mix well, allow to stand for 30 minutes, cool, measure the absorbance of the resulting solutions at 482 nm (Appendix IV A), calculate the dissolution of $\text{C}_{38}\text{H}_{72}\text{N}_2\text{O}_{12}$ from each capsule. Not less than 75% is dissolved.

Other requirements Comply with the general requirements for capsules (Appendix I E)

Assay Dissolve an accurately weighed quantity of the mixed contents obtained from the test for weight variation of contents equivalent to about 0.25 g of azithromycin in ethanol (using 1 ml of ethanol for 2 mg), dilute with sterile water to produce a solution of 1000 Units per ml. Carry out the Assay described under Azithromycin.

Category As described under Azithromycin.

Strength (1) 0.125 g (125000 Units)
(2) 0.25 g (250000 Units)

Storage Preserve in tightly closed containers, stored in a cool and dry place.

Azithromycin Dispersible Tablets

Azithromycin Dispersible Tablets contain not less than 90.0% and not more than 110.0% of the labelled amount of azithromycin ($C_{38}H_{72}N_2O_{12}$).

Description A white or almost white tablets.

Identification (1) Dissolve a quality of the powdered tablets in ethanol to produce a solution of 10 mg of azithromycin per ml and filter, using the successive filtrate as test solution. Dissolve a quality of azithromycin CRS in ethanol to produce a reference solution of 10 mg of azithromycin per ml. Carry out the method for Related substances. The colour and position of the principal spot in the chromatogram obtained with the test solution correspond to the principal spot obtained with the reference solution.

Related substance Comply with the test for Related Substance as described under Azithromycin, using a quantity of the powdered tablets.

Dissolution Carry out the dissolution test (Appendix X C, method 2), using a phosphate BS (to 6000 ml of 0.1 mol/L disodium hydrogen phosphate solution add 40 ml of hydrochloric acid, adjust the pH value to 6.0 ± 0.05) 900 ml as the dissolution medium, adjust the rotational speed of the paddle to 50 rpm. Withdraw the solution after exact 15 minutes and filter. Dilute an accurately measured quantity of the successive filtrate with the same solvent to produce a solution of 55 µg per ml, as test solution. Triturate 10 tablets, to an accurately weighed quantity equivalent to about the average weight of one tablet add a quantity of ethanol (using 1ml of ethanol for 2 mg of the labelled amount of azithromycin) and the dissolution medium, shake for 30 minutes or ultrasonicate for 10 minutes to make azithromycin dissolved. Dilute an accurately measured quantity of the successive filtrate with the dissolution medium to produce a solution of 55 µg per ml and filter, using the successive filtrate as the reference solution. Measure accurately 5 ml each of the two solution separately to two tubes with stoppers respectively, add accurately 5 ml of sulfuric acid solution (75→100), mix well, allow to stand for 30 minutes, cool to room temperature, measure the absorbance of the resulting solutions at 482 nm (Appendix IV A), calculate the dissolution of $C_{38}H_{72}N_2O_{12}$ from each tablets. Not less than 75% is dissolved.

Other requirements Comply with the general requirements for tablets (Appendix I A)

Assay Weigh accurately and triturate 10 tablets, dissolve a quantity of powdered tablets, weighed accurately, equivalent to 0.25 of azithromycin in 125 ml of ethanol, dilute with sterile water to produce a solution of 1000 Units

per ml, mix well and allow to stand. Carry out the Assay described under Azithromycin. 1000 Azithromycin Units equivalent to 1 mg of $C_{38}H_{72}N_2O_{12}$.

Category As described under Azithromycin.

Strength (1) 0.1 g (100000 units)
(2) 0.125 g (125000 units)
(3) 0.25 g (250000 units)
(4) 0.5 g (500000 units)

Storage Preserve in tightly closed containers, stored in a dry place.

Azithromycin for Suspension

Azithromycin for Suspension contains not less than 90.0% and not more than 110.0% of the labelled amount of azithromycin ($C_{38}H_{72}N_2O_{12}$).

Description A granules or powder; odour, fragrance; taste, sweet.

Identification Dissolve a quantity in methanol to produce a solution of 30 mg of azithromycin per ml and filter, using the successive filtrate as solution (1). Dissolve an accurately weighed quality of azithromycin CRS in methanol to produce solution (2) of 30 mg per ml. Mix equal volume of the two solutions as solution (3). Carry out test (1) for Identification described under Azithromycin. There is only one spot in the chromatogram obtained with solution (3). The colour and position of the principal spot in the chromatogram obtained with solution (1) correspond to the principal spot obtained with solution (3).

Water Not more than 2.0% (Appendix VIII M, method 1 A).

Alkalinity Dissolve a quantity in methanol (using 2.5 ml of methanol for 10 mg of azithromycin), dilute with water to produce a solution of 2 mg of azithromycin per ml, mix well, and perform the determination after 10 minutes, pH 9.0-11.0 (Appendix VI H).

Other requirements Complies with the general requirements for suspension except the Ratio of sedimental volume (Appendix I O).

Assay Dissolve an accurately weighed quantity of the mixed contents obtained from the test for weight variation of contents equivalent to about 0.25 g of azithromycin in ethanol (using 1 ml of ethanol for 2 mg), dilute with sterile water to produce a solution of 1000 Units per ml. Carry out the Assay described under Azithromycin.

Category As described under Azithromycin.

Strength 0.1 g (100000 Units)

Storage Preserve in tightly closed containers, stored in a dry place.

Azithromycin Granules

Azithromycin Granules contain not less than 90.0% and not more than 110.0% of the labelled amount of azithromycin ($C_{38}H_{72}N_2O_{12}$).

Description A suspension granules; taste, sweet.

Identification (1) Dissolve a quantity of the powdered granules in methanol to produce a solution of 30 mg of

azithromycin per ml and filter, using the successive filtrate as test solution. Dissolve a quantity of azithromycin CRS in methanol to produce a reference solution of 30 mg of azithromycin per ml. Mix equal volume of the two solutions as the mixture solution. Carry out the method for Related substances. There is only one spot in the chromatogram obtained with the mixture solution. The colour and position of the principal spot in the chromatogram obtained with the test solution correspond to the principal spot obtained with the reference solution.

Alkalinity Dissolve a quantity equivalent to 20 mg of azithromycin in 5 ml of methanol, add 5 ml of water, mix well and allow to stand for 10 minutes, pH 8.5-11.5 (Appendix VI H).

Related substance Comply with the test for Related Substance as described under Azithromycin, using a quantity of the powdered Granules.

Water Not more than 2.0 % (Appendix VIII M, Method 1 A)

Other requirements Comply with the general requirements for Granules (Appendix I N)

Assay Dissolve an accurately weighted quantity of the mixed contents obtained from the test for weight variation of contents equivalent to 250 mg of azithromycin with 125 ml of ethanol, dilute with sterile water to produce a solution of 1000 Units per ml, mix well and allow to stand. Carry out the Assay described under Azithromycin using the supernatant liquid. 1000 Azithromycin Units equivalent to 1 mg of $C_{38}H_{72}N_2O_{12}$.

Category As described under Azithromycin.

Strength (1) 0.1 g (100000 units)
(2) 0.125 g (125000 units)
(3) 0.25 g (250000 units)
(4) 0.5 g (500000 units)

Storage Preserve in tightly closed containers, stored in a dry place.

Azithromycin Tablets

Azithromycin Tablets contain not less than 90.0% and not more than 110.0% of the labelled amount of azithromycin ($C_{38}H_{72}N_2O_{12}$).

Description White tablets or film coated tablets with white or almost white core.

Identification Dissolve a quantity of the powdered tablets in ethanol to produce a solution of 10 mg of azithromycin per ml and filter, using the successive filtrate as a test solution. Dissolve a quantity of azithromycin CRS in ethanol to produce a reference solution of 10 mg of azithromycin per ml, the solutions comply with test (1) for Identification describe under Azithromycin.

Related substances Dissolve an accurately weighed quantity of the powdered tablets in dehydrate ethanol to produce a solution of 20 mg azithromycin per ml as the test solution. Transfer accurately 1.5 ml of the test solution and 30 mg of erythromycin CRS to a 50 ml volumetric flask, transfer separately 1.5 ml and 0.5 ml of the test solution to another two 50 ml volumetric flasks, dilute with dehydrate ethanol to volume respectively as reference solution (1), (2) and (3). Transfer 1.0 ml of the reference solution (3) to 10 ml volumetric flasks, dilute with dehydrate ethanol to volume as reference solution (4). Carry out the method for thin-layer

chromatography (Appendix V B), using silica gel G as the coating substance and a mixture of ethyl acetate-n-hexane-diethylamine (10 : 10 : 2) as the mobile phase. Apply separately to the plate 2 μ l each of above five solutions in dehydrated solutions containing (1) 20 mg per ml, (2) 0.6 mg of the substance being examined and 0.6 mg of erythromycin CRS respectively, (3) 0.4 mg per ml of the substance being examined (4) 0.2 mg per ml of the substance being examined and (5) 0.02 mg of the substance being examined. After developing and removal of the plate, dry it in air, spray with an indicator (dissolve 2.5 g of sodium molybdenate and 1 g of cerium sulfate in 10% sulfuric acid solution and dilute to 100 ml), heat at 105°C for a few minutes. The spots of azithromycin and erythromycin in the chromatogram obtained with reference solution (1) must be separated completely. The most intense secondary spot in the chromatogram obtained with test solution is not more intense than the principal spot obtained with reference solution (2) (3%), and any other secondary spots is not more intense than the principal spot obtained with reference solution (3) (1%). Reference solution (4) must appear a clear spot, otherwise repeat the test.

Dissolution Carry out the dissolution test (Appendix X C, method 2), using a phosphate BS (to 6000 ml of 0.1 mol/L disodium hydrogen phosphate solution add 40 ml of hydrochloric acid, adjust the pH value to 6.0) 900 ml as the dissolution medium, adjust the rotational speed of the paddle to 100 rpm. Withdraw the solution after exact 45 minutes and filter. Dilute an accurately measured quantity of the successive filtrate with the same solvent to produce a solution of 55 μ g per ml, as test solution. Triturate 10 tablets, to an accurately weighed quantity equivalent to about the average weight of one tablet add a quantity of ethanol (using 1 ml of ethanol for 2 mg of the labelled amount of azithromycin) and the dissolution medium, shake for 30 minutes or ultrasonicate for 10 minutes to dissolve Azithromycin. Dilute an accurately measured quantity of the successive filtrate with the dissolution medium to produce a solution of 55 μ g per ml and filter, using the successive filtrate as the reference solution. Measure accurately 5 ml each of the two solution separately to two tubes with stoppers respectively, add accurately 5 ml of sulfuric acid solution (75 \rightarrow 100), mix well, allow to stand for 30 minutes, cool, measure the absorbance of the resulting solutions at 482 nm (Appendix IV A), calculate the dissolution of $C_{38}H_{72}N_2O_{12}$ from each tablets. Not less than 75% is dissolved.

Other requirements Comply with the general requirements for tablets (Appendix I A).

Assay Weigh accurately and triturate 10 tablets, dissolve an accurately weighed quantity equivalent to 0.25 g azithromycin in 125 ml of ethanol, dilute with sterile water to produce a solution of 1000 Units per ml, mix well, carry out the Assay described under Azithromycin using the supernatant liquid (Appendix VI A).

Category As described under Azithromycin.

Strength (1) 0.125 g (125000 Units)
(2) 0.25 g (250000 Units)

Storage Preserve in tightly closed containers, stored in a dry place.

Bacitracin

[1405-87-4]

Bacitracin has a potency of not less than 55 bacitracin Units per mg, calculated on the dried basis.

Description An almost white to pale yellow powder; odourless; taste, bitter; hygroscopic; destroyed by oxidizing agents and precipitated by heavy metal salts in solution.

Freely soluble in water; soluble in ethanol; insoluble in acetone, chloroform or ether.

Identification Carry out the method for thin-layer chromatography (Appendix V B), using silica gel GF₂₅₄ as the coating substance and butanol-glacial acetic acid-water-pyridine-ethanol (60:15:10:6:5) as the mobile phase. Apply separately to the plate 5 µl each of two solutions in 1% disodium edetate solution containing (1) 6.0 mg per ml of the substance being examined, (2) 6.0 mg per ml of bacitracin RS. After developing and removal of the plate, dry it in air and spray with 1% solution of ninhydrin in butanol-pyridine (99:1), heat at 105°C for 5 minutes until brownish red spots develop. The colour and position of the principal spot in the chromatogram obtained with solution (1) correspond to that of the principal spot in the chromatogram obtained with solution (2).

Acidity or alkalinity An aqueous solution of 1000 Units per ml, pH 5.5-7.5 (Appendix VI H).

Loss on drying When dried to constant weight at 105°C, loses not more than 5.0% of its weight (Appendix VIII L).

Assay Dissolve an accurately weighed quantity in sterile water to produce a solution of 100 Units per ml. Carry out the Microbiological Assay of Antibiotics (Appendix XI A).

Category Antibiotic.

Storage Preserve in tightly closed containers, stored in a dry place.

Preparation (1) Bacitracin Ointment
(2) Bacitracin Eye Ointment
(3) Compound Neomycin Ointment

Bacitracin Eye Ointment

Bacitracin Eye Ointment contains not less than 90.0% and not more than 120.0% of the labelled amount of bacitracin.

Description A pale yellow or yellow ointment.

Identification To a quantity of the substance being examined, add a quantity of 1% disodium edetate solution, stir and heat in a water bath. Allow it to cool, filter, using the filtrate to make a solution containing 500 bacitracin Units per ml as the test solution. Dissolve a quantity of Bacitracin RS with 1% disodium edetate solution to produce a solution containing 250 bacitracin Units per ml as the reference solution. Carry out the test for Identification described under Bacitracin.

Other requirements Complies with the general requirements for eye preparations (Appendix I G).

Assay Transfer about 2 g, accurately weighed, in a

separator, add 20 ml of peroxide free ether, shake thoroughly to dissolve vaseline, extract with 3-4 portions each of 10 ml of phosphate BS (pH 6.0). Dilute the combined extracts with phosphate BS (pH 6.0). Measure accurately a quantity and carry out the assay described under Bacitracin.

Category As described under Bacitracin.

Strength 2 g (1000 Units)

Storage Preserve in tightly closed containers, stored in a cool and dry place.

Bacitracin Ointment

Bacitracin Ointment contains not less than 90.0% and not more than 120.0% of the labelled amount of bacitracin.

Description A pale yellow or yellow ointment.

Identification To a quantity of the substance being examined add a quantity of 1% disodium edetate solution, stir and heat in a water bath, allow it to cool, filter, using the filtrate to make a solution containing 500 bacitracin Units per ml as the test solution. Dissolve a quantity of Bacitracin RS with 1% disodium edetate solution to produce a solution containing 250 bacitracin Units per ml as the reference solution. Carry out the test for Identification described under Bacitracin.

Other requirements Complies with the general requirements for Ointment (Appendix I F).

Assay Transfer about 2 g, accurately weighed, in a separator, add 20 ml of peroxide free ether, shake thoroughly to dissolve vaseline, extract with 3-4 portions each of 10 ml of phosphate BS (pH 6.0). Dilute the combined extracts with phosphate BS (pH 6.0). Measure accurately a quantity and carry out the Assay described under Bacitracin.

Category As described under Bacitracin.

Strength 8 g (4000 Units)

Storage Preserve in tightly closed containers, stored in a cool and dry place.

Barium Sulfate (Type I)

BaSO₄ 233.39

[7727-43-7]

Description A fine, white, bulky powder; odourless; tasteless.

Insoluble in water, organic solvent, acids or sodium hydroxide solutions.

Identification Boil about 0.3 g with 10 ml of sodium carbonate TS and filter. Acidify the filtrate with hydrochloric acid; the solution yields the reactions characteristic of sulfate (Appendix III). Wash the residue with water, dissolve it in dilute acetic acid and filter again; the filtrate yields the reactions characteristic of barium salts (Appendix III).

Sedimentation Place 5.0 g to a 50 ml, glass-stoppered cylinder (the height of the graduation is 11-14 cm from the bottom). Add water to volume. Shake the mixture vigorously for 1 minute to make the powder suspend homogeneously. Allow it to stand for 15 minutes. The surface of the suspension does not settle below the 18 ml

graduation mark.

Acidity or alkalinity Stir 1.0 g with 20 ml of water in a water bath for 5 minutes, and filter. Divide the filtrate into two equal portions; To one portion add a drop of bromothymol blue TS, no blue colour is produced; to the other portion add a drop of bromocresol green IS, a blue colour is produced.

Acid-soluble substances Boil 10.0 g with 10 ml of dilute hydrochloric acid and 90 ml of water for 10 minutes, add water to restore approximately the original volume, and cool. Filter through paper previously washed with hydrochloric acid solution (1→40), repeat the filtration if necessary, to obtain a clear filtrate. Evaporate 50 ml of the clear filtrate on a water bath to dryness, add 2 drops of hydrochloric acid and 10 ml of hot water, and stir. Filter again through acid-washed paper, wash the residue with 10 ml of hot water, and evaporate the combined filtrate and washings to dryness in an evaporating dish previously dried at 105°C to constant weight. The residue, when dried to constant weight at 105°C, weighs not more than 15 mg (0.30%).

Acid-soluble barium salts Stir the residue obtained in the test for Acid-soluble substances with 10 ml of water, filter through paper previously washed with hydrochloric acid solution (1→40), add 0.5 ml of dilute sulfuric acid to the filtrate and allow to stand for 30 minutes; no opalescence is produced.

Sulfides Carry out the limit test for sulfides (Appendix VIII C), using 10 g; the lead acetate test paper shows no colour change.

Loss on drying When dried to constant weight at 105°C, loses not more than 1.0% of its weight (Appendix VIII L).

Heavy metals To 4.0 g add 4 ml of dilute acetate BS (pH 3.5) and a quantity of water to produce 50 ml, boil for 10 minutes and cool. Add water to restore 50 ml and filter. Carry out the limit test for heavy metals (Appendix VIII H, method 1), using 25 ml of the filtrate; not more than 0.001%.

Arsenic To 2.0 g add 23 ml of water and 5 ml of hydrochloric acid. Complies with the limit test for arsenic (Appendix VIII J, method 1) (0.0001%).

Category Diagnostic agent.

Storage Preserve in tightly closed containers.

Preparation Barium Sulfate (Type I) for Suspension

Barium Sulfate (Type I) for Suspension

Barium Sulfate (Type I) for Suspension is a dry suspension of barium sulfate (Type I) mixed with one or more suitable dispersing agents and flavours.

Description A fine, white, bulky powder; odour, fragrant.

Identification Complies with the tests for Identification described under Barium Sulfate (Type I), using 0.3 g.

Acidity or alkalinity Prepare an aqueous suspension of 100 g in 100 ml of water, pH 5.5-7.5 (Appendix VI H).

Ratio of sedimental volume Place 100 g in a 100 ml glass-stoppered, graduated cylinder, add water to make 100 ml. Shake thoroughly to produce an suspension and allow it to

stand for 3 hours; the surface of suspension does not settle below the 97 ml graduation mark.

Size of the particles To 0.5 g add water to make 50 ml, shake thoroughly, allow it to stand for 10 minutes, decant the supernatant liquid, leaving about 1 ml of the suspension. Place 1 drop of suspension on a microscope slide, examine the object for three fields of view using a microscope of 400 folds magnification. Most particles are less than 2 μm in diameter and no particle is larger than 10 μm in diameter.

Loss on drying When dried to constant weight at 105°C, loses not more than 1.0% of its weight (Appendix VIII L).

Viscosity To 100 g add water to produce 100 ml of suspension, determine the viscosity at 25°C (Appendix VI G, method 2), using model NDJ-1 rotating viscometer adjusting the rotor No. 1 speed at 60 rpm. The viscosity is not greater than 0.015 Pa · s.

Acid and alkali resistance Adjust the pH of the suspension described under the test of viscosity with hydrochloric acid solution (9→100) and sodium hydroxide TS to 1 and 14 respectively, carry out the determination of Apparent viscosity described above immediately. The viscosity is not greater than 0.03 Pa · s.

Other requirements Complies with the general requirements for suspension (Appendix I O).

Category As described under Barium Sulfate (Type I).

Storage Preserve in tightly closed containers.

Barium Sulfate (Type II)

BaSO₄ 233.39

Barium Sulfate Type II is a purified product of barite, a mineral of sulfate. It contains not less than 97.0% of BaSO₄, calculated on the dried basis.

Description White fine bulky powder; odourless, tasteless. Insoluble in water, organic solvent, acids or sodium hydroxide solution.

Identification Boil about 0.3 g with 10 ml of sodium carbonate TS and filter. Acidify the filtrate with hydrochloric acid; the solution yields the reactions characteristic of sulfates (Appendix III). Wash the residue with water, dissolve it in dilute acetic acid, filter, the filtrate yields the reactions characteristic of barium salts (Appendix III).

Acidity or alkalinity To 20.0 g add 20 ml freshly boiled and cooled water, stir thoroughly to produce a suspension, pH 6.0-8.0 (Appendix V H).

Acid-soluble substances Boil 10.0 g with 10 ml of dilute hydrochloric acid and 90 ml of water for 10 minutes in a beaker, add water to restore approximately the original volume and cool. Filter through a filter paper previously washed with hydrochloric acid solution (1→40), repeat the filtration if necessary, to obtain a clear filtrate. Evaporate 50 ml of the clear filtrate on a water bath to dryness, add 2 drops of hydrochloric acid and 10 ml of hot water, stir. Filter again through a filter paper previously washed with hydrochloric acid solution (1→40), wash the residue with 10 ml of hot water, evaporate the combined filtrate and washings to dryness in an evaporating dish previously dried at 105°C to constant weight. When dried to constant weight at 105°C, the weight of residue is not more than 15 mg (0.3%).

Acid-soluble barium salts Stir the residue obtained in the test

for acid-soluble substances with 10 ml of water, filter through a filter paper previously washed with hydrochloric acid solution (1→40), add 0.5 ml of dilute sulfuric acid to the filtrate, allow to stand for 30 minutes; no opalescence is produced.

Sulfides Carry out the limit test for sulfides (Appendix VIII C), using 10 g; the lead acetate test paper shows no colour change.

Loss on drying When dried to constant weight at 105°C, loses not more than 1.0% of its weight (Appendix VIII L).

Heavy metals To 4.0 g add 4 ml of acetate BS (pH 3.5) and a quantity of water to produce 50 ml, boil for 10 minutes, cool. Add water to restore 50 ml and filter. Carry out the limit test for heavy metals (Appendix VIII H, method 1), using 25 ml of the filtrate; not more than 0.001%.

Arsenic To 2.0 g add 23 ml of water and 5 ml of hydrochloric acid. Carry out the limit test for arsenic (Appendix VIII J, method 1); not more than 0.0001%.

Size of the particles To 0.5 g add water to 50 ml, shake thoroughly, place 1 drop of the suspension on a microscope slide immediately. Examine the object for three fields of vision, using a microscope of 400 folds in magnification. Particles are in the range of 0.5-50 µm in diameter; any particles larger than 50 µm in diameter are not more than two.

Assay Weigh accurately about 0.6 g in a weighed platinum crucible, add 10 g of anhydrous sodium carbonate, mix well, ignite until melted continue to ignite for 30 minutes, allow to cool. Place the crucible in a 400 ml beaker, add 250 ml of water, heat and stir with glass rod until melts are separated from the crucible. Remove the crucible and wash the crucible with water, combine the washings to the beaker, wash the inner part of the crucible with 2 ml of acetic acid solution (6 mol/L) then with water, combine the washings to the beaker. Heat and stir until melts are disintegrated, cool the beaker in an ice bath until the precipitate solidifies. Decant the supernatant liquid filter and suspended any fine precipitate on a filter paper cautiously. Wash the contents in the beaker with cold sodium carbonate solution (1→50) twice, each of about 10 ml, stir, filter again through the same filter paper cautiously. Put the beaker containing some large pieces of barium carbonate under the filtering funnel, wash the filter paper with hydrochloric acid solution (3 mol/L) for 5 times of 1 ml each, then wash with water (note: a slight turgidity may produce). To the beaker add 100 ml of water, 5 ml of hydrochloric acid, 10 ml of ammonium acetate solution (2→5), 25 ml of potassium dichromate solution (1→10) and 10 g of urea, cover with a watch glass, heat at 80-85°C for 16 hours, filter immediately. Transfer the precipitate completely to a sintered glass crucible, previously dried to constant weight, wash the precipitate with potassium dichromate solution (1→200) and then with 20 ml of water, dry at 105°C for 2 hours. The weight multiplied by 0.9213 represents the weight of BaSO₄.

Category Diagnostic agent.

Storage Preserve in tightly closed containers.

Preparation Barium Sulfate (Type II) for Suspension

Barium Sulfate (Type II) for Suspension

Barium Sulfate (Type II) for Suspension is a dry

suspension of barium sulfate (Type II) mixed with suitable amount of dispersing agents and flavours.

Description White bulky fine powder; odour, fragrant.

Identification Complies with the tests for Identification described under Barium Sulfate (Type II), using about 0.3 g.

Acidity and Alkalinity To 100 g add water to produce 100 ml of suspension, pH 5.0-9.0 (Appendix VI H).

Size of the particles Add 20 ml of water to 1.0 g, shake thoroughly to mix well, immediately place 1 drop of the suspension on a microscope slide, examine the object for three fields of vision, using a microscope of 400 folds of magnification, most particles are not less than 0.5 µm and more than 50 µm in diameter; the particles larger than 50 µm in diameter are not more than 2.

Loss on drying When dried to constant weight at 105°C, loses not more than 1.0% (Appendix VIII L).

Viscosity To 200 g add water to produce 100 ml of suspension, determine the viscosity at 25 °C (Appendix VI G, method 2). Using a model NDJ-1 rotating viscosimeter. The viscosity is not more than 0.150 Pa · s, adjust the speed of rotator no. 1 at 30 rpm.

Acid and alkali resistance To the suspension obtained in the test for viscosity, adjust the pH to 1 and 14 with hydrochloric acid solution (9→100) and sodium hydroxide TS respectively; carry out the determination of viscosity using method described above immediately. The viscosities are both not more than 0.150 Pa · s.

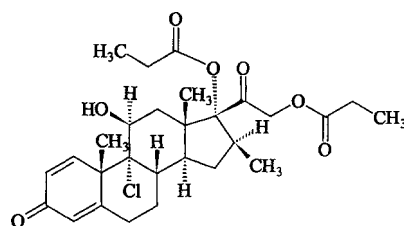
Carbon dioxide resistance To 3 g of double contrast medium gas producing agent composed citric acid (hydrate), sodium bicarbonate, antifoaming agent and excipient. The acid granules and base granules are prepared respectively and packed with the mixed ratio of 1:1.3. add 10 ml of water, combine the gas produced solution and the suspension obtained in the test for acid and alkali resistance, stir to mix well, carry out the determination of viscosity immediately using the method described above, The viscosity is not more than 0.150 Pa · s.

Other requirements Complies with the general requirements for suspension (Appendix I O).

Category As described under Barium Sulfate (Type II).

Storage Preserve in tightly closed containers.

Beclometasone Dipropionate



C₂₈H₃₇ClO₇ 521.05

[5534-09-8]

Beclometasone Dipropionate is 9-chloro-11β,17,21-trihydroxy-16β-methylpregna-1,4-diene-3,20-dione 17,21-dipropionate. It contains not less than 97.0% and not more than 103.0% of C₂₈H₃₇ClO₇,

calculated on the dried basis.

Description A white or almost white powder; odourless. Freely soluble in acetone or chloroform; soluble in methanol; sparingly soluble in ethanol; practically insoluble in water.

Specific optical rotation $+88^{\circ}$ to $+94^{\circ}$, in a solution of about 10 mg per ml in dioxane (Appendix VI E).

Identification (1) The retention time of principal peak of the substance being examined in the chromatogram obtained in the Assay is identical with that of beclometasone dipropionate CRS.

(2) The light absorption of a solution of 20 μg per ml in ethanol exhibits a maximum at 239 nm; the absorbance is about 0.57 to 0.60 (Appendix IV A). The ratio of the absorbance at 239 nm to that at 263 nm is 2.25 to 2.45.

(3) The infrared absorption spectrum (Appendix IV C) is concordant with the reference spectrum of beclometasone dipropionate (Appendix XVI).

(4) Weigh about 25 mg, carry out the method for oxygen-flask combustion (Appendix VII C), using a mixture of 20 ml of water and 1 ml of 0.4% sodium hydroxide solution as the absorbing liquid. The resulting solution yields the reactions characteristic of chlorides (Appendix III).

Related substances Carry out the method for thin-layer chromatography (Appendix V B), using silica gel G as the coating substance and a mixture of dichloromethane-methanol-water (95:5:0.2) as the mobile phase. Apply separately to the plate 5 μl each of two solutions in chloroform-methanol (9:1) containing (1) 3.0 mg per ml and (2) 60 μg per ml of the substance being examined. After developing and removal of the plate, dry it in air and then at 105°C for 10 minutes. Cool and spray with alkaline tetrazolium blue TS. Not more than 2 secondary spots are observed in the chromatogram obtained with solution (1); and any secondary spot is not more intensely coloured than the principal spot obtained with solution (2).

Loss on drying When dried to constant weight at 105°C , loses not more than 0.5% of its weight (Appendix VIII L).

Residue on ignition Not more than 0.1% (Appendix VIII N).

Assay Carry out the method for high performance liquid chromatography (Appendix V D), using a column packed with octadecylsilane bonded silica gel and a mixture of methanol-water (74:26) as the mobile phase. Detection wavelength is 240 nm. The number of theoretical plates of the column is not less than 2500, calculated with reference to the peak of beclometasone dipropionate. The resolution factor between the peaks of beclometasone dipropionate and internal standard is not less than 4.0.

Internal standard solution Dissolve methyltestosterone in mobile phase to produce a solution of 0.12 mg per ml.

Procedure Dissolve about 12.5 mg of the substance being examined, accurately weighed, transfer 74 ml of methanol in a 100 ml volumetric flask, and dilute with water to volume, mix well, as the reference solution. Transfer 10 ml of the reference solution and 5 ml of internal standard solution, both accurately measured, in a 50 ml volumetric flask, dilute with mobile phase to volume, mix well, inject 20 μl of the resulting solution into the column. Repeat the operation, using beclometasone dipropionate CRS, instead of the substance being examined, calculate the content of $\text{C}_{28}\text{H}_{37}\text{ClO}_7$ with respect to the peak area obtained in the chromatogram by the internal standard method.

Category Corticosteroid.

Storage Preserve in tightly closed containers, protected from light.

Preparation (1) Beclometasone Dipropionate Aerosol
(2) Beclometasone Dipropionate Cream

Beclometasone Dipropionate Aerosol

Beclometasone Dipropionate Aerosol is an aerosol with metered dose valve. It contains not less than 85.0% and not more than 120.0% of the labelled amount of beclometasone dipropionate ($\text{C}_{28}\text{H}_{37}\text{ClO}_7$).

Description A white suspension in pressurized container; spray out as foggy particles on release of the delivery valve.

Identification On the aluminum cover of the container punch a hole and insert an injection needle with a dry rubber tubing into the container (do not contact the surface of liquid). The other end of the rubber tubing is inserted into water, allow the propellant to expel completely, remove the aluminum cover and expel the remaining propellant on a water bath. Wash the residual content with a quantity of 3 ml of cyclohexane for 3 times, filter with the same filter paper. Expel cyclohexane, wash the residual content within the container and on filter paper with 50 ml of dehydrated ethanol and filter. Dilute an accurately measured quantity of the successive filtrate equivalent to about 1 mg of beclometasone dipropionate with dehydrated ethanol to 50 ml. Carry out the method for the spectrophotometry (Appendix IV A), the light absorption exhibits a maximum at 239 nm.

Other requirements Comply with the general requirements for aerosol (Appendix I L).

Assay Reference preparation Dissolve 20 mg of beclometasone dipropionate CRS, accurately weighed, in a 100 ml volumetric flask in dehydrated ethanol and dilute to volume.

Test preparation Carry out the tests for the content of ingredient per delivery under Aerosols (Appendix I L), dilute accurately with dehydrated ethanol to produce a solution of 0.2 mg of the substance being examined per ml.

Procedure To 2 ml each of two preparations, accurately measured, in separate 25 ml stoppered volumetric flasks add accurately 2 ml of triphenyltetrazolium chloride TS and mix well; then add accurately 2 ml of tetramethylammonium hydroxide TS and mix well. Allow to stand in the dark place at 35°C for 1 hour and cool. Carry out the method for spectrophotometry (Appendix IV A), measure the absorbance at 485 nm. Calculate the content of $\text{C}_{28}\text{H}_{37}\text{ClO}_7$.

Category As described under Beclometasone Dipropionate.

Strength

(1)	50 μg per delivery; 200 deliveries per container
(2)	80 μg per delivery; 200 deliveries per container
(3)	100 μg per delivery; 200 deliveries per container
(4)	200 μg per delivery; 200 deliveries per container
(5)	250 μg per delivery; 200 deliveries per container
(6)	250 μg per delivery; 80 deliveries per container

Storage Preserve in well closed containers, stored in a dark and cool place.

Beclometasone Dipropionate Cream

Beclometasone Dipropionate Cream contains not less than 85.0% and not more than 115.0% of the labelled amount of beclometasone dipropionate ($C_{28}H_{37}ClO_7$).

Description A white cream.

Identification The retention time of principal peak of the substance being examined in the chromatogram obtained in the Assay is identical with that of beclometasone dipropionate CRS.

Other requirements Complies with the general requirements for cream (Appendix I F).

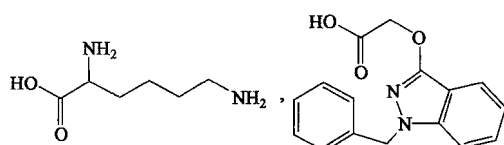
Assay Carry out the Assay described under Beclometasone Dipropionate. To an accurately weighed quantity of the ointment equivalent to 1.25 mg of beclometasone dipropionate add 30 ml of methanol. Heat in a water bath at 80°C for 2 minutes with stirring to dissolve beclometasone dipropionate, cool to room temperature. Add 5 ml of internal standard solution, accurately measured, dilute with methanol to 50 ml and mix well. Cool in an ice bath for at least 2 hours, filter swiftly. Inject 20 μ l of the successive filtrate into the column. Calculate the content of $C_{28}H_{37}ClO_7$.

Category As described under Beclometasone Dipropionate.

Strength 10 g:2.5 mg

Storage Preserve in tightly closed containers, protected from light and stored in a cool place.

Bendazac Lysine



$C_6H_{14}N_2O_2 \cdot C_{16}H_{14}N_2O_3$ 428.49 [81919-14-4]

Bendazac lysine is L-lysine [(1-Benzyl-1*H*-indazol-3-yl) oxy] acetate. It contains not less than 98.5% of $C_6H_{14}N_2O_2 \cdot C_{16}H_{14}N_2O_3$, calculated on the dried basis.

Description A white or almost white crystalline powder; odourless; taste, bitter. Soluble in water; practically insoluble in ethanol or chloroform.

Melting range 179-184°C (Appendix VI C).

Specific absorbance Measure the absorbance of a solution of 40 μ g per ml in water at 307 nm (Appendix IV A), the value of A (1%, 1 cm) is 125-135.

Identification (1) The light absorption of a solution of 30 μ g per ml in water exhibits a maximum at 307 nm, and a minimum at 272 nm (Appendix IV A).

(2) The infrared absorption spectrum (Appendix IV C) is concordant with the spectrum of bendazac lysine CRS.

Acidity or alkalinity Dissolve 1.0 g in 50 ml of water, pH 5.5-7.5 (Appendix VI H).

Clarity and colour of solution A solution of 0.1 g in 10 ml of

water is clear and colourless; any colour produced is not more intense than that of reference solution Y_1 (Appendix IX A, method 1).

Related substances Carry out the method for thin-layer chromatography (Appendix V B), using silica gel G as the coating substance and a mixture of toluene-glacial acetic acid (15:1) as the mobile phase. Apply separately to the plate 10 μ l each of two solutions in ethanol (70%) containing (1) 10 mg of substance being examined per ml, (2) 20 μ g of 3-hydroxy-1-Benzyl-indazol CRS per ml. After developing and removal of the plate, dry it in air and examine under ultra-violet light (254 nm). Not more than one, other than the principal spot in the chromatogram, obtained with solution (1) is observed. Any spot, other than the principal spot in the chromatogram, obtained with solution (1) is not more intense than the principal spot obtained with solution (2) (0.2%).

Loss on drying When dried to constant weight at 105°C, loses not more than 1.0% of its weight (Appendix VIII L).

Residue on ignition Not more than 0.2% (Appendix VIII N), using 1.0 g.

Heavy metals Carry out the limit test for heavy metals (Appendix VIII H, method 2), using the residue obtained in the test for Residue on ignition; not more than 0.002%.

Assay Dissolve about 0.2 g, accurately weighed, in 20 ml of glacial acetic acid, add 1 drop of crystal violet IS, titrate with perchloric acid (0.1mol/L) VS until the colour changes to bluish green. Perform a blank determination and make any necessary correction. Each ml of perchloric acid (0.1mol/L) VS is equivalent to 21.42mg of $C_6H_{14}N_2O_2 \cdot C_{16}H_{14}N_2O_3$.

Category Ophthalmics.

Storage Preserve in tightly closed containers, stored in a dry place.

Preparation Bendazac lysine eye drops

Bendazac Lysine Eye Drops

Bendazac lysine eye drops are a solution of bendazac lysine and suitable bacteriostatic agent in water. It contains not less than 90.0% and not more than 110.0% of the labelled amount of bendazac lysine ($C_6H_{14}N_2O_2 \cdot C_{16}H_{14}N_2O_3$).

Description A clear, colourless or almost colourless liquid.

Identification (1) Use a quantity of the eye drops as test solution, dissolve a quantity of bendazac lysine CRS in water to produce a solution of 5 mg per ml as reference solution. Carry out the test for Related substances described under Bendazac lysine, the fluorescent colour and position of the principal spot in the chromatogram obtained with the test solution correspond to the principal spot obtained with reference solution.

(2) The light absorption of the solution obtained in Assay exhibits a maximum at 307 nm, and a minimum at 272 nm (Appendix IV A).

pH value 6.8-7.8 (Appendix VI H).

Osmotic pressure ratio 0.90-1.10 (Appendix IX G).

Other requirements Comply with the general requirements for eye preparations (Appendix I G).

Assay Dilute an accurately measured quantity with water to produced a solution of 40 μ g of bendazac lysine per ml. Measure the absorbance of the solution at 307 nm (Appendix

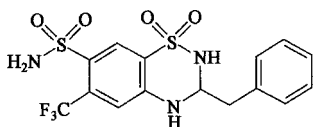
[V A]. Calculate the content of $C_6H_{14}N_2O_2 \cdot C_{16}H_{14}N_2O_3$, taking 130 as the value of A (1%, 1 cm).

Category As described under Bendazac Lysine.

Strength (1) 5 ml:25 mg (2) 8 ml:40 mg

Storage Preserve in tightly closed containers, protected from light.

Bendrofluazide



$C_{15}H_{14}F_3N_3O_4S_2$ 421.41

[71-48-3]

Bendrofluazide is 3 - (phenylmethyl) - 6 - (tri - fluoromethyl) - 7 - sulfonamide - 3,4 - dihydro - 2H - 1,2,4-benzothiadiazine-1,1-dioxide. It contains not less than 98.0% and not more than 102.0% of $C_{15}H_{14}F_3N_3O_4S_2$, calculated on the dried basis.

Description A white or almost white crystalline powder; odourless; tasteless.

Freely soluble in acetone; soluble in ethanol; slightly soluble in ether; insoluble in water or chloroform; soluble in alkali solution.

Identification (1) Warm about 20 mg with 1 ml of 5% potassium permanganate solution, acidified with sulfuric acid; the odour of phenyl acetaldehyde is perceptible.

(2) Heat gently about 20 mg in a small test tube until it becomes carbonized; the odour of sulfur dioxide is perceptible.

(3) The light absorption of a solution of 15 µg per ml in 0.01 mol/L sodium hydroxide solution exhibits maxima at 274 nm and 329 nm, the absorbance is about 0.62 and 0.12 respectively (Appendix IV A).

(4) The infrared absorption spectrum (Appendix IV C) is concordant with the reference spectrum of bendrofluazide (Appendix XVI).

(5) Yields reactions characteristic of organic fluorides (Appendix III).

Aromatic primary amine Dissolve about 80 mg, accurately weighed, in acetone in a 100 ml volumetric flask, add acetone to volume, mix well. Measure accurately 1 ml, add 9 ml of 1 mol/L hydrochloric acid solution and immediately 0.1 ml of 4% sodium nitrite solution, mix well and allow to stand for 1 minute. Add 0.2 ml of 10% ammonium sulfamate solution, mix well, allow to stand for 3 minutes. Add 0.8 ml of 2% N-(1-naphthyl)-ethylene-diamine dihydrochloride solution in dilute ethanol, mix well, allow to stand for 2 minutes. Maintain the temperature at 20°C throughout the tests. The absorbance of the resulting solution at 518 nm is not more than 0.11 (Appendix IV A).

Loss on drying When dried to constant weight at 105°C, loses not more than 0.5% of its weight (Appendix VIII L).

Residue on ignition No more than 0.1% (Appendix VIII N), using 1.0 g and a platinum crucible.

Heavy metals Carry out the limit test for heavy metals (Appendix VIII H, method 2), using the residue obtained in the test for Residue on ignition; not more than 0.002%.

Assay Weigh accurately about 0.2 g and dissolve in 40 ml of dimethylformamide, add 3 drops of azo violet IS. Titrate in

an atmosphere of N_2 with sodium methoxide (0.1 mol/L) VS until a blue colour is produced. Perform a blank determination and make any necessary correction. Each ml of sodium methoxide (0.1 mol/L) VS is equivalent to 21.07 mg of $C_{15}H_{14}F_3N_3O_4S_2$.

Category Diuretic.

Storage Preserve in tightly closed containers.

Preparation Bendrofluazide Tablets

Bendrofluazide Tablets

Bendrofluazide Tablets contain not less than 90.0% and not more than 110.0% of the labelled amount of bendrofluazide ($C_{15}H_{14}F_3N_3O_4S_2$).

Description White tablets.

Identification Dissolve a quantity of the powdered tablets equivalent to about 50 mg of bendrofluazide in 5 ml of acetone with shaking, filter, evaporate the filtrate to dryness on a water bath. The residue complies with test (1), (2) and (5) for Identification described under Bendrofluazide.

Content uniformity Comply with the requirements (Appendix X E).

Pulverize 1 tablet in a mortar. Triturate with a quantity of 0.4% sodium hydroxide solution and transfer it to 25 ml volumetric flask with 0.4% sodium hydroxide solution, shake thoroughly, dilute with 4% sodium hydroxide solution to volume, mix well. Filter, measure accurately 2 ml of successive filtrate in another 25 ml volumetric flask, dilute to volume and mix well. Measure the absorbance (Appendix IV A) as described under Assay and calculate the content of $C_{15}H_{14}F_3N_3O_4S_2$.

Other requirements Comply with the general requirements for tablets (Appendix I A).

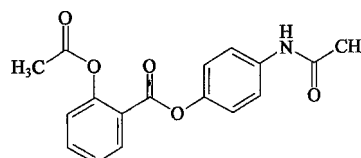
Assay Weigh accurately and powder 20 tablets. Weigh accurately a quantity of the powder equivalent to 15 mg of bendrofluazide in a 100 ml volumetric flask. Shake frequently with 0.4% sodium hydroxide solution for 10 minutes and then dilute to volume with 0.4% sodium hydroxide solution, mix well. Filter, measure accurately 5 ml of the successive filtrate to a 50 ml volumetric flask, dilute to volume with water and mix well. Measure the absorbance at 274 nm (Appendix IV A). Weigh accurately a quantity of bendrofluazide CRS, add 0.01 mol/L sodium hydroxide solution to produce a solution of 15 µg per ml. Measure the absorbance in the same manner, calculate the content of $C_{15}H_{14}F_3N_3O_4S_2$.

Category As described under Bendrofluazide.

Strength 5 mg

Storage Preserve in tightly closed containers.

Benorilate



$C_{17}H_{15}NO_5$ 313.31

[5003-48-5]

Benorilate is 4-acetamidophenyl acetylsalicylate. It contains not less than 98.5% of $C_{17}H_{15}NO_5$, calculated on dried basis.

Description White crystal or crystalline powder; odourless, tasteless.

Freely soluble in boiling ethanol; soluble in boiling methanol; slightly soluble in methanol or ethanol; insoluble in water.

Melting range 177-181°C (Appendix VI C).

Identification (1) To about 0.2 g add 5 ml of sodium hydroxide TS, boil and cool, filter. Acidify slightly the filtrate with a quantity of hydrochloric acid, add 2 drops of ferric trichloride TS; a violet colour is produced.

(2) The light absorption of a solution (Appendix IV A) obtained in the Assay exhibits a maximum at 240 nm. The absorption coefficient ($E_{1\%}^{1\text{cm}}$) is 730-760 calculated on the dried basis.

(3) The infrared absorption spectrum (Appendix IV C) is concordant with the reference spectrum of benorilate (Appendix XVI).

(4) To about 0.1 g add 5 ml of dilute hydrochloric acid, boil and cool, filter. The filtrate yields the reactions characteristic of primary aromatic amines (Appendix III).

Chlorides To 2.0 g add 100 ml of water, heat to boil and cool, add water to 100 ml, mix well and filter. Carry out the limit test for chlorides (Appendix VIII A), using 25 ml of the filtrate. Any opalescence produced is not more pronounced than that of a reference solution using 5 ml of sodium chloride standard solution (0.01%).

Sulfates Carry out the limit test for sulfate (Appendix VIII B), using 25 ml of the remained filtrate obtained in test for chlorides. Any opalescence produced is not more pronounced than that of a reference solution using 1 ml of potassium sulfate standard solution (0.02%).

4-Amiophenol To 1.0 g add 20 ml of methanol solution (1→2), stir well, add 1 ml of alkaline sodium nitroprusside TS, mix well, allow to stand for 30 minutes; no bluish-green colour is produced.

Salicylic acid Dissolve 0.1 g in 5 ml of ethanol by heat, add a quantity of water, mix well, filter into a 50 ml cylinder, add water to volume and add immediately 1 ml of freshly prepared dilute ferric ammonium sulfate solution (to 1 ml of 1 mol/L hydrochloric acid solution, add 2 ml of ferric ammonium sulfate IS, add water to produce 100 ml), mix well; any colour produced in 30 seconds is not more intense than that of a reference solution (dissolve 0.1 g of salicylic acid, accurately weighed, in water, add 1 ml of glacial acetic acid, mix well, add water to produce 1000 ml, mix well. Measure accurately 1 ml, add 5 ml of ethanol, 44 ml of water and 1 ml of above freshly prepared dilute ferric ammonium sulfate, mix well) (0.1%).

Related substances Carry out the method for thin-layer chromatography (Appendix V B), using silica gel GF₂₅₄ as the coating substance and a mixture of methylene dichloride-ether-glacial acetic acid (80:15:4) as the mobile phase. Apply separately to the plate 10 µl each of four solutions in a mixture of chloroform-methanol (9:1), containing (1) 40 mg per ml (2) 0.4 mg per ml of substance being examined (3) 80 µg per ml of substance being examined (4) 80 µg per ml of paracetamol. After developing and removal of the plate, dry it in air, examine under an ultraviolet light (254 nm). The secondary spots in the chromatogram obtained with solution (1) are not more than four spots and not more intense than the corresponding spots obtained with solution (4). The secondary spots in the chromatogram obtained with solution (1) above the

principal spot are not more intense than the principal spot obtained with solution (2) and the other secondary spots are not more intense than the principal spot obtained with solution (3).

Loss on drying When dried to constant weight at 105°C, loses not more than 0.5% of its weight (Appendix VIII L).

Residue on ignition Not more than 0.1% (Appendix VIII N), using 1.0 g.

Heavy metals Carry out the limit test for heavy metals (Appendix VIII H, method 2) using the residue obtained in the test for Residue on ignition; not more than 0.001%.

Assay dissolve a quantity, accurately weighed, in dehydrated ethanol, and dilute to produce a solution of about 7.5 µg per ml, measure the absorbance at 240 nm (Appendix IV A). Proceed as the same procedure, using benorilate CRS, accurately measured. Calculate the content of $C_{17}H_{15}NO_5$.

Category Antipyretic, anti-inflammatory and analgesic.

Storage Preserve in tightly closed containers, protected from light.

Preparation Benorilate Tablets

Benorilate, Pseudoephedrine Hydrochloride and Chlorphenamine Maleate Tablets

Benorilate, Pseudoephedrine Hydrochloride and Chlorphenamine Maleate Tablets contain not less than 90.0% and not more than 110.0% of the labelled amount of benorilate ($C_{17}H_{15}NO_5$), pseudoephedrine hydrochloride ($C_{10}H_{15}NO \cdot HCl$) and chlorphenamine maleate ($C_{16}H_{19}ClN_2 \cdot C_4H_4O_4$).

Formula	
Benorilate	300 g
Pseudoephedrine Hydrochloride	30 g
Chlorphenamine Maleate	2 g
Exipient	a quantity
to make	1000 tablets

Description White tablets.

Identification (1) The retention time of principal peaks of pseudoephedrine hydrochloride and chlorphenamine maleate in the substance being examined in the chromatogram obtained in the Assay of pseudoephedrine hydrochloride and chlorphenamine maleate are identical with that of principal peaks of pseudoephedrine hydrochloride CRS and chlorphenamine maleate CRS in the chromatogram of the reference solution correspondingly.

(2) The retention time of principal peak of benorilate in the substance being examined in the chromatogram obtained in the Assay of benorilate is identical with that of principal peak of benorilate CRS in the chromatogram of the reference solution.

Content uniformity Carry out the method for content uniformity (Appendix X E). Triturate and transfer 1 tablet with 80 ml of 50% ethanol solution to a 100 ml volumetric flask, ultrasonic for 5 minutes, dilute to volume with water, mix well and filter. Carry out the procedure described under the Assay of chlorphenamine maleate using the successive filtrate. Calculate the content of $C_{16}H_{19}ClN_2 \cdot$

$C_4H_4O_4$. The limit of content uniformity is $\pm 20\%$.

Dissolution Carry out the dissolution test (Appendix X C, method 2), using 1000 ml of 1% sodium dodecyl sulphate solution as the dissolution medium, adjust the rotational speed of the paddle to 75 rpm. Withdraw 10 ml of the solution after exactly 45 minutes and filter. Measure accurately 5 ml of the successive filtrate into a 50 ml volumetric flask, dilute to volume with anhydrous ethanol, and mix well; Dissolve about 15 mg of benorilate CRS accurately weighed, in a quantity of anhydrous ethanol in a 100 ml volumetric flask, dilute to volume with anhydrous ethanol, mix well, measure accurately 5 ml to a 25 ml volumetric flask, add 2.5 ml of 1% sodium dodecyl sulphate solution, dilute to volume with anhydrous ethanol, mix well. Measure the absorbances of the resulting solutions at 280 nm (Appendix IV A). Calculate the dissolution of $C_{17}H_{15}NO_5$ from each tablet. Not less than 70% of the labelled amount is dissolved.

Other requirements Comply with the general requirements of tablets (Appendix I A).

Assay Benorilate Carry out the method for high performance liquid chromatography (Appendix V D), using a column packed with phenylsilane bonded silica gel and a mixture of methanol-water (70 : 30) as the mobile phase. Detection wavelength is 245 nm and the number of theoretical plates of the column is not less than 2000, calculated with reference to the peak of benorilate.

Procedure Weigh accurately and powder 20 tablets. Transfer a quantity of the powder equivalent to about 50 mg of benorilate, accurately weighed, to a 100 ml volumetric flask, add 1 ml of 1% sodium dodecyl sulphate solution and 50 ml of methanol, ultrasonic for 5 minutes to dissolve benorilate, dilute to volume with methanol, mix well and filter. Measure accurately 5 ml of the successive filtrate to a 25 ml volumetric flask, dilute to volume with mobile phase, mix well. Inject 20 μ l of the resulting solution into the column, and record the chromatogram. Repeat the operation, using benorilate CRS instead of the substance being examined, calculate the content of $C_{17}H_{15}NO_5$.

Pseudoephedrine Hydrochloride and Chlorphenamine Maleate Carry out the method for high performance liquid chromatography (Appendix V D), using a column packed with octadecylsilane bonded silica gel and a mixture of acetonitrile-methanol-water-glacial acetic acid (37 : 36 : 27 : 0.3) (containing 0.35% sodium dodecyl sulphate) as the mobile phase. The column temperature is maintained at 30°C. Detection wavelength is 260 nm and the number of the theoretical plates of the column is not less than 2000, calculated with reference to the peak of chlorphenamine. The resolution factor between the peaks of pseudoephedrine and chlorphenamine complies with related requirements.

procedure Transfer a quantity of the powder equivalent to about 24 mg pseudoephedrine hydrochloride and 1.6mg of chlorphenamine maleate, accurately weighed, to a 100 ml volumetric flask, add 80 ml of 50% ethanol solution, ultrasonic for 5 minutes to dissolve pseudoephedrine hydrochloride and chlorphenamine maleate, dilute to volume with water, mix well and filter. Inject 20 μ l of the successive filtrate into the column, and record the chromatogram; Dissolve a quantity of pseudoephedrine hydrochloride CRS and chlorphenamine maleate CRS, accurately weighed, in 50% ethanol solution and dilute to produce a solution of about 0.24 mg pseudoephedrine hydrochloride and 0.016 mg chlorphenamine maleate per ml, repeat the operation, calculate the content of $C_{10}H_{15}NO \cdot HCl$ and $C_{16}H_{19}ClH_2 \cdot C_4H_4O_4$ respectively with respect to the peak areas obtained in the chromatogram by the external

standard method.

Category Analgesic and antipyretic, non-steroids anti-inflammatory, vasoconstrictor, histamine H_2 receptor antagonist.

Storage Preserve in tightly closed containers, protected from light.

Benorilate Tablets

Benorilate Tablets contain not less than 95.0% and not more than 105.0% of the labelled amount of benorilate ($C_{17}H_{15}NO_5$).

Description White tablets.

Identification A quantity of the finely powdered tablets complies with the tests for Identification (1) (4) described under Benorilate.

Dissolution Comply with the requirement for dissolution test (Appendix X C, method 2), using 1000 ml of 1% sodium laurylsulfate solution as the dissolution medium, adjust the rotational speed of the paddle to 90 rpm. Withdraw 10 ml of the solution after exactly 45 minutes and filter. Dilute 2 ml of the successive filtrate, accurately weighed, with water to 100 ml, mix well as the test solution; Dissolve 20 mg of benorilate CRS, accurately weighed, in anhydrous ethanol to make 50 ml, dilute 2 ml with 0.025% sodium laurylsulfate solution to 100 ml as the reference solution. Measure the absorbances of the resulting solutions at 240 nm (Appendix IV A). Calculate the dissolution of $C_{17}H_{15}NO_5$ from each tablet.

Other requirements Comply with the general requirements for tablets (Appendix I A).

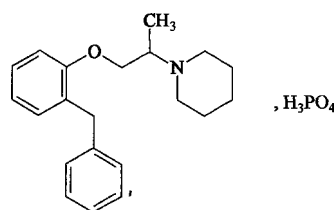
Assay Weigh and powder 10 tablets. Dissolve a quantity of the powder equivalent to about 15 mg of Benorilate in a 100 ml volumetric flask with dehydrated ethanol, by gently warm and shaking. Cool, dilute with anhydrous ethanol to volume, mix well and filter. Measure accurately 5 ml of the successive filtrate to 100 ml volumetric flask, dilute with dehydrated ethanol to volume and mix well. Measure the absorbance of the resulting solution at 240 nm (Appendix IV A). Calculate the content of $C_{17}H_{15}NO_5$, taking 745 as the value of A (1%, 1 cm).

Category As described under Benorilate.

Strength (1) 0.2 g (2) 0.5 g

Storage Preserve in tightly closed containers, protected from light.

Benproperine Phosphate



$C_{21}H_{27}NO \cdot H_3PO_4$ 407.44

[2156-27-6]

Benproperine phosphate is 1-[2-(2-benzy-

lphenoxy)-1-methylethyl] piperidine phosphate. It contains not less than 98.5% of $C_{21}H_{27}NO \cdot H_3PO_4$, calculated on the dried basis.

Description A white or almost white powder; with a faint characteristic odour; taste, bitter.

Freely soluble in water; sparingly soluble in ethanol, chloroform or benzene; insoluble in acetone or ether.

Melting range 148-153°C (Appendix VI C).

Identification (1) Dissolve 20 mg in 5 ml of water, add 1 ml of dilute hydrochloric acid and 3-5 drops of ammonium reineckate TS (or a few granules), a pink precipitate is formed.

(2) Dissolve a quantity in 0.5 ml of water, add 3 ml of 0.2% *p*-dimethylaminobenzaldehyde TS, mix well. A pink or red colour is produced after a few minutes.

(3) Dissolve a quantity in 1 ml of water, add 5 drops of dilute nitric acid and then 1 ml of sulfuric acid alongside the tube wall to form a subjacent layer, a grey bluish violet film and a purple ring are formed at the junction of the liquids.

(4) Dissolve about 20 mg in 5 ml of water, add 1 ml of dilute nitric acid and 1 ml of ammonium molybdate TS, a yellow precipitate is produced on heating.

(5) The light absorption of 0.01% aqueous solution exhibits two maxima at 270 nm and 276 nm (Appendix IV A).

(6) The infrared absorption spectrum (Appendix IV C) is concordant with the reference spectrum of benproperine phosphate (Appendix XVI).

Clarity and colour of solution A solution of 0.50 g in 25 ml of water is clear and colourless; any opalescence produced is not more pronounced than that of reference suspension I (Appendix IX B); any colour produced is not more intense than that of reference solution (Dilute 12.5 ml of reference solution Y_3 with water to 25 ml) (Appendix IX A).

Chloride Carry out the limit test for chloride (Appendix VIII A), using 0.50 g, any opalescence produced is not more intense than that of a reference solution using 5.0 ml of sodium chloride standard solution (0.01%).

Related substances Carry out the method for thin-layer chromatography (Appendix V B), using silica H as the coating substance (with the binder of 0.1% carboxymethyl-cellulose sodium, thickness is 5 nm) and a mixture of butanol-concentrated ammonia solution (30:1) as the mobile phase. Apply separately to the plate 10 μ l of each of two solutions in methanol containing (1) 10 mg per ml, (2) 0.1 mg per ml of the substance being examined. After developing and removal of the plate, dry it in air and visualize in iodine vapour. Any spot, other than the principal spot in the chromatogram, obtained with solution (1) is not more intense than the principal spot obtained with solution (2).

Barium Dissolve 2.0 g in 8 ml of water and 2 ml of dilute hydrochloric acid [filter with the filter paper washed by hydrochloric acid solution (1→40), if necessary], add 1 ml of dilute sulfuric acid. Any opalescence produced is not more intense than that of reference solution prepared by diluting 5.0 ml of barium standard solution [dilute 1 ml of 0.178% barium chloride ($BaCl_2 \cdot 2H_2O$) solution with water to 100 ml, mix well. It contains 10 μ g of Ba] with water to 10 ml, add 1 ml of dilute sulfuric acid and allow to stand for 30 minutes (0.0025%).

Loss on drying When dried to constant weight at 105°C, loses not more than 2.0% of its weight (Appendix VIII L).

Iron Dissolve 1.0 g in 30 ml of water in a separator, add 4 ml of dilute hydrochloric acid and 50 mg of ammonium persulfate. Add 3 ml of 30% ammonium thiocyanate solution and mix well, add 50 ml of butanol, shake thoroughly,

allow to stand until the extract separates into two layers. Transfer 25 ml of the butanol layer to a Nessler cylinder. Any colour produced is not more intense than that of reference solution prepared in the same manner using 2.0 ml of standard iron solution (0.002%).

Heavy metals Dissolve 1.0 g in a quantity of water, add 0.5 g of ascorbic acid, carry out the limit test for heavy metals (Appendix VIII H, method 1); not more than 0.001%.

Assay Dissolve about 0.3 g, accurately weighed, in 20 ml of glacial acetic acid and 4 ml of acetic anhydride, add 1 drop of crystal violet IS. Titrate with perchloric acid (0.1 mol/L) VS until the colour changes to green. Perform a blank determination and make any necessary correction. Each ml of perchloric acid (0.1 mol/L) VS is equivalent to 40.74 mg of $C_{21}H_{27}NO \cdot H_3PO_4$.

Category Antitussive.

Storage Preserve in tightly closed containers, protected from light.

Preparation (1) Benproperine Phosphate Capsules
(2) Benproperine Phosphate Granules
(3) Benproperine Phosphate Oral Solution
(4) Benproperine Phosphate Tablets

Benproperine Phosphate Capsules

Benproperine Phosphate Capsules contain not less than 90.0% and not more than 110.0% of the labelled amount of benproperine phosphate calculated as benproperine ($C_{21}H_{27}NO$).

Identification (1) Comply with the tests for Identification described under Benproperine Phosphate Tablets, using the contents of the capsules.

(2) To a quantity of the contents of the capsules equivalent to about 40 mg of benproperine phosphate, add 10 ml of water to dissolve benproperine phosphate and filter. To 5 ml of the filtrate add 1 ml of dilute nitric acid and 1 ml of ammonium molybdate TS, a yellow precipitate is produced on heating.

(3) Transfer a quantity of the contents of the capsules equivalent to about 10 mg of benproperine phosphate to a 100 ml volumetric flask, add a quantity of water to dissolve benproperine phosphate, dilute to volume, mix well and filter. The light absorption of the filtrate exhibits two maxima at 270 nm and 276 nm. (Appendix IV A)

Other requirements Comply with the general requirements for capsules (Appendix I E).

Assay Weigh accurately a quantity of the mixed contents obtained in the test for weight variation of contents equivalent to about 10 mg of benproperine phosphate in a 100 ml volumetric flask add a quantity of water and shake to dissolve benproperine phosphate, dilute with water to volume and mix well, filter with a No.5 sintered glass funnel. Measure the absorbance of the successive filtrate at 270 nm (Appendix IV A). Dissolve an accurately weighed quantity of benproperine phosphate CRS in water to produce a solution of 0.1 mg per ml. Measure the absorbance in the same manner. Calculate the content of $C_{21}H_{27}NO \cdot H_3PO_4$ and multiply the result by 0.7594.

Category As described under Benproperine Phosphate.

Strength 20 mg (Calculated as $C_{21}H_{27}NO$)

Storage Preserve in tightly closed containers, protected from light.

Benproperine Phosphate Granules

Benproperine Phosphate Granules contain not less than 90.0% and not more than 110.0% of the labelled amount of benproperine ($C_{21}H_{27}NO$).

Description Soluble granules; taste, sweet.

Identification (1) A quantity of powdered granules complies with the tests (1) and (4) for Identification described under Benproperine Phosphate.

(2) The retention time of the principal peak of the substance being examined in the chromatogram obtained in the Assay is identical with that of benproperine phosphate CRS.

Loss on drying When dried in vacuum over phosphorous pentoxide to constant weight at 80°C, loses not more than 2.0% of its weight (Appendix VIII L).

Other Requirements Comply with the general requirement for granules (Appendix I N).

Assay Carry out the method for high performance chromatography (Appendix V D), using a column packed with octadecylsilane bonded silica gel and a mixture of methanol-0.1 mol/L ammonium acetate BS (dissolve 7.7 g of ammonium acetate in 800 ml of water, adjust to pH 3.3 with glacial acetic acid, add water to 1000 ml) (65:35) as the mobile phase. Detection wavelength is 270 nm and the number of theoretical plates of the column is not less than 2000, calculated with reference to the peak of benproperine phosphate.

Procedure Weigh accurately a quantity of the powdered and mixed contents, equivalent to about 20 mg of benproperine phosphate, obtained in the test for weight variation into a 50 ml volumetric flask, dissolve benproperine phosphate with 20 ml of water, add 2.5 ml of 2% sodium hydroxide solution, shake for 1 minute until a white precipitate is produced, add 10 ml of 4% phosphoric acid solution to make the precipitate disappear, dilute with water to volume, mix well and filter, take the successive filtrate as test solution. Inject 10 µl of the test solution into the column, record the peak areas correspondingly obtained in the chromatogram. Repeat the operation, using a reference solution containing 0.4 mg of benproperine phosphate CRS per ml in mobile phase. Calculate the content of $C_{21}H_{27}NO \cdot H_3PO_4$ with respect to the peak area obtained in the chromatogram by the external standard method and multiply the result by 0.7594.

Category As described under Benproperine Phosphate.

Strength 20 mg (calculated as $C_{21}H_{27}NO$)

Storage Preserve in tightly closed containers, stored in a dry place.

Benproperine Phosphate Oral Solution

Benproperine Phosphate Oral Solution contains not less than 90.0% and not more than 110.0% of the labelled amount of benproperine ($C_{21}H_{27}NO$).

Description A slightly yellow to pale brownish-yellow viscous liquid; taste, numb.

Identification (1) To a quantity, equivalent to about 2 mg of benproperine phosphate, add 3 ml of water and 1 ml of dilute hydrochloric acid, add dropwise ammonium reineckate

TS a pink precipitate is formed.

(2) The retention time of the principal peak in the chromatogram of the test preparation obtained under the Assay corresponds with that of the principal peak in the chromatogram of the reference preparation.

pH value 3.0-5.0 (Appendix VI H).

Relative density Not less than 1.08 (Appendix VI A).

Other Requirements Complies with the general requirement for oral solution (Appendix I O).

Assay Carry out the method for high performance chromatography (Appendix V D), using a column packed with octadecylsilane bonded silica gel and a mixture of methanol-0.1 mol/L ammonium acetate BS (dissolve 7.7 g of ammonium acetate in 800 ml of water, adjust to pH 3.3 with glacial acetic acid, add water to 1000 ml) (65:35) as the mobile phase. Detection wavelength is 270 nm and the number of theoretical plates of the column is not less than 2000, calculated with reference to the peak of benproperine phosphate.

Procedure Measure accurately a quantity of the substance being examined, equivalent to about 20 mg of benproperine phosphate, into a 50 ml volumetric flask, dissolve benproperine phosphate with the mobile phase, and dilute with the same solution to volume as test solution. Inject 10 µl of the test solution into the column, record the peak areas correspondingly obtained in the chromatogram. Repeat the operation, using a reference solution containing 0.4 mg of benproperine phosphate CRS per ml in mobile phase. Calculate the content of $C_{21}H_{27}NO \cdot H_3PO_4$ with respect to the peak area obtained in the chromatogram by the external standard method and multiply the result by 0.7594.

Category As described under Benproperine Phosphate.

Strength (1) 10 ml:10 mg (2) 10 ml:20 mg
(3) 80 ml:80 mg (4) 100 ml:100 mg
(5) 100 ml:200 mg
(6) 120 ml:120 mg (calculated as $C_{21}H_{27}NO$)

Storage Preserve in tightly closed containers, protected from light.

Benproperine Phosphate Tablets

Benproperine Phosphate Tablets contain not less than 90.0% and not more than 110.0% of the labelled amount of benproperine phosphate calculated as benproperine ($C_{21}H_{27}NO$).

Description White tablets or sugar coated tablets or film coated tablets with white cores.

Identification (1) Comply with test (1), (2) and (3) for Identification described under Benproperine Phosphate, using a quantity of the powdered tablets.

(2) To a quantity of the powdered tablets equivalent to about 40 mg of benproperine phosphate add 10 ml of water to dissolve benproperine phosphate, filter. To 5 ml of the filtrate add 1 ml of dilute nitric acid and 1 ml of ammonium molybdate TS, a yellow precipitate is formed on heating.

(3) Transfer a quantity of the powdered tablets equivalent to about 10 mg of benproperine phosphate to a 100 ml volumetric flask, add a quantity of water to dissolve benproperine phosphate, dilute to volume, mix well and filter. The light absorption of the filtrate exhibits two maxima at 270 nm and 276 nm (Appendix IV A).

Other requirements Comply with the general requirements

for tablets (Appendix I A).

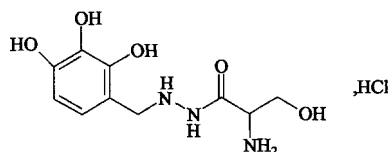
Assay Weigh accurately and powder 20 tablets with the coating removed. To an accurately weighed quantity of the powder equivalent to about 10 mg of benproperine phosphate in a 100 ml volumetric flask add a quantity of water and shake to dissolve benproperine phosphate, dilute with water to volume and mix well, filter with a No. 5 sintered glass funnel. Measure the absorbance of the successive filtrate at 270 nm (Appendix IV A). Dissolve an accurately weighed quantity of benproperine phosphate CRS in water to produce a solution of 0.1 mg per ml. Measure the absorbance in the same manner. Calculate the content of $C_{21}H_{27}NO \cdot H_3PO_4$ and multiply the result by 0.7594.

Category As described under Benproperine Phosphate.

Strength 20 mg (Calculated as $C_{21}H_{27}NO$)

Storage Preserve in tightly closed containers, protected from light.

Benserazide Hydrochloride



$C_{10}H_{15}N_3O_5 \cdot HCl$ 293.71 [14919-77-8]

Benserazide Hydrochloride is 2- [2,3,4 - (tri - hydroxyphenyl) methyl] hydrazidyl - DL - serine hydrochloride. It contains not less than 95.0% and not more than 102.0% of $C_{10}H_{15}N_3O_5 \cdot HCl$, calculated on the dried basis.

Description A white or almost white crystalline powder; hygroscopic; colour darkens on exposure to light. Freely soluble in water; sparingly soluble in methanol; insoluble in ethanol or acetone.

Identification (1) Dissolve a small quantity in 2 ml of water in a clean test tube, add 1 ml of ammoniacal silver nitrate TS, a brown colour is produced, silver sets free and forms a silver mirror on the tube wall on heating in a water bath.

(2) Dissolve a quantity in 2 ml of water, add 1 ml of ferric chloride TS, a brownish-green colour is produced.

(3) The retention time of principal peak of the substance being examined in the chromatogram obtained in the Assay is identical with that of benserazide hydrochloride CRS.

(4) The infrared absorption spectrum (Appendix IV C) is concordant with the reference spectrum of benserazide hydrochloride (Appendix XVI).

(5) An aqueous solution yields reactions characteristic of chlorides (Appendix III).

Related substances Dissolve a quantity of the substance being examined, accurately weighed, in mobile phase to produce a solution of 1.5 mg per ml (solution 1), measure accurately 2 ml, dilute with mobile phase to 100 ml and mix well (solution 2). Carry out the method as described under the Assay. Inject 10 μ l of solution (2) into the column, adjust the attenuation so that the principal peak height in the chromatogram is about 10%-15% of the full scale of the chart. Inject separately 20 μ l of above two solutions, and record the chromatogram for twice the retention time of the principal peak. The sum of the areas of all peaks other than

the principal peak in the chromatogram obtained with solution (1) is not greater than the area of the principal peak in the chromatogram obtained with solution (2).

Loss on drying When dried to constant weight under reduced pressure in a desiccator over phosphorus pentoxide, loses not more than 0.5% of its weight (Appendix VIII L).

Assay Carry out the method for high performance liquid chromatography (Appendix V D), using a column packed with octadecylsilane bonded silica gel and a mixture of trifluoroacetic acid-methanol-water (1 : 20 : 1000) as the mobile phase. Detection wavelength is 220 nm and the number of theoretical plates of the column is not less than 1000, calculated with reference to the peak of benserazide hydrochloride. The resolution factor between benserazide hydrochloride and dopamine complies with the related requirements.

Internal standard solution Dissolve a quantity of dopamine hydrochloride in mobile phase and dilute to a solution of 7 mg per ml.

Procedure Transfer about 15 mg, accurately weighed, into 50 ml amber-coloured volumetric flask, add 5 ml of internal standard solution, accurately measured, dilute with mobile phase to volume and mix well, inject 10 μ l into the column. Repeat the operation, using benserazide hydrochloride CRS instead of the substance being examined, calculate the content of $C_{10}H_{15}N_3O_5 \cdot HCl$.

Category Decarboxylase inhibitor.

Storage Preserve in tightly closed containers, protected from light.

Preparation (1) Levodopa and Benserazide Hydrochloride Capsules (2) Levodopa and Benserazide Hydrochloride Tablets

Benzalkonium Bromide

[1050-48-2]

Benzalkonium Bromide is a mixture of alkyl-benzyl-dimethylammonium bromides; It contains not less than 95.0% and not more than 105.0% of alkylbenzyl-dimethylammonium bromides, calculated as $C_{22}H_{40}BrN$ on the anhydrous basis.

Description Yellow gel or gelatinous masses. At low temperature it may form a waxy solid gradually. The aqueous solution yields alkaline reaction, foams on shaking. Freely soluble in water or ethanol; slightly soluble in acetone; insoluble in ether or benzene.

Identification (1) Dissolve about 0.2 g in 1 ml of sulfuric acid, add 0.1 g of sodium nitrate, heat on a water bath for 5 minutes, cool. Add 10 ml of water and 0.5 g of zinc powder, warm on a water bath for 5 minutes. To 2 ml of the supernatant add 1 ml of 5% sodium nitrite solution, cool in an ice bath, add 3 ml of alkaline β -naphthol TS, an reddish-orange colour is produced.

(2) To 10 ml of a 1% solution, add 0.5 ml of dilute nitric acid, a white precipitate is formed. Filter, the precipitate dissolves easily in ethanol, and the filtrate yields the reactions characteristic of bromides (Appendix III).

Ammonium compounds Heat 5 ml of a 2% solution (2 \rightarrow 100) with 3 ml of sodium hydroxide TS to boil. No ammonia odour is perceptible.

Non-quaternary ammonium compound Dissolve 4.0 g in sufficient water to produce 100 ml. Transfer 25.0 ml of the

solution to a separator, add 25 ml of chloroform, 10 ml of sodium hydroxide solution (0.1 mol/L) VS, and 10 ml of a freshly prepared 5% potassium iodide solution, accurately measured, shake and allow to stand until separation takes place. Wash the aqueous layer with three portions of 10 ml each of chloroform, discard the chloroform layers. To the aqueous layer add 40 ml of hydrochloric acid, cool, add 40 ml of 50% potassium bromide solution and titrate with potassium iodate (0.05 mol/L) VS until the solution becomes pale brown. Add 2 ml of chloroform, continue the titration with shaking until the red colour of the chloroform layer disappears. Transfer 25.0 ml of above benzalkonium bromide solution to another separator, add 25 ml of chloroform and 10 ml of 0.1 mol/L hydrochloric acid solution, proceed as described above, beginning with the addition of freshly prepared 5% potassium iodide solution. The difference of the amount of potassium iodate (0.05 mol/L) VS consumed between the two titrations is not more than 0.5 ml.

Water Not more than 10.0% (Appendix VIII M, method 1 A).

Assay Transfer accurately about 0.25 g to a stoppered conical flask, add 50 ml of water and 1 ml of sodium hydroxide TS, shake thoroughly. Add 0.4 ml of bromophenol blue IS and 10 ml of chloroform, titrate with sodium tetraphenylborate (0.02 mol/L) VS, shaking vigorously towards the end of titration until the blue colour of the chloroform layer disappears. Each ml of sodium tetraphenylborate (0.02 mol/L) VS is equivalent to 7.969 mg of $C_{22}H_{40}BrN$.

Category Antiseptic disinfectant.

Storage Preserve in tightly closed containers, protected from light.

Preparation Benzalkonium Bromide Solution

Benzalkonium Bromide Solution

Benzalkonium Bromide Solution is an aqueous solution of benzalkonium bromide. It contains not less than 4.75% and not more than 5.25% of alkylbenzyltrimethylammonium bromides, calculated as $C_{22}H_{40}BrN$.

Description A clear, colourless to pale yellow liquid; odour, aromatic; taste, very bitter. Foams on vigorous shaking. An opalescence or a sediment may appear at low temperature.

Identification Evaporate 6 ml on a water bath to dryness, the residue complies with the tests for Identification described under Benzalkonium Bromide.

Assay Carry out the Assay described under Benzalkonium Bromide, using 5 ml, accurately measured.

Category As described under Benzalkonium Bromide.

Storage Preserve in well closed containers, protected from light.

Benzalkonium Chloride

[8001-54-5]

Benzalkonium Chloride is a mixture of alkylbenzyltrimethylammonium chlorides. It contains

not less than 95.0% and not more than 105.0% of alkylammonium salts, calculated as $C_{22}H_{40}ClN$ on the anhydrous basis.

Description A white waxy solid or yellow gelatinous mass. The aqueous solution yields neutral or weakly alkaline reaction, foams on shaking.

Very soluble in water or ethanol; slightly soluble in ether.

Identification (1) Dissolve about 0.2 g in 1 ml of sulfuric acid, add 0.1 g of sodium nitrate, heat on a water bath for 5 minutes and cool. Add 10 ml of water and 0.5 g of zinc powder, warm on a water bath for 5 minutes. To 2 ml of the supernatant liquid add 1 ml of 5% sodium nitrite solution, cool in an ice bath, add 3 ml of alkaline β -naphthol TS, a scarlet colour is produced.

(2) The light absorption of a solution of 0.5 mg per ml in water exhibits three maxima at 257 nm, 262 nm and 269 nm (Appendix IV A).

(3) To 10 ml of 1% solution add 0.5 ml of dilute nitric acid, a white precipitate is formed. Filter, the precipitate dissolves in ethanol, and the filtrate yields the reactions characteristic of chlorides (Appendix III).

Water insoluble matter Dissolve 1.0 g in 10 ml of water, no turbidity is produced and no insoluble matter is observed.

Ammonium Compounds Dissolve 0.1 g in 5 ml of water, add 3 ml of sodium hydroxide TS, heat to boil; no ammonia odour is perceptible.

Water Carry out the determination of water (Appendix VIII M, method 1 A): not more than 10.0%.

Assay Weigh accurately about 0.5 g in a beaker, transfer to a 250 ml separator with the aid of 35 ml of water in portions. Add 10 ml of 0.1 mol/L sodium hydroxide solution, 25 ml of chloroform and measured accurately 10 ml of freshly prepared 5% potassium iodide solution. Shake and allow to stand until separation takes place. Extract the aqueous layer with 10 ml each of chloroform for 3 times, discard the chloroform layers. Transfer the aqueous layer to a 250 ml conical flask with stopper, rinse the separator with about 15 ml of water in three portions, combine the washing solutions and aqueous solution. Add 40 ml of hydrochloric acid, allow to cool, titrate with potassium iodate (0.05 mol/L) VS to light brown colour, add 5 ml of chloroform, shaking vigorously towards the end of titration until the colour of the chloroform layer just disappears. Perform a blank determination and make any necessary correction. Each ml of potassium iodate (0.05 mol/L) VS is equivalent to 35.40 mg of $C_{22}H_{40}ClN$.

Category Antiseptic disinfectant.

Storage Preserve in tightly closed containers, protected from light.

Preparation Benzalkonium Chloride Solution

Benzalkonium Chloride Solution

Benzalkonium Chloride Solution is an aqueous solution of benzalkonium chloride. It contains not less than 95.0% and not more than 105.0% of the labelled amount of alkylammonium salts calculated as $C_{22}H_{40}ClN$.

Description A clear, colourless to pale yellow liquid; Odour, flavour; taste, very bitter; foams vigorously on shaking.

Identification Evaporate the solution on a water bath to dryness, the residue complies with the test for Identification described under Benzalkonium Chloride.

Ammonium salts To 1 ml of the solution in a test tube add 4 ml of water and 3 ml of sodium hydroxide TS, heat to boil; no ammonia odour is perceptible.

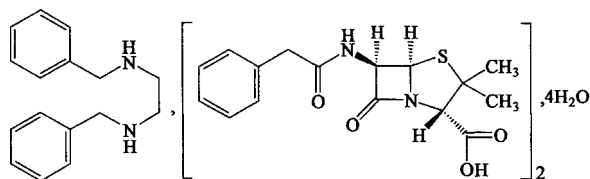
Assay Measure accurately 5 ml of the solution equivalent to about 0.5 g of Benzalkonium Chloride and proceed the Assay described under Benzalkonium Chloride.

Category As described under Benzalkonium Chloride.

Strength 10%

Storage Preserve in well closed containers, protected from light.

Benzathine Benzylpenicillin



$(C_{16}H_{18}N_2O_4S)_2 \cdot C_{16}H_{20}N_2 \cdot 4H_2O$ 981.18

Benzathine benzylpenicillin is a sterile mixture of *N*, *N'*-dibenzylethane-1,2-diamine compound (1 : 2) with (2*S*, 5*R*, 6*R*)-3,3-dimethyl-7-oxo-6-[2-(phenylacetyl) amino]-4-thia-1-azabicyclo [3.2.0] heptane-2-carboxylic acid tetrahydrate. Dispersing or suspend agents may be added. It has a potency of not less than 1180 Benzylpenicillin Units per mg, calculated on the anhydrous basis.

Description A white crystalline powder.

Freely soluble in dimethylformamide and in formamide; slightly soluble in alcohol, very slightly soluble in water.

Identification (1) The retention time of principal peak of the substance being examined in the chromatogram obtained in the Assay is identical with that of benzylpenicillin CRS. (2) Shake about 0.2 g with 2 ml of sodium hydroxide TS, extract the mixture with 10 ml of ether, evaporate 3 ml of the ether extract to dryness and dissolve the residue in 2 ml of glacial acetic acid. Add 1 ml of potassium dichromate TS, a golden precipitate is formed. (3) The infrared absorption spectrum (Appendix IV C) is concordant with the reference spectrum of Benzathine Benzylpenicillin (Appendix XVI).

Acidity or alkalinity Suspend 50 mg in 10 ml of water, pH 5.0-7.5 (Appendix VI H).

***N,N'*-dibenzylethylenediamine** Dissolve about 1 g, accurately weighed, in 30 ml of saturated sodium chloride solution and 10 ml of 5 mol/L sodium hydroxide solution, mix well, transfer to separator and extract with four quantities, each of 50 ml of ether. Combine the ether extracts, wash with three quantities, each of 10 ml, of water. Combine the aqueous extracts and extract with 25 ml of ether. Combine the all ether extracts, evaporate the ether extracts to about 5 ml and add 2 ml of absolute ethanol, evaporate the above solution to dryness. Dissolve the residue in 50 ml of acetic acid glacial and 1 ml of 0.2% naphtholbenzein IS, titrate with perchloric acid (0.1 mol/L) VS until yellow solution becomes green. Perform a blank determination and make any necessary correction. Each ml of perchloric acid (0.1 mol/L)

VS is equivalent to 12.02 mg of $C_{16}H_{20}N_2$. It contains not less than 24.0% and not more than 27.0% of *N,N'*-dibenzylethylenediamine, calculated on the anhydrous basis.

Water 5.0%-8.0% (Appendix VIII M, method 1 A).

Consistence Shake 1.5 g with 5 ml of water, mix well.

The aqueous suspension passes readily through a No. 5 $\frac{1}{2}$ hypodermic needle without blockage.

Bacterial endotoxin Carry out the test for bacterial endotoxin (Appendix XI E); not more than 0.25 EU per 1000 benzathine benzylpenicillin Units.

Sterility Complies with the test for sterility (Appendix XI H). Each portion is inactivated by penicillinase.

Assay Carry out the method for high performance liquid chromatography (Appendix V D), using a column packed with octadecylsilane bonded silica gel and a mixture of 0.05 ml/L phosphate buffer solution (dissolve 6.8 g of potassium dihydrogen phosphate in 900 ml of water, adjust the pH value with 1 mol/L sodium hydroxide solution to 6.0 and dilute with water to 1000 ml, mix well)-acetonitrile (75:25) as the mobile phase. Detection wavelength is 225 nm and the number of the theoretical plates of the column is not less than 2000, the flow rate is 1 ml per minute calculated with reference to the peak of benzylpenicillin. The resolution factor between the peaks of benzyl penicillin and the neighbor peaks complies with the related requirement.

Procedure Dissolve about 53 mg of benzathine benzylpenicillin, accurately weighed, in 10 ml of acetonitrile and 5 ml of methanol in a 50 ml volumetric flask, add the 0.05 ml/L phosphate buffer solution to volume, mix well. Inject 20 μ l of the resulting solution into the column. Repeat the operation, using benzylpenicillin CRS instead of the substance being examined. Calculate the content of benzylpenicillin with respect to the peak area obtained in the chromatogram by the external standard method. Each mg of $C_{16}H_{18}N_2O_4S$ is equivalent to 1780 Benzylpenicillin Units.

Category β -lactam antibiotics, penicillins.

Storage Preserve in tightly closed containers, stored in a cool and dry place and protected from light.

Preparation Benzathine Benzylpenicillin for Injection

Benzathine Benzylpenicillin for Injection

Benzathine Benzylpenicillin for Injection is a sterile mixture of *N,N'*-dibenzylethylenediamine salt of benzylpenicillin [$(C_{16}H_{18}N_2O_4S)_2 \cdot C_{16}H_{20}N_2$] with suitable amount of buffer and suspension agent. It has a potency of not less than 1180 Benzylpenicillin Units per mg, calculated on the anhydrous basis. Each container contains not less than 95.0% and not more than 105.0% of the labelled amount of Benzylpenicillin, calculated on the basis of the average weight of contents.

Description A white crystalline powder.

Identification Complies with the tests for Identification described under Benzathine Benzylpenicillin.

Acidity or alkalinity, *N,N'*-dibenzylethylenediamine, Water, Consistence, Bacterial endotoxin and Sterility Complies with the corresponding tests described under Benzathine

Benzylpenicillin.

Other requirements Complies with the general requirements for injections (Appendix I B), except the weight variation is not more than $\pm 7\%$.

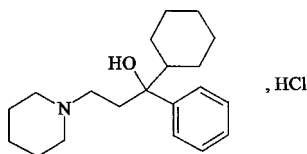
Assay Shake and dissolve about 53 mg, weighed accurately, of the mixed contents obtained in the test for weight variation of contents in a 50 ml volumetric flask in 10 ml of acetonitrile and 5 ml of methanol, dilute with 0.05 mol/L phosphate buffer solution to volume and mix well. Carry out the Assay described under Benzathine Benzylpenicillin. Each mg of $C_{16}H_{18}N_2O_4S$ is equivalent to 1780 Benzylpenicillin Unit.

Category As described under Benzathine Benzylpenicillin.

Strength (1) 300000 Units (2) 600000 Units
(3) 1200000 Units

Storage Preserve in tightly closed containers, stored in a dry place

Benzhexol Hydrochloride



$C_{20}H_{31}NO \cdot HCl$ 337.93

[52-49-3]

Benzhexol Hydrochloride is α -cyclohexyl- α -phenyl-1-piperidinepropanol hydrochloride. It contains not less than 98.0% of $C_{20}H_{31}NO \cdot HCl$, calculated on the dried basis.

Description A white, light crystalline powder; odourless; taste, slightly bitter then irritant and numbing. Soluble in methanol, ethanol or chloroform; slightly soluble in water.

Identification (1) Dissolve about 0.1 g in 5 ml of warm ethanol, make alkaline with sodium hydroxide TS dropwise, the precipitate thus produced is recrystallized from ethanol and dried. It melts at 112-116°C (Appendix VI C).

(2) The infrared spectrum (Appendix IV C) is concordant with the reference spectrum of benzhexol hydrochloride (Appendix XVI).

(3) The aqueous solution yields the reactions characteristic of chlorides (Appendix III).

Acidity Dissolve 0.50 g in 50 ml of water by heating to about 80°C, cool; pH 5.0-6.0 (Appendix VI H).

Piperidylpropiofenone Dissolve 0.10 g in a mixture of 40 ml of water and 1 ml of hydrochloric acid solution (9→100) by heating, cool and add sufficient water to produce 100 ml. The light absorbance of the resulting solution at 247 nm is not more than 0.50 (Appendix IV A).

Loss on drying When dried to constant weight at 105°C, loses not more than 0.5% of its weight (Appendix VIII L).

Residue on ignition Not more than 0.1% (Appendix VIII N).

Assay Dissolve about 0.2 g, accurately weighed, in 10 ml of glacial acetic acid, add 4 ml of mercuric acetate TS and 1 drop of crystal violet IS. Titrate with perchloric acid (0.1 mol/L) VS until the colour changes to bluish-green. Perform a blank determination and make any necessary correction. Each ml of perchloric acid (0.1 mol/L) VS is equivalent to 33.79 mg of $C_{20}H_{31}NO \cdot HCl$.

Category Anti-Parkinsonian.

Storage Preserve in tightly closed containers.

Preparation Benzhexol Hydrochloride Tablets

Benzhexol Hydrochloride Tablets

Benzhexol Hydrochloride Tablets contain not less than 93.0% and not more than 107.0% of the labelled amount of benzhexol hydrochloride ($C_{20}H_{31}NO \cdot HCl$).

Description White tablets.

Identification (1) To a quantity of the powdered tablets equivalent to about 20 mg of benzhexol hydrochloride add 20 ml of water, shake to dissolve benzhexol hydrochloride and filter. Divide the filtrate into two portions. To one portion add trinitrophenol TS, a yellow precipitate is produced; To another portion add 20% sodium hydroxide solution, a white precipitate is produced.

(2) Carry out the method for thin-layer chromatography (Appendix V B), using silica gel G as the coating substance and a mixture of chloroform-methanol (9:1) as the mobile phase. Apply separately to the plate 10 μ l each of two chloroform solution containing (1) 2 mg of the substance being examined per ml and (2) 2 mg of benzhexol hydrochloride CRS per ml. After developing and removal of the plate, dry it in air and spray with dilute potassium iodobismuthate TS. The principal spot in the chromatogram obtained with solution (1) corresponds in position with the principal spot obtained with solution (2).

Content uniformity Comply with the requirements (Appendix X E).

Shake 1 tablet with 6 ml of water in a 50 ml flask with stoppered, add 2 ml of dilute sulfuric acid, 10 ml of chloroform, and 0.2 ml of dimethyl yellow-methylene blue IS. Titrate with 0.05% sodium dioctyl sulfosuccinate solution, shake vigorously towards the end of titration, continue to titrate until the chloroform layer changes from green to reddish-grey. Dissolve about 20 mg of benzhexol hydrochloride CRS, accurately weighed, with 20 ml of dilute sulfuric acid in a 50 ml volumetric flask, dilute to volume with water and mix well. Transfer 5 ml of the solution, accurately measured, to a 50 ml flask with stopper, add 3 ml of water, 10 ml of chloroform and 0.2 ml of dimethyl yellow-methylene blue IS, titrate in the same manner as described above. Calculate the content of $C_{20}H_{31}NO \cdot HCl$ (Appendix X E).

Other requirements Comply with the general requirements for tablets (Appendix I A).

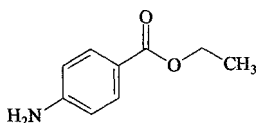
Assay Weigh accurately and powder 25 tablets. Weigh accurately a quantity of the powder equivalent to about 20 mg of benzhexol hydrochloride in a flask with stopper, add 8 ml of water, 3 ml of dilute sulfuric acid, 25 ml of chloroform and 0.5 ml of dimethyl yellow-methylene blue IS. Titrate with 0.25% sodium dioctyl sulfosuccinate solution, shake vigorously towards the end of titration, continue the titration until the chloroform layer changes from green to reddish-grey. Perform a titration in the same manner, using 20 mg of benzhexol hydrochloride CRS instead of the substance being examined. Calculate the content of $C_{20}H_{31}NO \cdot HCl$.

Category As described under Benzhexol Hydrochloride.

Strength 2 mg

Storage Preserve in tightly closed containers.

Benzocaine



$C_9H_{11}NO_2$ 165.19

[94-09-7]

Benzocaine is ethyl 4-aminobenzoate. It contains not less than 99.0% of $C_9H_{11}NO_2$, calculated on the dried basis.

Description A white crystalline powder; odourless; taste, slightly bitter and followed by a sensation of numbness; the colour becomes yellow gradually on exposure to light. Freely soluble in ethanol, chloroform or ether; sparingly soluble in fixed oils; very slightly soluble in water; soluble in diluted acids.

Melting point 88-91°C (Appendix VI C).

Identification (1) Boil 0.1 g with 5 ml of sodium hydroxide TS, ethanol is liberated. Then heat with iodine TS, a yellow precipitate is produced and the characteristic odour of iodoform is perceptible.

(2) The infrared absorption spectrum (Appendix IV C) is concordant with the reference spectrum of benzocaine (Appendix XVI).

(3) Yields the reaction characteristic of primary aromatic amines (Appendix III).

Acidity Dissolve 1.0 g in 10 ml of ethanol previously neutralized to phenolphthalein IS, add 2 drops of phenolphthalein IS. Not more than 0.10 ml of sodium hydroxide (0.1 mol/L) VS is required to produce a slightly pink colour.

Chloride Dissolve 0.2 g in 5 ml of ethanol, add 3 drops each of dilute nitric acid and silver nitrate TS, no opalescence is produced immediately.

Loss on drying When dried over phosphorous pentoxide in a desiccator to constant weight, loses not more than 0.5% of its weight (Appendix VIII L).

Residue on ignition Not more than 0.1% (Appendix VIII N), using 1.0 g.

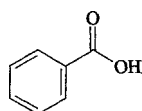
Heavy metals Carry out the limit test for heavy metals (Appendix VIII H, method 2), using the residue obtained in the residue on ignition test: not more than 0.001%.

Assay Weigh accurately about 0.35 g, carry out the method for dead-stop titration (Appendix VIII A), titrate with sodium nitrite (0.1 mol/L) VS. Each ml of sodium nitrite (0.1 mol/L) VS is equivalent to 16.52 mg of $C_9H_{11}NO_2$.

Category Local anesthetic.

Storage Preserve in tightly closed containers, protected from light.

Benzoic Acid



$C_7H_6O_2$ 122.12

[65-85-0]

Benzoic acid contains not less than 99.0% of $C_7H_6O_2$.

Description White light flakes with silky lustre or needle crystals or a crystalline powder, odourless, or almost odourless; slightly volatile in warm air; the aqueous solution exhibits an acidic reaction.

Freely soluble in ethanol, chloroform and ether; soluble in boiling water; slightly soluble in water.

Melting point 121-124.5°C (Appendix VI C).

Identification (1) To about 0.2 g add 15 ml of 4% sodium hydroxide solution, shake and filter. To the filtrate add 2 drops of ferric chloride TS, a reddish-brown precipitate is produced.

(2) The infrared absorption spectrum (Appendix IV C) is concordant with the reference spectrum of benzoic acid (Appendix XVI).

Oxidizable substances Add 1.5 ml of sulfuric acid to 100 ml of water, heat to boil, add dropwise potassium permanganate (0.02 mol/L) VS until the pink colour persists for 30 seconds. Dissolve 1.0 g of the substance being examined in the hot solution, not more than 0.25 ml of potassium permanganate (0.02 mol/L) VS is required to produce a pink colour that persists for 15 seconds.

Residue on ignition Not more than 0.1% (Appendix VIII N).

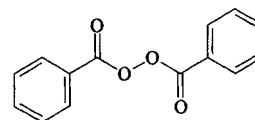
Heavy metals Dissolve 1.0 g in 22 ml of ethanol, add 2 ml of acetate BS (pH 3.5) and sufficient water to produce 25 ml. Carry out the limit test for heavy metals (Appendix VIII H, method 1); not more than 0.001%.

Assay Dissolve about 0.25 g, accurately weighed, in 25 ml of dilute ethanol (neutral to phenolphthalein IS), add 3 drops of phenolphthalein IS and titrate with sodium hydroxide (0.1 mol/L) VS. Each ml of sodium hydroxide (0.1 mol/L) VS is equivalent to 12.21 mg of $C_7H_6O_2$.

Category Antiseptic disinfectant.

Storage Preserve in tightly closed containers.

Benzoyl Peroxide



$C_{14}H_{10}O_4$ 242.23

[94-36-0]

Benzoyl peroxide is hydrous dibenzoyl peroxide. It contains not less than 70.0% and not more than 77.0% of $C_{14}H_{10}O_4$, and not less than 20.0% of water.

Description A white crystalline powder; odour characteristic. Freely soluble in acetone or chloroform; sparingly soluble in methanol or ethanol; very slightly soluble in water.

Identification (1) The light absorption of a solution of 5 µg per ml in dehydrated ethanol exhibits maximum at 235 nm (Appendix IV A).

(2) The infrared absorption spectrum (Appendix IV C) is concordant with the reference spectrum of benzoyl peroxide (Appendix XVI).

Chloride Carry out the limit test for chlorides (Appendix VIII A). To 100 mg, accurately weighed, in a 50 ml Nessler

cylinder add 15 ml of acetone to dissolve benzoyl peroxide, dilute to 25 ml with acetone. Any opalescence produced is not more pronounced than that of a reference solution using 7.0 ml of sodium chloride standard solution (0.07%).

Related substances Carry out the method for thin-layer chromatography (Appendix V B), using silica gel GF₂₅₄ as the coating substance and a mixture of toluene-dichloromethane-glacial acetic acid (50:2:1) as the mobile phase. Apply separately to the plate 10 µl each of two solutions in acetone containing (1) 10 mg per ml and (2) 0.2 mg per ml of the substance being examined. After developing and removal of the plate, dry it in air and examine under ultraviolet light (254 nm). Any spot other than the principal spot, obtained with solution (1) is not more intense than the principal spot obtained with solution (2).

Assay Anhydrous Benzoyl Peroxide Dissolve 0.25 g, accurately weighed, in a 250 ml iodine flask with 30 ml of acetone on shaking. Add 5 ml of potassium iodide TS, stopper and mix well, allow to stand in the dark for 15 minutes. Titrate with sodium thiosulfate (0.1 mol/L) VS until the colour disappears. Perform a blank determination and make any necessary correction. Each ml of sodium thiosulfate (0.1 mol/L) VS is equivalent to 12.11 mg of C₁₄H₁₀O₄.

Water Dissolve about 0.12 g, accurately weighed, in 5 ml of dimethylformamide. Add 20 ml of dehydrated methanol and 3 ml of dimethylformamide solution which contains 10% potassium iodide and stir for 5 minutes. Carry out the determination for water (Appendix VIII M, method 1 A). Calculate the content of water which is the result of the determination of water plus the content of anhydrous benzoyl peroxide multiplied by 0.0744.

Category Antiseptic disinfectant.

Storage Preserve in tightly closed containers, protected from light, stored with a quantity of moisture.

Preparation (1) Benzoyl Peroxide Cream
(2) Benzoyl Peroxide Gel

Benzoyl Peroxide Cream

Benzoyl Peroxide Cream contains not less than 90.0% and not more than 110.0% of the labelled amount of benzoyl peroxide (C₁₄H₁₀O₄).

Description A white cream.

Identification To a quantity of benzoyl peroxide cream equivalent to 100 mg of benzoyl peroxide, add 10 ml of acetone, shake till well-dispersed and filter, use the filtrate as the test solution. Dissolve Benzoyl Peroxide CRS in acetone to produce a solution of 10 mg per ml as the reference solution. Carry out the method for thin-layer chromatography (Appendix V B), using silica gel GF₂₅₄ as the coating substance and a mixture of toluene-dichloromethane-glacial acetic acid (50:2:1) as the mobile phase. Apply separately to the plate 5 µl each of the two solutions. After developing and removal of the plate, dry it in air and examine under ultraviolet light (365 nm). The principal spots in the chromatogram obtained with the two solutions are identical in position and colour.

pH value 2.8-7.0 (Appendix VI H).

Other requirements Complies with the general requirements for ointment (Appendix I F).

Assay Place a quantity of the cream equivalent to about 250 mg of benzoyl peroxide, accurately weighed, in a 100 ml conical flask with stopper, add 30 ml of acetone, shake till well-dispersed, add 5 ml of potassium iodide TS, stopper and shake for 1 minute. Titrate with sodium thiosulfate (0.1 mol/L) VS until the colour disappears. Each ml of sodium thiosulfate (0.1 mol/L) VS is equivalent to 12.11 mg of C₁₄H₁₀O₄.

Category As described under Benzoyl Peroxide.

Strength (1) 5% (2) 10%

Storage Preserve in tightly closed containers, protected from light and stored in a cool place.

Benzoyl Peroxide Gel

Benzoyl Peroxide Gel contains not less than 90.0% and not more than 110.0% of the labelled amount of benzoyl peroxide (C₁₄H₁₀O₄).

Description A creamy white, viscous gel.

Identification (1) To a quantity of the substance being examined equivalent to about 50 mg of benzoyl peroxide, add 5 ml of acetone, extrude the specimen with a glass rod to dissolve benzoyl peroxide. Add 2 ml of potassium iodide TS; a reddish-brown colour is produced and it disappears upon the addition of 5 ml of thiosulfate TS.

(2) To a quantity of the substance being examined equivalent to about 100 mg of benzoyl peroxide, add 10 ml of acetone, extrude the specimen with a glass rod to dissolve benzoyl peroxide. Filter and use the filtrate as the test solution. Dissolve benzoyl peroxide CRS in acetone to produce a solution of 10 mg per ml as the reference solution. Carry out the method for thin-layer chromatography (Appendix V B), using silica gel GF₂₅₄ as the coating substance and a mixture of toluene-dichloromethane-glacial acetic acid (50:2:1) as the mobile phase. Apply separately to the plate 5 µl each of above two solutions. After developing and removal of the plate, dry it in air and examine under ultraviolet light (254 nm). The colour and position of the principal spot in the chromatogram obtained with the test solution correspond to the principal spot obtained with reference solution.

pH value 4.5-7.0 (Appendix VI H).

Other requirements Complies with the general requirements for gel (Appendix I U).

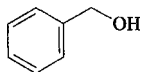
Assay Transfer a quantity of the substance being examined equivalent to about 200 mg of benzoyl peroxide, accurately weighed, in a 100 ml conical flask with stopper, allow to stand for a few minutes so that distribute the specimen evenly in the bottom of the conical flask with stopper. Add 30 ml of acetone, extrude the specimen with a glass rod to dissolve benzoyl peroxide. Wash the glass rod with a small quantity of acetone and add the washings to the main solution. Add 5 ml of potassium iodide TS, stopper and mix well, allow to stand in the dark for 10 minutes. Titrate with sodium thiosulfate (0.1 mol/L) VS until the colour disappears, shake vigorously for 30 seconds, allow to stand for 2 minutes and the end point is obtained if the solution is still colourless. Each ml of sodium thiosulfate (0.1 mol/L) VS is equivalent to 12.11 mg of C₁₄H₁₀O₄.

Category As described under Benzoyl Peroxide.

Strength (1) 10 g±0.5 g (2) 18 g±0.9 g

Storage Preserve in tightly closed containers, stored in a cool place.

Benzyl Alcohol



C_7H_8O 108.14

[100-51-6]

Benzyl Alcohol contains not less than 98.0% of C_7H_8O .

Description A colourless liquid; odour, slightly characteristic; taste, burning. It oxidizes gradually to benzaldehyde and benzoic acid on exposure to air. Soluble in water, miscible with ethanol, chloroform or ether.

Relative density 1.043-1.050 (Appendix VI A).

Distilling range Carry out the determination of distilling range (Appendix VI B), not less than 95% (ml/ml) is distilled at 203-206°C.

Refractive index 1.538-1.541 (Appendix VI F).

Acidity Not more than 0.3 (Appendix VI H).

Identification (1) Add 2-3 drops to 2 ml of potassium permanganate TS and 2 ml of dilute sulfuric acid, mix well, the benzylaldehyde characteristic odour is perceptible. (2) The infrared absorption spectrum (Appendix IV C) is concordant with the reference spectrum of benzyl alcohol (Appendix XVI).

Benzaldehyde The substance being examined is used as the test solution. Weigh accurately about 50 mg of benzaldehyde to a 250 ml volumetric flask, add water to dissolve and dilute with water to volume, mix well, as the reference solution. Carry out the method for gas chromatography (Appendix V E), using a column packed with polyethylene glycol 20 M as the stationary phase (about 10%), and maintain the column temperature at 130°C. Inject separately into the column same volume each of two solutions, calculate the content of benzaldehyde. It is not more than 0.2%.

Solubility in water To 2 ml add 58 ml of water and shake, the solution is clear.

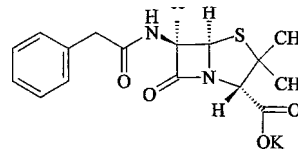
Organic chlorine compounds Burn a piece of copper plate in a nonluminous flame, until the green colour is disappeared, cool. Moisten the copper plate with the substance being examined and burn again in a nonluminous flame, no green colour is observed.

Assay To about 1.2 g, weighed accurately, add accurately 15 ml a mixture of acetic anhydride-pyridine (1:7), heat and reflux on a water bath for 30 minutes, cool. Add 25 ml of water and 2 drops of phenolphthalein IS, titrate with sodium hydroxide (1 mol/L) VS. Perform a blank determination and make any necessary correction. Each ml of sodium hydroxide (1 mol/L) VS is equivalent to 108.1 mg of C_7H_8O .

Category Local anesthetic, antiseptic-disinfectant.

Storage Preserve in tightly closed containers, protected from light.

Benzylpenicillin Potassium



$C_{16}H_{17}KN_2O_4S$ 372.49

[113-98-4]

Benzylpenicillin Potassium is potassium (2S, 5R, 6R)-3,3-dimethyl-6-(2-phenylacetamido)-7-oxo-4-thia-1-azabicyclo [3.2.0] heptane-2-carboxylate. It contains not less than 96.0% of penicillins, calculated as $C_{16}H_{17}KN_2O_4S$ on the anhydrous basis.

Description A white crystalline powder; odourless or slightly characteristic; hygroscopic; inactivated immediately by acid, alkaline or oxidizing agents. The aqueous solution loses its activity easily at room temperature. Very soluble in water; sparingly soluble in ethanol; insoluble in fixed oil or liquid paraffin.

Identification (1) Carry out the method for high performance liquid chromatography as described under the Assay. The retention time of the principal peak of the substance being examined in the chromatogram is identical with that of benzylpenicillin CRS.

(2) The infrared absorption spectrum (Appendix IV C) is concordant with the reference spectrum of benzylpenicillin potassium (Appendix XVI).

(3) Yields the flame reaction of potassium salts (Appendix III).

Light absorption The absorbance of an aqueous solution of 1.88 mg per ml at 280 nm (Appendix IV A) is not more than 0.10; the absorbance at the maximum at 264 nm is 0.80-0.88.

Acidity or alkalinity, Clarity and colour of solution, Water, Benzylpenicillin polymer, Bacterial endotoxin and Sterility Complies with the corresponding requirements described under Benzylpenicillin Sodium.

Assay Carry out the Assay described under benzylpenicillin sodium. Calculate the content with respect to the peak area obtained in the chromatogram by the external standard method, and multiply the result by 1.1136. Each mg of $C_{16}H_{17}N_2KO_4S$ is equivalent to 1598 benzylpenicillin Units.

Category β -lactam antibiotic, penicillins.

Storage Preserve in hermetically sealed containers, protected from light and stored in a dry and cool place.

Preparation Benzylpenicillin Potassium for Injection

Benzylpenicillin Potassium for Injection

Benzylpenicillin Potassium for Injection is a sterile crystalline powder of benzylpenicillin potassium. It contains not less than 96.0% of $C_{16}H_{17}KN_2O_4S$, calculated as basis anhydrous. It contains not less than 95.0% and not more than 115.0% of the labelled amount of benzylpenicillin potassium,

calculated on the basis of the average weight of contents.

Description A white crystalline powder.

Identification Complies with the tests for Identification described under Benzylpenicillin Potassium.

Clarity and colour of solution Complies with the corresponding test described under Benzylpenicillin Sodium for Injection.

Benzylpenicillin polymer Carry out the test for benzylpenicillin polymer described under Benzylpenicillin Sodium, using an accurately weighed quantity of the mixed contents obtained in the test for weight variation of contents. The benzylpenicillin polymer is not more than 0.10%.

Water Not more than 1.0% (Appendix VIII M, method 1 A).

Acidity or alkalinity, Bacterial endotoxin and Sterility Complies with the corresponding requirements described under Benzylpenicillin Sodium.

Other requirements Complies with the general requirements for injection (Appendix I B).

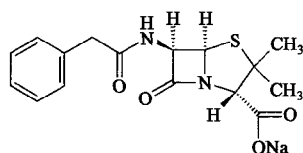
Assay Carry out the Assay described under Benzylpenicillin Sodium, using an accurately weighed quantity of the mixed contents obtained in the test for weight variation of contents. Each mg of $C_{16}H_{17}N_2KO_4S$ is equivalent to 1598 benzylpenicillin Units.

Category As described under Benzylpenicillin Potassium.

Strength (1) 0.125 g (200000 Units)
(2) 0.25 g (400000 Units)
(3) 0.5 g (800000 Units)
(4) 0.625 g (1000000 Units)
(calculated as $C_{16}H_{17}KN_2O_4S$)

Storage Preserve in tightly closed containers, protected from light, stored in a dry and cool place.

Benzylpenicillin Sodium



$C_{16}H_{17}N_2NaO_4S$ 356.38

[69-57-8]

Benzylpenicillin Sodium is sodium (2*S*, 5*R*, 6*R*)-3,3-dimethyl-6-(2-phenylacetamido)-7-oxo-4-thia-1-azabicyclo [3.2.0] heptane-2-carboxylate. It contains not less than 96.0% of penicillins, calculated as $C_{16}H_{17}N_2NaO_4S$ on the anhydrous basis.

Description A white crystalline powder; odourless or slightly characteristic; hygroscopic; inactivated immediately by acid, alkaline or oxidizing agents. The aqueous solution loses its activity easily at room temperature. Very soluble in water; soluble in ethanol; insoluble in fixed oils or liquid paraffin.

Identification (1) Carry out the method for high performance liquid chromatography as described under the Assay. The retention time of the principal peak of the substance being examined in the chromatogram is identical

with that of benzylpenicillin CRS.

(2) The infrared absorption spectrum (Appendix IV C) is concordant with the reference spectrum of benzylpenicillin sodium (Appendix XVI).

(3) Yields the flame reaction of sodium salts (Appendix III).

Crystallinity Complies with the test for crystallinity (Appendix IX D).

Acidity or alkalinity An aqueous solution of 30 mg per ml, pH 5.0-7.5 (Appendix VI H).

Clarity and colour of solution To each of 5 portions add water to produce solutions of 60 mg per ml, the solutions are clear and colourless; any opalescence produced is not more pronounced than that of the reference suspension I (Appendix IX B); any colour produced is not more intense than that of the reference solution Y₁ or YG₁ (Appendix IX A, method 1).

Light absorption The absorbance of a solution of 1.80 mg per ml in water at 280 nm is not more than 0.10; the light absorption of the solution exhibits a maximum at 264 nm and the absorbance is 0.80-0.88 (Appendix IV A).

Benzylpenicillin polymer Carry out the method for column chromatography (Appendix V C), using a column with 1.3-1.6 cm in internal diameter and 30-40 cm height packed with sephadex G-10 (40-120 μ m), a 0.1 mol/L phosphate buffer solution [0.1 mol/L disodium hydrogen phosphate solution-0.1 mol/L dihydrogen phosphate sodium (61:39), pH 7.0] as mobile phase A and water as mobile phase B. The flow rate is 1.5 ml per minute and the detection wavelength is 254 nm. Inject 200 μ l of a solution of 0.1 mg/ml dextran blue 2000 per ml into the column separately using mobile A and mobile B. The number of the theoretical plates of the column is not less than 700 and the tailing factor is not more than 2.0, calculated with reference to the peak of dextran blue 2000, using mobile phase A and B as eluent. The ratio of retention time of dextran blue 2000 peaks in the two mobile phases is between 0.93-1.07. The ratio of retention time of the polymer peak of the test solution and the dextran blue 2000 peak is between 0.93-1.07 in mobile phase A. The ratio of retention time of the principle peak of reference solution and the dextran blue 2000 peak is between 0.93-1.07 in mobile phase B. The relative standard deviation (RSD) of the areas of the principal peak in chromatogram obtained with 200 μ l of the reference solution for five replicate injections is not more than 5.0%, using mobile phase B as the eluent.

Reference solution Dissolve an accurately weighed quantity of benzylpenicillin CRS 20 mg, in water to produce a solution of 0.1 mg per ml.

Procedure Dissolve an accurately weighed quantity of the substance being examined 0.4 g in a 10 ml volumetric flask, dilute to volume with water, mix well as test solution. Inject immediately 200 μ l into the column and record the chromatogram, using mobile phase A as the eluent. Inject 200 μ l the reference solution into the column and record the chromatogram, using mobile phase B as the eluent. The content of benzylpenicillin polymer is not more than 0.08%, calculate as benzylpenicillin with respect to the peak area obtained in the chromatogram by the external standard method.

Water Not more than 0.5% (Appendix VIII M, method 1 A).

Bacterial endotoxin Carry out the test for bacterial endotoxin (Appendix XI E); not more than 0.01 EU per 100 benzylpenicillin Units.

Sterility Complies with test for Sterility (Appendix XI H, membrane filtration method). Each portion is inactivated by penicillinase or dissolved in appropriate solvent, add not more than 500 ml of 0.9% sterile sodium chloride solution.

Assay Carry out the method for high performance liquid chromatography (Appendix V D), using a column packed with octadecylsilane bonded silica gel and a mixture of 0.1 mol/L potassium dihydrogen phosphate solution (adjust pH to 2.5 with phosphate acid) -acetonitrile (70 : 30), detection wavelength is 225 nm. The flow rate is 1.0 ml per minute. Dissolve a weighed quantity of benzylpenicillin CRS and 2-acetamide in water to produce a mixed solution of 0.2 mg per ml. Inject 20 μ l of the solution into the column, the number of the theoretical plate of the column is not less than 1600, calculated with reference to the peak of benzylpenicillin. The resolution factor between the peak of 2-acetamide and that of the benzylpenicillin is not less than 2.0. And The order of the peaks in the chromatogram is 2-acetamide and benzylpenicillin.

Procedure Dissolve an accurately weighed quantity in water to produce a solution of 0.5 mg per ml, mix well as the test solution. Inject 10 μ l of the test solution into the column and record the chromatogram. Repeat the operation, using benzylpenicillin CRS instead of the substance being examined. Calculate the content with respect to the peak area obtained in the chromatogram by the external standard method, and multiply the result by 1.7658. Each mg of $C_{16}H_{17}N_2NaO_4S$ is equivalent to 1670 benzylpenicillin units.

Category β -lactam antibiotic, penicillins.

Storage Preserve in hermetically sealed container, protected from light, stored in a dry and cool place.

Preparation Benzylpenicillin Sodium for Injection

Benzylpenicillin Sodium for Injection

Benzylpenicillin Sodium for Injection is a sterile powder of benzylpenicillin sodium. It contains not less than 96.0% of $C_{16}H_{17}N_2NaO_4S$, calculated as anhydrous basis. Each container contains not less than 95.0% and not more than 115.0% of the labelled amount of benzylpenicillin sodium, calculated on the basis of the average weight of contents.

Description A white crystalline powder.

Identification Complies with the tests for Identification described under Benzylpenicillin Sodium.

Clarity and colour of solution Add water to each of 5 containers to produce solutions of 60 mg per ml (calculated on the basis of labelled amount). The solutions are clear and colourless; any opalescence produced is not more pronounced than that of reference suspension I (Appendix IX B); any colour produced is not more intense than that of reference solution Y₂ or YG₂ (Appendix IX A, method 1).

Benzylpenicillin polymer Carry out the test for benzylpenicillin polymer described under benzylpenicillin sodium, using an accurately weighed quantity of the mixed contents obtained in the test for weight variation of contents. The benzylpenicillin polymer is not more than 0.10%.

Water Not more than 1.0% (Appendix VIII M, method 1 A).

Acidity or alkalinity, Bacterial endotoxin and Sterility

Complies with the corresponding requirements described under Benzylpenicillin Sodium.

Other requirements Complies with the general requirements for injection (Appendix I B).

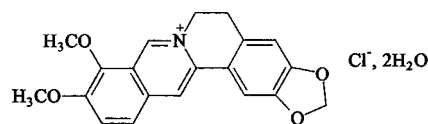
Assay Carry out the Assay described under benzylpenicillin sodium, using an accurately weighed quantity of the mixed contents obtained in the test for weight variation of contents. Each mg $C_{16}H_{17}N_2NaO_4S$ is equivalent to 1670 benzylpenicillin Units.

Category As described under Benzylpenicillin Sodium.

Strength (1) 0.12 g (200000 Units)
(2) 0.24 g (400000 Units)
(3) 0.48 g (800000 Units)
(4) 0.6 g (1000000 Units)
(5) 0.96 g (1600000 Units)
(6) 2.4 g (4000000 Units)
(calculated as $C_{16}H_{17}N_2NaO_4S$)

Storage Preserve in tightly closed containers, stored in a cool and dry place.

Berberine Hydrochloride



$C_{20}H_{18}ClNO_4 \cdot 2H_2O$ 407.85

[633-65-8]

Berberine Hydrochloride is 5,6-dihydro-9,10-dimethoxy benzo [g]-1,3-benzodioxolo [5,6- α] quinolizinium hydrochlorate dihydrate. The extracted product contains not less than 97.0% of the alkaloid and the synthetic product contains not less than 98.0% of the alkaloid, both calculated as berberine hydrochloride ($C_{20}H_{18}ClNO_4$) on the dried basis.

Description A yellow crystalline powder; odourless; taste, very bitter.

Soluble in hot water; slightly soluble in water or ethanol; very slightly soluble in chloroform; insoluble in ether.

Identification (1) Dissolve 0.1 g in 10 ml of water on gentle heating, add 4 drops of sodium hydroxide TS, cool (filter if necessary), add 8 drops of acetone, a turbidity is produced immediately.

(2) Stir about 5 mg with 2 ml of dilute hydrochloric acid, add a small quantity of bleaching powder, a cherry-red colour is produced.

(3) Dissolve about 2 mg in 1 ml of sulfuric acid, add 5 drops of 5% solution of gallic acid in ethanol, heat on a water bath, an emerald colour is produced.

(4) The infrared absorption spectrum (Appendix IV C) is concordant with the reference spectrum of berberine hydrochloride (Appendix XVI).

(5) Dissolve about 0.1 g in 20 ml of water on gently heating, add 0.5 ml of nitric acid, cool, allow to stand for 10 minutes and filter, the filtrate yields the reactions characteristic of chlorides (Appendix III).

Other alkaloids Carry out the method for thin-layer chromatography (Appendix V B), using silica gel G containing 0.1% of carboxymethylcellulose sodium as the coating substance and a mixture of ethyl acetate-chloroform-

methanol-diethylamine (8:2:2:1) as the mobile phase. Apply separately to the plate 3 μ l each of two solutions in ethanol containing (1) 2.0 mg per ml of the substance being examined and (2) 0.10 mg per ml of jatrorrhizine CRS. After developing and removal of the plate, examine immediately. The spot due to jatrorrhizine in the chromatogram obtained with solution (1) is not more intensely coloured than the principal spot obtained with solution (2). To another plate apply separately 3 μ l each of solution (1) and a 0.04 mg per ml solution of palmatine CRS in ethanol (solution 3), using *n*-butanol-glacial acetic acid-water (7:1:2) as the mobile phase. After developing and removal of the plate, dry it in air, examine the plate under ultraviolet light (365 nm). The fluorescent spot due to palmatine in the chromatogram obtained with solution (1) is not more intensely coloured than the principal spot obtained with solution (3) (extracted product).

Cyanide Comply with the limit test for cyanides (Appendix VIII F, method 1), using 0.5 g.

Organic nitrile Carry out the method for the thin-layer chromatography (Appendix V B), using silica gel G as the coating substance and a mixture of benzen-glacial acetic acid (25:0.1) as the mobile phase. Shake 0.5 g of the substance being examined with 5 ml of dehydrated ether in a stoppered conical flask for 5 minutes, filter on a sintered glass funnel (G5) and wash with 3-4 portions of 2 ml each of dehydrated ether, combine the filtrate and washings, concentrate to about 0.5 ml (solution 1). Prepare a 0.1 mg per ml solution of piperacetone CRS in chloroform solution (2). Apply separately to the plate (0.5 mm in thickness) 10 μ l of solution (2) and all of solution (1), after developing and removal the plate, dry in air, spray with 5% of ammonium molybdate-sulfuric acid solution, and dry at 105°C for 10-20 minutes. No secondary spots in the chromatogram obtained with solution (1) correspond in position to the principal spot in the chromatogram obtained with solution (2) (Synthetic product).

Loss on drying When dried for 5 hours at 100°C, loses not more than 12.0% of its weight (Appendix VIII L).

Residue on ignition Not more than 0.2% (extracted product) or 0.1% (synthetic product), using 1.0 g (Appendix VIII N).

Heavy metals Carry out the limit test for heavy metals (Appendix VIII H, method 2), using residue obtained in the test for Residue on ignition; not more than 0.002%. This test is applicable to synthetic product only.

Assay Dissolve about 0.3 g, accurately weighed, in a beaker in 150 ml of boiling water and allow to cool. Transfer the solution to a 250 ml volumetric flask, add accurately 50 ml of potassium dichromate (0.01667 mol/L) VS and dilute with water to volume. Shake for 5 minutes, filter with dry filter paper. Transfer accurately 100 ml of the successive filtrate to a 250 ml conical flask with glass stopper. Add 2 g of potassium iodide, shake to dissolve, then add 10 ml of hydrochloric acid solution (1→2), stopper tightly, shake well and allow to stand for 10 minutes in the dark. Titrate with sodium thiosulfate (0.1 mol/L) VS, add 2 ml of starch IS towards the end of titration and continue to titrate until the blue colour disappears and a bright green colour is produced. Perform a blank determination and make any necessary correction. Each ml of potassium dichromate (0.01667 mol/L) VS is equivalent to 12.39 mg of $C_{20}H_{18}ClNO_4$.

Category Antibacterial.

Storage Preserve in tightly closed containers.

Preparation (1) Berberine Hydrochloride Capsules

(2) Berberine Hydrochloride Tablets

Berberine Hydrochloride Capsules

Berberine Hydrochloride Capsules contain not less than 90.0% and not more than 110.0% of labelled amount of berberine hydrochloride ($C_{20}H_{18}ClNO_4 \cdot 2H_2O$).

Identification Dissolve a quantity of contents (equivalent to about 0.1 g of berberine hydrochloride) in 10 ml of water, on heat gently and filter. The filtrate complies with the following tests.

(1) To 5 ml of filtrate add 2 drops of sodium hydroxide TS, an orange-red colour is produced. Cool, add 4 drops of acetone, a turbidity is produced immediately and yellow precipitate is produced on standing. To the supernatant liquid add a quantity of acetone to precipitate the alkaloid completely, filter, the filtrate yields the reactions characteristic of chlorides (Appendix III).

(2) Stir 0.5 ml of the filtrate with 2 ml of dilute hydrochloric acid, add a small quantity of bleaching powder, a cherry-red colour is produced.

(3) To 0.2 ml of filtrate add 1 ml of sulfuric acid in a white porcelain dish, add 3 drops of 5% solution of gallic acid in ethanol, heat on water bath, an emerald colour is produced.

Loss on drying When dried for 5 hours at 100°C, loses not more than 12.0% of its weight (Appendix VIII L).

Dissolution Carry out the dissolution test (Appendix X C, method 1), using 1000 ml of water as the dissolution medium, adjust the rotational speed of the basket to 120 rpm. Withdraw 5 ml of the solution after exactly 45 minutes and filter. Dilute 2 ml of the successive filtrate to volume with water in a 25 ml volumetric flask and mix well. Measure the absorbance of the resulting solution at 263 nm (Appendix IX A). Calculate the dissolution of $C_{20}H_{18}ClNO_4 \cdot 2H_2O$ from each capsule, taking 724 as the value of A (1%, 1 cm). Not less than 70% of the labelled amount is dissolved.

Other requirement Comply with the general requirement for capsules (Appendix I E).

Assay Carry out the method for high performance liquid chromatography (Appendix V D), using a column packed with octadecylsilane bonded silica gel and a mixture of phosphate buffer [0.05 mol/L potassium dihydrophosphate mixed with 0.05 mol/L heptane sodium sulfonate (1:1) containing 0.2% triethylamine, adjust to pH 3.0 with phosphoric acid]-acetonitrile (60:40) as the mobile phase. Detective wavelength is 263 nm, and the number of theoretical plates of the column is not less than 3000, calculated with reference to the peak of berberine hydrochloride. The resolution factor between the peaks of berberine hydrochloride and adjacent peak should agree with the requirement.

Procedure Dissolve an accurately weighed quantity of the mixed contents obtained in the test for weight variation of contents equivalent to about 40 mg of berberine hydrochloride in proper boiling water in a 100 ml volumetric flask and cool to room temperature, dilute to volume with water, mix well, filter with filter membrane (0.45 μ m), discard about 8 ml of the initial filtrate. Transfer 2 ml of successive filtrate, accurately measured, into a 25 ml volumetric flask, dilute to volume with water, mix well. Inject 20 μ l into the column and record the chromatogram. Dissolve an accurately weighed quantity of berberine hydrochloride CRS in boiling water and dilute with boiling water to produce a solution of

about 32 μg per ml. Repeat the operation, calculate the content of $\text{C}_{20}\text{H}_{18}\text{ClO}_4 \cdot 2\text{H}_2\text{O}$ with respect to the peak area obtained in the chromatogram by the external standard method.

Category As described under Berberine hydrochloride.

Strength 0.1 g

Storage Preserve in tightly closed container and protected from light.

Berberine Hydrochloride Tablets

Berberine Hydrochloride Tablets contain not less than 93.0% and not more than 107.0% the labelled amount of berberine hydrochloride ($\text{C}_{20}\text{H}_{18}\text{ClNO}_4 \cdot 2\text{H}_2\text{O}$).

Description A yellow sugar-coated or film-coated tablet with yellow core.

Identification To a quantity of powdered tablets (equivalent to about 0.1 g of berberine hydrochloride) add 10 ml of water, heat gently to dissolve, filter. The filtrate complies with the tests (1), (2), (3), (5) for Identification described under Berberine Hydrochloride.

Dissolution Carry out the dissolution test (Appendix X C, method 1), using 1000 ml of water as the dissolution medium, adjust the rotational speed of the basket to 120 rpm, withdraw 5 ml of the solution after exactly 45 minutes and filter. Dilute 2 ml of the successive filtrate, to a 25 ml volumetric flask, dilute with water to volume, mix well. Measure the absorbance at 263 nm (Appendix IV A) and calculate the dissolution of $\text{C}_{20}\text{H}_{18}\text{ClNO}_4 \cdot 2\text{H}_2\text{O}$ from each tablet, taking 724 as the value of A (1%, 1 cm). Not Less than 70% of the Labelled amount is dissolved.

Other requirements Comply with the general requirements for tablets (Appendix I A).

Assay Carry out the method for high performance liquid chromatography (Appendix V D), using a column packed with octadecylsilane bonded silica gel and a mixture of phosphate buffer [0.05 mol/L potassium dihydrophosphate mixed with 0.05 mol/L heptane sodium sulfonate (1:1) containing 0.2% triethylamine, adjust to pH 3.0 with phosphoric acid,]-acetonitrile (60:40) as the mobile phase. Detective Wavelength is 263 nm, and the number of theoretical plates of the column is not less than 3000, calculated with reference to the peak of berberine hydrochloride. The resolution factor between the peaks of berberine hydrochloride and adjacent peak should agree with the requirement.

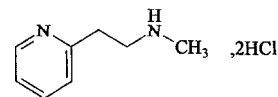
Procedure Weigh accurately and powder 20 tablets. Dissolve an accurately weighed quantity of the powder equivalent to about 40 mg of berberine hydrochloride in a quantity of boiling water in 100 ml volumetric flask, and cool to room-temperature, then dilute with water to volume, mix well, filter by filter membrane (0.45 μm), discard about 8 ml of the initial filtrate, then accurately measure 5 ml of successive filtrate in a 50 ml volumetric flask and dilute with water to volume, mix well, inject 20 μl into the column and record the chromatogram. Dissolve an accurately weighed quantity of berberine hydrochloride CRS in boiling water and dilute to produce a solution of about 40 μg per ml, calculate the content of $\text{C}_{20}\text{H}_{18}\text{ClO}_4 \cdot 2\text{H}_2\text{O}$ with respect to the peak area obtained in the chromatogram by the external standard method.

Category As described under Berberine Hydrochloride.

Strength (1) 0.025 g (2) 0.05 g (3) 0.1 g

Storage Preserve in tightly closed containers, protected from light.

Betahistine Hydrochloride



$\text{C}_8\text{H}_{12}\text{N}_2 \cdot 2\text{HCl}$ 209.12

[5579-84-0]

Betahistine Hydrochloride is *N*-methyl-2-pyridineethanamine dihydrochloride. It contains not less than 98.0% of $\text{C}_8\text{H}_{12}\text{N}_2 \cdot 2\text{HCl}$, calculated on the dried basis.

Description White or almost white crystals or crystalline powder; odourless; taste, slightly bitter; hygroscopic. Freely soluble in water; slightly soluble in ethanol; practically insoluble in acetone.

Identification (1) The infrared absorption spectrum (Appendix IV C) is concordant with the reference spectrum of betahistine hydrochloride (Appendix XVI).

(2) The aqueous solution yields the reactions characteristic of chlorides (Appendix III).

Related substances Carry out the method for thin-layer chromatography (Appendix V B), using silica gel G as the coating substance and chloroform-methanol-strong ammonia solution (40:10:1) as the mobile phase. Apply separately to the plate 10 μl of each of two solutions in methanol containing (1) 20 mg per ml and (2) 0.1 mg per ml of the substance being examined. After developing and removal of the plate, dry it in air and examine in iodine vapour. Any spot, other than the principal spot in the chromatogram obtained with solution (1) is not more intense than the principal spot obtained with solution (2).

Clarity of solution A solution of 0.1 g in 10 ml of water is clear.

Acidity Dissolve 0.1 g in 10 ml of water, pH 2.0-3.0 (Appendix VI H).

Loss on drying When dried over phosphorous pentoxide to constant weight at 100°C, loses not more than 1.0% of its weight (Appendix VIII L).

Residue on ignition Not more than 0.1% (Appendix VIII N).

Assay Dissolve about 0.1 g, accurately weighed, in 20 ml of glacial acetic acid, add 5 ml of mercuric acetate TS and 1 drop of crystal violet IS. Titrate with perchloric acid (0.1 mol/L) VS until the colour changes to bluish-green. Perform a blank determination and make any necessary correction. Each ml of perchloric acid (0.1 mol/L) VS is equivalent to 10.46 mg of $\text{C}_8\text{H}_{12}\text{N}_2 \cdot 2\text{HCl}$.

Category Vasodilator.

Storage Preserve in tightly closed containers, protected from light.

Preparation Betahistine Hydrochloride Tablets

Betahistine Hydrochloride Tablets

Betahistine Hydrochloride Tablets contain not less than 90.0% and not more than 110.0% of the labelled amount of betahistine hydrochloride ($C_8H_{12}N_2 \cdot 2HCl$).

Description Sugar coated tablets with white or almost white core.

Identification (1) To a quantity of the powdered tablets equivalent to about 10 mg of betahistine hydrochloride add 1 drop of sodium nitroprusside TS and 2 drops of 5% sodium carbonate solution, mix well, dip a strip of filter paper in the mixture. To another test tube add about 0.5 g of potassium hydrogen sulfate and 1-2 drops of glycerin, place the filter paper prepared above on top of the test tube and heat the mixture cautiously, the filter paper turns to blue. Remove the filter paper and add a few drops of 2% sodium hydroxide solution, the colour of the filter paper changes to red.

(2) The light absorption of the solution obtained in the Assay exhibits a maximum at 261 nm (Appendix IV A).

(3) To a quantity of the powdered tablets add water to dissolve betahistine hydrochloride, filter, the filtrate yields the reactions characteristic of chlorides (Appendix III).

Content uniformity Comply with the requirements (Appendix X E). Shake thoroughly 1 tablet with coating removed in a 50 ml (for strength 4 mg and 5 mg) or 100 ml (for strength 10 mg) volumetric flask with a quantity of hydrochloric acid solution (9 → 1000), dilute to volume, mix well and filter. Measure accurately 20 ml of the successive filtrate and proceed as described under Assay, beginning at the words "to a 100 ml volumetric flask...", calculate the content of $C_8H_{12}N_2 \cdot 2HCl$.

Other requirements Comply with the general requirements for tablets (Appendix I A).

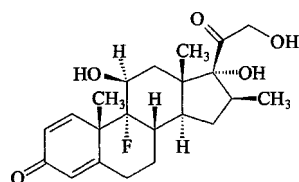
Assay Weigh accurately and powder 20 tablets with coating removed. Shake thoroughly an accurately weighed quantity of the powder, equivalent to about 15 mg of betahistine hydrochloride in a 50 ml volumetric flask, with a quantity of hydrochloric acid solution (9 → 1000), dilute to volume, mix well and filter. Measure accurately 5 ml of the successive filtrate to a 100 ml volumetric flask, dilute to volume and mix well. Measure the absorbance of the resulting solution at 261 nm (Appendix IV A), calculate the content of $C_8H_{12}N_2 \cdot 2HCl$, taking 352 as the value of A (1%, 1 cm).

Category As described under Betahistine Hydrochloride.

Strength (1) 4 mg (2) 5 mg (3) 10 mg

Storage Preserve in tightly closed containers, stored in a dry place.

Betamethasone



$C_{22}H_{29}FO_5$ 392.47

[378-44-9]

Betamethasone is 16β-methyl-11β, 17α, 21-trihydroxy-9α-fluoro-pregna-1,4-diene-3,20-dione. It contains not less than 97.0% and not more than 103.0% of $C_{22}H_{29}FO_5$, calculated on the dried basis.

Description A white or almost white crystalline powder; odourless; taste, bitter.

Sparingly soluble in ethanol or dioxane; slightly soluble in chloroform; practically insoluble in water.

Melting range 236-244°C, with decomposition (Appendix VI C).

Specific optical rotation +115° to +121°, in a solution of 10 mg per ml in dioxane (Appendix VI E).

Specific absorbance Measure the absorbance of a solution of 10 μg per ml in ethanol at 239 nm (Appendix IV A), the value of A (1%, 1 cm) is 382-406.

Identification (1) Dissolve about 10 mg in 1 ml of methanol by warming, add 1 ml of hot alkaline cupric tartrate TS; a brick-red precipitate is produced.

(2) The retention time of principal peak of betamethasone in the substance being examined in the chromatogram obtained in the Assay is identical with that of betamethasone CRS.

(3) The infrared absorption spectrum (Appendix IV C) is concordant with the reference spectrum of betamethasone (Appendix XVI).

(4) It yields the reactions characteristic of organic fluorine compounds (Appendix III).

Related substances Dissolve a quantity of the substance being examined in mobile phase and dilute with the same solvent to produce a solution of 0.4 mg per ml, and use this solution as a test solution. Transfer 1 ml, accurately measured, into 100 ml volumetric flask, dilute to volume with mobile phase, mix well, as a reference solution. Carry out the method as described under Assay. Inject 20 μl of the reference solution into the column, adjust the attenuation so that the principal peak height in the chromatogram is about 40% of full scale of the chart. Inject separately 20 μl each of the two solutions into the column, and record the chromatogram for twice the retention time of the principal peak. The largest area of all peaks other than the principal peak in the chromatogram obtained with the test solution is not greater than the area of the principal peak in the chromatogram obtained with the reference solution, each area of such peaks is not greater than 1/2 area of the principal peak in the chromatogram obtained with reference solution, the sum of the areas of such peaks in the chromatogram obtained with test solution is not greater than twice the area of the principal peak in the chromatogram obtained with reference solution.

Loss on drying When dried to constant weight at 105°C, loses not more than 0.5% of its weight (Appendix VIII L).

Residue on ignition Not more than 0.1% (Appendix VIII N).

Assay Carry out the method for high performance liquid chromatography (Appendix V D), using a column packed with octadecylsilane bonded silica gel and a mixture of methanol-water (56 : 44) as the mobile phase. Detective Wavelength is 240 nm. Dissolve a quantity of methylprednisolone CRS in the solution of substance being examined to produce a solution of betamethasone and methylprednisolone each 40 μg per ml, inject 20 μl into the column. The resolution factor between the peaks of betamethasone and methylprednisolone is not less than 2.2.

Procedure Dissolve a quantity of the substance being examined, accurately weighed, in the mobile phase to produce a solution of about 40 μg per ml, inject 20 μl into

the column and record the chromatogram. Repeat the operation, using betamethasone CRS instead of the substance being examined. Calculate the content of $C_{22}H_{29}FO_5$ With respect to the peak area obtained in the chromatogram by the external standard method.

Category Corticosteroid.

Storage Preserve in tightly closed containers, protected from light.

Preparation (1) Betamethasone Cream
(2) Betamethasone Tablets

Betamethasone Cream

Betamethasone cream contains not less than 90.0% and not more than 110.0% of the labelled amount of betamethasone ($C_{22}H_{29}FO_5$).

Description A white cream.

Identification The retention time of principal peak in the substance being examined in the chromatogram obtained in the Assay is identical with that of betamethasone CRS.

Other requirements Complies with the general requirements of cream (Appendix I F).

Assay Dissolve a quantity of the substance being examined, equivalent to about 1 mg of betamethasone, accurately weighed, in 50 ml methanol and mix 30 seconds at 9500 rpm by homogenizer after that filter by organic filter membrane (0.45 μ m), discard 5 ml of the initial filtrate, take the successive filtrate as the solution of substance being examined. Dissolve a quantity of betamethasone CRS, accurately weighed, in the mobile phase to make the reference solution of 20 μ g per ml. Carry out the method as described under the Assay of Betamethasone and calculate the content of $C_{22}H_{29}FO_5$.

Category As described under Betamethasone.

Strength (1) 4 g : 4 mg (2) 10 g : 10 mg
(3) 15 g : 15 mg

Storage Preserve in tightly closed containers, stored in cool place.

Betamethasone Tablets

Betamethasone Tablets contain not less than 90.0% and not more than 110.0% of the labelled amount of betamethasone ($C_{22}H_{29}FO_5$).

Description White tablets.

Identification (1) To a quantity of powdered tablets equivalent to 2 mg of betamethasone add 5 ml of methanol, heat gently and shake thoroughly until betamethasone is dissolved. Filter, add 0.5 ml of sulfuric acid to 1 ml of the filtrate and mix well. Allow to stand for about 5 minutes; an intense reddish-orange colour is produced.

(2) The retention time of principal peak in the chromatogram of the substance being examined obtained in the Assay is identical with that of betamethasone CRS.

Dissolution Carry out the dissolution test (Appendix X C, method 2), using 900 ml of water as the dissolution medium, adjust the rotational speed of the paddle to 50 rpm. Withdraw the solution after exactly 45 minutes and filter,

take the successive filtrate as the test solution. Dissolve 21 mg of betamethasone CRS with methanol in a 100 ml volumetric flask, dilute with water to volume, mix well. Measure accurately 2 ml of the solution in a 1000 ml volumetric flask, dilute with water to volume, mix well as the reference solution. Carry out the method for high performance liquid chromatography (Appendix V D), using a column packed with octadecylsilane bonded silica gel and a mixture of methanol-water (60 : 40) as the mobile phase. Detective Wavelength is 240 nm, and the number of theoretical plates of the column is not less than 2000, calculated with reference to the peak of betamethasone. Inject 100 μ l of the reference solution into the column, adjust the RSD of the principal peak area between the continuous six injections is not larger than 3.0%. Then separately inject 100 μ l of the test solution and reference solution into the column, record the chromatogram, calculate the dissolution of $C_{22}H_{29}FO_5$ from each tablet. Not less than 75% of the labelled amount is dissolved.

Content uniformity Comply with the requirement (Appendix X E). Put 1 tablet into a 25 ml volumetric flask, add a quantity of mobile phase and ultrasonic for 30 minutes to dissolve betamethasone, then cool to room temperature, dilute to the volume with mobile phase, mix well, centrifugate for 20 minutes at 4000 rpm, take the supernate as the test solution. Dissolve a quantity of betamethasone CRS, accurately weighed, in the mobile phase to produce a solution of about 20 μ g as the reference solution. Carry out the method described under the Assay, calculate the content of $C_{22}H_{29}FO_5$.

Other requirements Comply with the general requirements for tablets (Appendix I A).

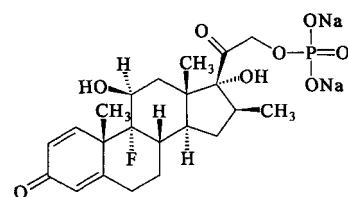
Assay Weigh accurately and powder 20 tablets. Transfer an accurately weighed quantity of the powder equivalent to about 1 mg of betamethasone into a 50 ml volumetric flask, add a quantity of mobile phase, ultrasonic for 30 minutes until betamethasone is dissolved. Cool to room temperature, dilute with mobile phase to volume, mix well and centrifugate for 20 minutes at 4000 rpm, take the supernate as the test solution. Carry out the method described under the Assay of Betamethasone, calculate the content of $C_{22}H_{29}FO_5$.

Category As described under Betamethasone.

Strength 0.5 mg

Storage Preserve in tightly closed containers, protected from light.

Betamethasone Sodium Phosphate



$C_{22}H_{28}FN_2O_8P$ 516.41

[151-73-5]

Betamethasone Sodium Phosphate is disodium 16 β -methyl-11 β ,17 α , 21-trihydroxy-9 α -fluoro-pregna-1,4-diene-3,20-dione-21-diphosphate. It contains not less than 96.0% and not more than 103.0% of $C_{22}H_{28}FN_2O_8P$, calculated on the dried basis.

Description A white or almost powder; odourless or almost odourless; hygroscopic. Freely soluble in water; practically insoluble in acetone and chloroform.

Specific optical rotation $+95^{\circ}$ to $+102^{\circ}$, in a 1% aqueous solution (Appendix VI E).

Identification (1) Carry out the method for thin layer chromatography (Appendix V B), using silica gel G as the coating substance and a solution of *n*-butanol saturated with dilute hydrochloric acid as the mobile phase. Apply separately to the plate 10 μ l each of solution containing (1) 1 mg of betamethasone sodium phosphate CRS per ml and (2) 1 mg of the substance being examined per ml. After developing and removal of the plate, dry it in air, spray with a mixture of sulfuric acid-methanol-nitric acid (10:10:1), and heat for 10 minutes at 105°C . The position of principal spot in the chromatogram obtained with the solution (2) correspond to that in the chromatogram obtained with the solution (1).

(2) Dry it for 3 hours at 105°C . The infrared absorption spectrum (Appendix IV C) is concordant with the reference spectrum of betamethasone sodium phosphate (Appendix XI).

(3) Heat gently 40 mg with 2 ml of sulfuric acid until the sulfuric acid fumes are expelled, add nitric acid dropwise and heat until the nitrous oxide fumes is evolved and removed, ignite at 500°C and cool. To the residue add 5 ml, neutralized to litmus paper when necessary, and filter. The filtrate yields the reactions characteristic of sodium salts and phosphates (Appendix III).

Alkalinity Dissolve 5 mg in 1 ml of water, pH 7.0-9.0 (Appendix VI H).

Free phosphate Weigh accurately 20 mg, carry out the test as described under Dexamethasone Sodium Phosphate. The absorbance of the test preparation is not more than that of the reference preparation.

Related substances Carry out the method for high performance liquid chromatography (Appendix V D), using a column packed with octadecylsilane bonded silica gel and a mixture of potassium dihydrophosphate hexylamine solution (mix 1.36 g of potassium dihydrophosphate with 0.60 g of hexylamine, stand for 10 minutes, then dissolve it in 185 ml of water)-acetonitrile (74:26) as the mobile phase. Detective Wavelength is 254 nm. Dissolve a quantity of the substance being examined, accurately weighed, in mobile phase to produce the test solution (1) of about 2.5 mg per ml. Measure accurately 1 ml the test solution into a 50 ml volumetric flask and dilute to volume by mobile phase, mix well as the reference solution (2). Dissolve a quantity of betamethasone sodium phosphate and dexamethasone sodium phosphate in mobile phase to make a solution (3) of each 40 μg per ml. Inject 20 μl of the solution (3) into the column. The resolution factor between the peaks of betamethasone sodium phosphate and dexamethasone sodium phosphate is not less than 2.0 and that between the peaks of betamethasone sodium phosphate and adjacent peak should comply with the requirement. Inject 20 μl of the solution (2) into the column. Adjust the attenuation so that the principal peak height in the chromatogram is 70%-90% of full scale of the chart. Inject separately accurately 20 μl each of the solution (1) and (2) into the column, and record the chromatogram for three times the retention time of the principal peak. Each peak area and the sum of the areas of all peaks other than the principal peak in the chromatogram obtained with solution (1) is not greater than the area of the principal peak and 1.5 time the area of the principal peak obtained with solution (2) respectively. Among such peaks. There is not more than one peak whose area is

greater than 1/2 time the area of the principal peak obtained with solution (2).

Loss on drying When dried in vacuum to constant weight at 100°C for 4 hours, loses not more than 8.0% of its weight (Appendix VIII L).

Assay Reference preparation Dissolve accurately a quantity of betamethasone sodium phosphate CRS, equivalent to 20 mg of betamethasone, in methanol to produce a solution of 0.4 mg per ml.

Test preparation To a quantity of the substance being examined, equivalent to 20 mg of betamethasone, in methanol in a 50 ml volumetric flask add methanol to volume and shake thoroughly (filter if necessary).

Procedure To 1 ml of each of two preparations, accurately measured, in separate 25 ml volumetric flasks add accurately 20 ml of a solution of isoniazid (dissolve 75 mg of isoniazid and 0.1 ml of hydrochloric acid in methanol to make up to 100 ml), and mix well. Heat on 60°C water bath for 1 hour and cool. Dilute with methanol to volume, mix well, and measure the absorbance at 420 nm (Appendix IV B). Calculate the content of $\text{C}_{22}\text{H}_{28}\text{FN}_2\text{O}_5\text{P}$.

Category Corticosteroid.

Storage Preserve in tightly closed containers, protected from light.

Preparation Betamethasone Sodium Phosphate Injection

Betamethasone Sodium Phosphate Injection

Betamethasone Sodium Phosphate Injection is a sterile solution of Betamethasone Sodium Phosphate in Water for Injection. It contains not less than 90.0% and not more than 110.0% of the labelled amount of betamethasone ($\text{C}_{22}\text{H}_{28}\text{FO}_5$). Suitable amount of stabilizer may be added.

Description A clear, colourless liquid.

Specific optical rotation $+88^{\circ}$ to $+108^{\circ}$, in a solution of the substance being examined (Appendix VI E).

Identification Evaporate an amount of the injection on a water bath to dryness, use the residue for the following tests: (1) Dissolve 2 mg in 2 ml of sulfuric acid TS; a yellow colour is produced, changing to brownish red on standing for a moment.

(2) The retention time of principal peak of the substance being examined in the chromatogram obtained in the Assay is identical with that of betamethasone sodium phosphate CRS.

(3) It yields the reactions characteristic of organic fluorine compounds (Appendix III).

pH value 7.0-9.0 (Appendix VI H).

Other requirements Complies with the general requirements for injection (Appendix I B).

Assay Carry out the method for high performance liquid chromatography (Appendix V D), using a column packed with octadecylsilane bonded silica gel and a mixture of 0.05 mol/L potassium dihydrophosphate solution-methanol (1:1) as the mobile phase. Detective Wavelength is 254 nm, and the number of theoretical plates of the column is not less than 2000. The resolution factor between the peaks of betamethasone sodium phosphate and internal standard should agree with the requirement.

Internal standard solution Dissolve a quantity of ethyl *p*-hydroxybenzoate in methanol to produce a solution of 0.1 mg per ml.

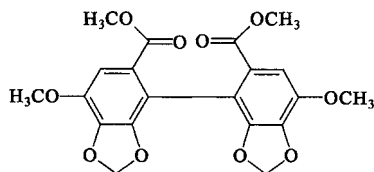
procedure Transfer 2 ml, accurately measured, to a 50 ml volumetric flask, dilute with water to the volume, mix well, then accurately measure 5 ml to a 25 ml volumetric flask, add accurately 5 ml internal standard solution, dilute with water to the volume, mix well. Inject 20 μ l into the volume and record the chromatogram. Dissolve a quantity of betamethasone sodium phosphate CRS, accurately weighed in water to produce a solution of about 0.21 mg per ml. Measure accurately the reference solution and internal standard solution each of 5 ml into a 25 ml volumetric flask, dilute with water to volume, mix well, repeat the operation above, calculate the content of $C_{22}H_{28}FN_2O_8P$ with respect to the peak area obtained in the chromatogram by the internal standard method.

Category As described under Bethamason Sodium Phosphate.

Strength 1 ml : 5.26 mg (equivalent to 4 mg of Betamethasone)

Storage Preserve in well closed containers, protected from light.

Bifendate



$C_{20}H_{18}O_{10}$ 418.36

Bifendate is 4,4'-dimethoxy-5,6,5',6'-dimethylenedioxy-2,2'-di (methyl-formate) diphenyl. It contains not less than 97.0% and not more than 103.0% of $C_{20}H_{18}O_{10}$, calculated on the dried basis.

Description A white crystalline powder; odourless; tasteless. Freely soluble in chloroform; practically insoluble in ethanol or water.

Melting point 180-183°C, insert the capillary tube into the bath at 150°C (Appendix VI C).

Identification (1) To about 20 mg add 6 drops of hydroxylamine hydrochloride TS, alkalinize the solution with saturated ethanolic potassium hydroxide solution dropwise, boil gently for a moment, cool, acidify the solution with dilute hydrochloric acid, add 1 drop of ferric chloride TS, a dark violet colour is produced.

(2) To about 5 mg add 1 ml of chromotropic acid TS, shake thoroughly, heat in the water bath for a moment, a violet colour is produced.

(3) The light absorption of the solution obtained in Assay exhibits a maximum at 278 nm and a minimum at 260 nm.

(4) The infrared absorption spectrum (Appendix IV C) is concordant with the reference spectrum of bifendate (Appendix XVI).

Related substances Carry out the method for thin-layer chromatography (Appendix V B), using silica gel G as the coating substance and a mixture of petroleum ether (30-60°C)-ethyl acetate-chloroform (65:20:15) as the mobile phase. Apply separately to the plate 10 μ l each of two

solutions of the substance being examined, in chloroform containing (1) 10 mg per ml and (2) 0.1 mg per ml. After developing and removal of the plate, dry it in air and spray with 50% sulfuric acid solution in dehydrated ethanol, heat at 110°C for 30 minutes. The principal spot should be revealed clearly in the chromatogram obtained with solution (2), and any spot, other than the principal spot in the chromatogram obtained with solution (1) is not revealed.

Loss on drying When dried to constant weight at 105°C, loses not more than 1.0% of its weight (Appendix VIII L).

Residue on ignition Not more than 0.1% (Appendix VIII N), using 1.0 g.

Heavy metals Carry out the limit test for heavy metals (Appendix VIII H), using the residue obtained in the test for Residue on ignition: not more than 0.002%.

Assay Weigh accurately about 15 mg in a 100 ml volumetric flask, add 80 ml of ethanol, heat to dissolve bifendate in a water bath, cool, dilute with ethanol to volume and mix well. Measure accurately 5 ml to a 50 ml volumetric flask, dilute to volume and mix well. Measure the absorbance of the resulting solution at 278 nm (Appendix IV A). Repeat the procedure using about 15 mg of bifendate CRS instead of the substance being examined. Calculate the content of $C_{20}H_{18}O_{10}$.

Category Anti-hepatitis.

Storage Preserve in tightly closed containers, protected from light.

Preparation Bifendate Pills

Bifendate Pills

Bifendate Pills contain not less than 90.0% and not more than 110.0% of the labelled amount of bifendate ($C_{20}H_{18}O_{10}$).

Description Sugar coated dripping pills.

Identification To 15 pills add 5 ml of water, shake to dissolve the excipient, centrifuge for 10 minutes, discard supernatant, then add 5 ml of water, centrifuge for 10 minutes, discard supernatant. The sediment complies with the tests (1), (2) and (3) for Identification described under Bifendate.

Content uniformity Comply with the requirements (Appendix X E). Shake to dissolve 10 pills individually with 1 ml of water in 25 ml ground-glass stoppered test tube, add accurately 10 ml of chloroform, shake for 5 minutes, allow to stand until the extract separate into two layers. Discard the upper water layer, add 1 g of anhydrous, sodium sulfate shake for 1 minute, allow to stand until the chloroform layer becomes clear. Measure accurately 5 ml of the chloroform solution to a small beaker, evaporate to dryness on a water bath, add 10 ml of ethanol to dissolve the residue by heating on a water bath, cool and transfer it to a 50 ml volumetric flask, dilute with ethanol to volume and mix well. Prepare a blank solution in the same manner. Measure the absorbances of the solutions at 278 nm (Appendix IV A), calculate the content of $C_{20}H_{18}O_{10}$, taking 363 as the value of A (1%, 1 cm).

Other requirements Comply with the general requirements for pills (Appendix I H).

Assay Weigh accurately and triturate 20 pills. To a quantity, accurately weighed, equivalent to about 3 mg of bifendate in a 25 ml ground-glass stoppered test tube add 1

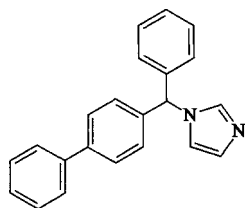
ml of water, shake for 2 minutes, then add accurately 20 ml of chloroform, shake for 5 minutes, allow to stand until the extract separate into two layers. Discard the upper water layer, add 1 g of anhydrous, sodium sulfate, shake for 1 minute, allow to stand until the chloroform layer becomes clear. Measure accurately 5 ml of the chloroform solution in a small beaker, evaporate to dryness on a water bath. Add 10 ml of ethanol to dissolve the residue by heating on a water bath cool and transfer it to a 50 ml volumetric flask, dilute with ethanol to volume and mix well. Prepare a blank solution in the same manner with 20 ml of chloroform. Measure the absorbance of the solutions at 278 nm (Appendix IV A), calculate the content of $C_{20}H_{18}O_{10}$, taking 363 as the value of A (1%, 1 cm).

Category As described under Bifendate.

Strength 1.5 mg

Storage Preserve in tightly closed containers, stored in a dry place.

Bifonazole



$C_{22}H_{18}N_2$ 310.40

Bifonazole is (\pm) 1-(α -biphenyl-4-benzyl)-1H-imidazole. It contains not less than 99.0% of $C_{22}H_{18}N_2$, calculated on the dried basis.

Description An almost white to slightly yellow crystalline powder; odourless; tasteless. Freely soluble in chloroform; sparingly soluble in methanol or dehydrated ethanol; practically insoluble in water.

Melting range 148-153°C (Appendix VI C).

Identification (1) Dissolve about 0.1 g in 2 ml of chloroform in a test tube, add a small quantity of anhydroalcohol along the wall, a purplish red or purple is produced.

(2) To about 10 mg add 10 drops of citric-acetic anhydride TS, and mix, a yellow to purple is developed on warming.

(3) The light absorption of a solution of 10 μ g per ml in methanol exhibits a maximum at 254 nm (Appendix IV A).

(4) The infrared absorption spectrum (Appendix IV C) is concordant with the reference spectrum of bifonazole (Appendix XVI).

Bifonol Carry out the method for high performance liquid chromatography (Appendix V D), using a column packed with octadecylsilane bonded silica gel and a mixture of methanol-water-tetrahydrofuran (84 : 15 : 1) as the mobile phase. Detection wavelength is 254 nm, and the number of theoretical plates of the column is not less than 700, calculated with reference to the peak of bifonazole. Dissolve a quantity in mobile phase to produce a solution containing 1.0 mg of the substance being examined per ml as solution (1). Dissolve a quantity of the bifonol CRS in mobile phase to produce a solution of 5 μ g per ml as solution (2). Dissolve a quantity of bifonazole CRS and bifonol CRS in mobile phase to produce solution (3) containing 1.0 mg of bifonazole CRS and 5 μ g of bifonol CRS per ml. Inject 10 μ l

of solution (3) into the column, adjust the attenuator of the detector, so that the peak height of bifonol in the chromatogram is about 10% of full scale of the chart and the resolution factor between the peaks of bifonazole and bifonol complies with related requirements. Inject separately 10 μ l of solution (1) and solution (2) into the column and record the chromatogram. The peak area of bifonol obtained from solution (1) is not greater than that obtained from solution (2) (0.5%).

Loss on drying When dried to constant weight at 105°C, loses not more than 0.5% of its weight (Appendix VIII L).

Residue on ignition Not more than 0.1% (Appendix VIII N), using 1.0 g.

Assay Dissolve about 0.25 g, accurately weighed, in 20 ml of glacial acetic acid, add 1 drop of crystal violet IS. Titrate with perchloric acid (0.1 mol/L) VS until the solution becomes bluish-green. Perform a blank determination and make any necessary correction. Each ml of perchloric acid (0.1 mol/L) VS is equivalent to 31.04 mg of $C_{22}H_{18}N_2$.

Category Antifungal.

Storage Preserve in tightly closed containers, protected from light.

Preparation (1) Bifonazole Cream
(2) Bifonazole Solution
(3) Bifonazole Suppositories

Bifonazole Cream

Bifonazole Cream contains not less than 90.0% and not more than 110.0% of the labelled amount of bifonazole ($C_{22}H_{18}N_2$).

Description A white to slight yellow cream.

Identification The retention time of principal peak of bifonazole in the substance being examined in the chromatogram obtained in the Assay is identical with that of bifonazole CRS.

Other requirement Complies with the general requirement for cream (Appendix I F).

Assay Carry out the method for high performance liquid chromatography (Appendix V D), using a column packed with octadecylsilane bonded silica gel and a mixture of methanol-water-tetrahydrofuran (84 : 15 : 1) as the mobile phase. The detection wavelength is 254 nm. The number of theoretical plates of the column is not less than 700, calculated with reference to the peak of bifonazole.

Procedure To an accurately weighed quantity equivalent to 5 mg of bifonazole in a 100 ml volumetric flask add a quantity of methanol, shake thoroughly to disperse well and dissolve bifonazole. Dilute with methanol to volume, mix well and cool in an ice bath over 2 hours. Filter immediately and cool successive filtrate to room temperature as the test solution. Dissolve an accurately weighed quantity of bifonazole CRS in methanol and dilute to produce a solution of 0.05 mg per ml as the reference solution. Inject separately 10 μ l of the test solution and the reference solution into the column. Calculate the content of $C_{22}H_{18}N_2$ with respect to the peak area obtained in the chromatogram by the external standard method.

Category As described under Bifonazole.

Strength 15 g : 150 mg

Storage Preserve in tightly closed containers, stored in a

cool place.

Bifonazole Solution

Bifonazole Solution contains not less than 90.0% and not more than 110.0% of the labelled amount of bifonazole ($C_{22}H_{18}N_2$).

Description A clear, colourless liquid; odour, characteristic of ethanol; readily volatile.

Identification The retention time of principal peak of bifonazole in the substance being examined in the chromatogram obtained in the Assay is identical with that of bifonazole CRS.

Fill Complies with the general requirement of test for minimum fill (Appendix X F).

Assay Carry out the method for high performance liquid chromatography (Appendix V D), using a column packed with octadecylsilane bonded silica gel and a mixture of methanol-water-tetrahydrofuran (84:15:1) as the mobile phase. The detection wavelength is 254 nm. The number of theoretical plates of the column is not less than 700, calculated with reference to the peak of bifonazole.

Procedure Measure accurately 5 ml to a 100 ml volumetric flask, dilute with methanol to volume and mix well. Transfer accurately 1 ml of the solution into a 10 ml volumetric flask, dilute with methanol to volume and mix well as a test solution. Dissolve a quantity of bifonazole CRS, accurately weighed, in mobile phase and dilute to produce a solution of 0.05 mg per ml as a reference solution. Inject separately 10 μ l of the test solution and the reference solution into the column. Calculate the content of $C_{22}H_{18}N_2$ with respect to the peak area obtained in the chromatogram by the external standard method.

Category As described under Bifonazole.

Strength 10 ml:100 mg

Storage Preserve in tightly closed containers, stored in a cool place.

Bifonazole Suppositories

Bifonazole suppositories contain not less than 90.0% and not more than 110.0% of the labelled amount of bifonazole ($C_{22}H_{18}N_2$).

Description Creamy white or pale yellow suppositories.

Identification To 2 suppositories add 10 ml of petroleum ether, warm gently on a water bath until dissolved. Allow to cool, discard the petroleum ether, wash the residue with a small quantity of petroleum ether twice, discard the washings, heat on a water bath to expel petroleum ether. Dissolve the residue in chloroform to produce a solution of 2 mg per ml as test solution. Dissolve a quantity of bifonazole CRS in chloroform to produce a solution of 2 mg per ml as reference solution. Carry out the thin-layer chromatography (Appendix V B), using silica gel G as the coating substance and a mixture of isopropyl ether (saturated with ammonia vapour) as the mobile phase. Apply separately to the plate 10 μ l each of the above two solutions, after developing and removal of the plate, dry it in air, expose to iodine vapour. The colour and position of the principal spot in the chromatogram obtained with the test

solution correspond to the principal spot obtained with reference solution.

Other requirements Comply with the general requirements for suppositories (Appendix I D).

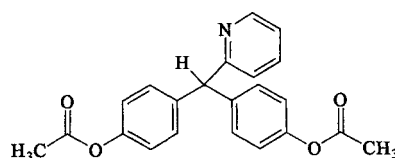
Assay Weigh accurately 10 suppositories, melt together in an evaporating dish on a water bath and allow to cool, stirring continuously until well mixed. Dissolve a quantity equivalent to 50 mg of bifonazole, accurately weighed, in a conical flask with a stopper, in 30 ml of chloroform. Add 15 ml of water and 5 ml of dilute sulfuric acid TS, add 0.6 ml of dimethyl yellow-solvent blue 19 IS, titrate with dioctyl sodium sulfosuccinate TS. Towards the end of titration shake vigorously and continue the titration until chloroform layer changes from green to reddish grey. Repeat the operation, using 50 mg of bifonazole CRS, accurately measured, instead of the substance being examined. Calculate the content of $C_{22}H_{18}N_2$ from the volume ratio of dioctyl sodium sulfosuccinate TS consumed in the titrations.

Category As described under bifonazole.

Strength 0.15 g

Storage Preserve in tightly closed containers, stored in a cool place and protected from light.

Bisacodyl



$C_{22}H_{19}NO_4$ 361.40

[603-50-9]

Bisacodyl is 4,4'-(2-Pyridylmethylene) diphenyl diacetate. It contains not less than 98.0% of $C_{22}H_{19}NO_4$, calculated on the dried basis.

Description A white or almost white crystalline powder; odourless; tasteless.

Freely soluble in chloroform; soluble in acetone; slightly soluble in ethanol or ether; insoluble in water.

Melting range 132-136°C (Appendix VI C).

Identification (1) The light absorption of a solution of 10 μ g per ml in 0.1 mol/L methanolic potassium hydroxide solution exhibits a maximum at 248 nm, the absorbance is 0.62-0.68 (Appendix IV A).

(2) The infrared absorption spectrum (Appendix IV C) is concordant with the reference spectrum of bisacodyl (Appendix XVI).

Acidity or alkalinity To 1.0 g add 20 ml of water, heat to boil, allow to cool and filter, the pH value of the filtrate is 5.0-7.5 (Appendix VI H).

Related substances Carry out the method for thin-layer chromatography (Appendix V B), using silica gel GF₂₅₄ as the coating substance and a mixture of xylene-butanone (1:1) as the mobile phase. Apply separately to the plate 10 μ l each of the two solutions of the substance being examined in acetone containing (1) 20 mg per ml and (2) 0.20 mg per ml. After developing and removal of the plate, dry it in air and examine under ultraviolet light (254 nm). Any spot other than the principal spot in the chromatogram obtained with solution (1) is not more intense than the principal spot obtained with solution (2).

Loss on drying When dried to constant weight at 105°C, loses not more than 1.0% of its weight (Appendix VIII L).

Residue on ignition Not more than 0.1% (Appendix VIII N).

Assay Dissolve about 0.3 g, accurately weighed, in 25 ml of glacial acetic acid, add 2 drops of naphtholbenzein IS, titrate with perchloric acid (0.1 mol/L) VS until the colour changes to yellowish green. Perform a blank determination and make any necessary correction. Each ml of perchloric acid (0.1 mol/L) VS is equivalent to 36.14 mg of $C_{22}H_{19}NO_4$.

Category Cathartic.

Storage Preserve in tightly closed containers, protected from light.

Preparation (1) Bisacodyl Enteric-coated Tablets
(2) Bisacodyl Suppositories

Bisacodyl Enteric-coated Tablets

Bisacodyl Tablets contain not more than 93.0% and not more than 107.0% of the labelled amount bisacodyl ($C_{22}H_{19}NO_4$).

Description Enteric coated tablets with white cores.

Identification (1) Dissolve quantity of powdered tablets equivalent to about 50 mg of bisacodyl in 30 ml of chloroform with shaking. Filter and evaporate the filtrate to dryness, add 10 ml of 1% sulfuric acid solution to dissolve the residue, the solution complies with following tests.

To 2 ml add 1 drop of mercuric potassium iodide TS, a white precipitate is produced.

To 2 ml add dropwise sulfuric acid, a purple colour is produced.

To 2 ml add 1-2 drops of nitric acid, heat, a yellow colour is produced, cool and add sodium hydroxide TS dropwise, the colour changes to yellowish brown.

(2) Carry out the method for thin-layer chromatography (Appendix V B), using silica gel GF₂₅₄ as the coating substance and a mixture of xylene-butanone (1:1) as the mobile phase. To a quantity of powdered tablets equivalent to 20 mg of bisacodyl add 2 ml of acetone, shake for 10 minutes and centrifuge, use the supernate as the test solution. Prepare reference solution of 10 mg bisacodyl CRS per ml in acetone. Apply separately to the plate 2 µl each of the two solutions. After developing and removal of the plate, dry it in air and examine under ultraviolet light (254 nm). The position of the principal spot in the chromatogram obtained with the test solution corresponds to the principal spot obtained with the reference solution.

Related substances Carry out the method for thin-layer chromatography (Appendix V B), using silica gel GF₂₅₄ as the coating substance and a mixture of xylene-butanone (1:1) as the mobile phase. To a quantity of powdered tablets equivalent to 20 mg of bisacodyl add 2 ml of acetone, shake for 10 minutes and centrifuge, use the supernate as the test solution. Measure accurately 0.3 ml of the test solution, dilute with acetone to 10 ml as the reference solution. Apply separately to the plate 10 µl each of the two solutions. After developing and removal of the plate, dry it in air and examine under ultraviolet light (254 nm). Any spot other than the principal spot in the chromatogram obtained with test solution is not intense than the principal spot obtained with the reference solution.

Content uniformity Comply with the requirements

(Appendix X E). Triturate 1 enteric coated stripped tablet with a quantity of chloroform, and transfer to a 25 ml volumetric flask with chloroform in portions, shake to dissolve bisacodyl, dilute with chloroform to volume and mix well. Filter, measure accurately 5 ml of successive filtrate to another 25 ml volumetric flask, dilute to volume, mix well. Carry out the method described under Assay. Calculate the content of $C_{22}H_{19}NO_4$ in each tablet.

Other requirements Comply with the general requirements of tablets (Appendix I A).

Assay Weigh accurately and powder 20 enteric coat stripped tablets. Dissolve a quantity of the powder equivalent to about 20 mg of bisacodyl, accurately weighed, in a quantity of chloroform in a 50 ml volumetric flask, dilute with chloroform to volume, mix well, filter, measure accurately 5 ml of the successive filtrate to another 50 ml volumetric flask, dilute to volume and mix well. Measure the absorbance at 264 nm (Appendix IV A), calculate the content of $C_{22}H_{19}NO_4$, taking 148 as the value of A (1%, 1 cm).

Category As described under Bisacodyl.

Strength 5 mg

Storage Preserve in tightly closed containers, protected from light.

Bisacodyl Suppositories

Bisacodyl Suppositories contain not less than 90.0% and not more than 110.0% of the labelled amount of bisacodyl ($C_{22}H_{19}NO_4$).

Description White suppositories.

Identification (1) To 1 suppository add 3 ml of 1% sulfuric acid solution, heat to melt, add 4-5 drops of nitric acid dropwise and heat; a yellow colour is produced, add 10 drops of 20% sodium hydroxide solution, the colour changes to brownish-red.

(2) Carry out the method for thin-layer chromatography (Appendix V B), using silica gel GF₂₅₄ as the coating substance and a mixture of xylene-butanone (1:1) as the mobile phase. To 1 suppository add 20 ml of water, stir to mix well and filter, wash the residue with a little quantity of water, allow to dry, dry in a vacuum desiccator over phosphorus pentoxide for 2 hours, dissolve the residue in 2 ml of acetone as the test solution. Prepare reference solution of 5 mg bisacodyl CRS per ml in acetone. Apply separately to the plate 10 µl of each of the two solutions. After developing and removal of the plate, dry it in air and examine under ultraviolet light (254 nm). The colour and position of the principal spot in the chromatogram obtained with the test solution correspond to the principal spot obtained with the reference solution.

(3) The light absorption of the test solution obtained in Assay exhibits a maximum at 264 nm (Appendix IV A).

Content uniformity Comply with the requirements for content uniformity (Appendix X E). Dissolve 1 suppository in a quantity of 1 mol/L hydrochloric acid solution in a 100 ml volumetric flask, dilute with 1 mol/L hydrochloric acid solution to volume, mix well, measure accurately 10 ml to a 50 ml volumetric flask, dilute to volume with the same solvent, mix well. Carry out the procedure described under Assay. Calculate the content of $C_{22}H_{19}NO_4$.

Other requirements Comply with the general requirements of suppositories (Appendix I D).

Assay Place 10 suppositories in an evaporating dish, heat to melt on a water bath, cool, stir to mix well. Dissolve a quantity equivalent to about 20 mg of bisacodyl, accurately weighed, in a quantity of 1 mol/L hydrochloric acid solution in a 100 ml volumetric flask, dilute to volume with 1 mol/L hydrochloric acid solution, mix well, measure accurately 10 ml to another 100 ml volumetric flask, dilute to volume with the same solvent and mix well, measure the absorbance at 264 nm (Appendix IV A). Repeat the operation, using the reference solution of 20 µg bisacodyl CRS per ml in 1 mol/L hydrochloric acid solution instead of the test solution, calculate the content of $C_{22}H_{19}NO_4$.

Category As described under Bisacodyl.

Strength 10 mg

Storage Preserve in tightly closed containers, stored at a temperature below 30°C.

Bismuth Aluminate

$Bi_2 (Al_2O_4)_3 \cdot 10H_2O$ 951.99

Bismuth Aluminate contains not less than 51% and not more than 55% of bismuth (Bi); contains not less than 19.5% and not more than 21.5% of aluminium (Al), calculated with reference to the substance ignited to constant weight.

Description A white or almost white powder; odourless; tasteless.

Insoluble in water or ethanol.

Identification (1) Dissolve about 50 mg in 1 ml of nitric acid by heating, cool, add 10 ml of water. To 2 ml of the resulting solution add dropwise potassium iodide TS, a brownish black precipitate is produced, it dissolves in an excess of potassium iodide TS to produce an orange yellow solution.

(2) To about 0.2 g add 10 ml of dilute hydrochloric acid, heat, cool and filter. To 5 ml of the filtrate add ammonia TS dropwise until a white precipitate is produced, add a few drops of sodium alizarin sulfonate TS, the precipitate becomes cherry red in colour.

Chlorides Dissolve 0.20 g add 4 ml of nitric acid by heating gently to boiling, cool, add water to produce 20 ml and mix well. Carry out the limit test for chlorides (Appendix VIII A), using 5 ml of the resulting solution. Any opalescence produced is not more pronounced than that of a reference solution using 7.0 ml of sodium chloride standard solution (0.14%).

Sulfates Dissolve 1.0 g in 4 ml of nitric acid by heating, cool, add 30 ml of water, the white precipitate is produced. Add dropwise ammonia TS to neutralize the solution and dilute with water to produce 50 ml, mix well and filter. Carry out the limit test for sulfates (Appendix VIII B), using 25 ml of the filtrate. Any opalescence produced is not more pronounced than that of a reference solution using 1.0 ml of potassium sulfate standard solution (0.02%).

Nitrate Dissolve 50 mg in about 40 ml of sulfuric acid solution (1→2) by heating, dilute to 50 ml and mix well. To 1.0 ml add 4.0 ml of water and 0.5 ml of 10% sodium chloride solution and mix well. Add 1 ml of dilute indigocarmine solution [mix indigo-carmin TS with equal volume of water. Before using, dilute 1 ml of this solution, accurately measured, to 50 ml with water. Measure the absorbance of the resulting solution at 610 nm (Appendix IV B), the absorbance is 0.30-0.40], accurately measured,

mix well. Add alongside the wall 4.5 ml of sulfuric acid slowly, shake gently for 1 minute, allow to stand for 10 minutes. Any colour produced is not more intense than that of a reference solution using 0.50 ml of potassium nitrate standard solution (dissolve 81.5 mg of potassium nitrate, previously ignited to constant weight at 105°C and accurately weighed in a 50 ml volumetric flask with water and dilute to volume. Measure accurately 5 ml and dilute to 100 ml with water. Each ml of this solution is equivalent to 50 µg of NO_3 .) (2.5%).

Barium Dissolve 0.4 g in 4 ml of nitric acid by heating, cool, add 20 ml of water. Divide this solution into two equal portions. To one portion add 1 ml of dilute sulfuric acid, and to the other portion add 1 ml of water, allow to stand for 15 minutes, the solutions should be equally clear.

Lead, silver and copper To 3.0 g add 6 ml of nitric acid, heat gently to boiling for 2 minutes, cool. Add 100 ml of water, stir, filter. Evaporate the filtrate to about 30 ml on a water bath, cool, filter, add water to produce 30 ml. Mix 5 ml of this solution with an equal volume of dilute sulfuric acid; no turbidity is produced. To 5 ml of this solution add hydrochloric acid; no precipitate is produced that is insoluble in an excess of hydrochloric acid but soluble in ammonia TS. To 5 ml of this solution add a slight excess of ammonia TS; the supernatant liquid does not exhibit blue.

Arsenic To 1.0 g add 10 ml of dilute sulfuric acid, heat to boiling, cool, add 5 ml of hydrochloric acid and a quantity of water to produce 28 ml. Carry out the limit test for arsenic (Appendix VIII J, method 1); not more than 0.0002%.

Loss on ignition When ignited to constant weight at 700°C, loses not more than 22.0% of its weight.

Assay Bismuth To about 0.2 g, accurately weighed, in a 500 ml conical flask add 15 ml of nitric acid solution (3→10), place a funnel on the conical flask, heat gently until dissolved completely, cool. Add 200 ml of water, ammonia TS dropwise to adjust the solution to about pH 1, and 5 drops of xylenol orange IS, titrate with disodium edetate (0.05 mol/L) VS until the colour changes to yellow. Each ml of disodium edetate (0.05 mol/L) VS is equivalent to 10.45 mg of Bi.

Aluminum To the solution retained in the Assay for Bi add ammonia TS dropwise until a precipitate is just formed and redissolve it by adding dropwise dilute nitric acid (pH is about 6). Add 10 ml of acetic acid-ammonia acetate BS (pH 6.0) and 30 ml of disodium edetate, accurately measured, boil for 5 minutes. Cool to room temperature, add 10 drops of xylenol orange IS, titrate with zinc (0.05 mol/L) VS until the colour changes from yellow to red. Perform a blank determination and make any necessary correction. Each ml of disodium edetate (0.05 mol/L) VS is equivalent to 1.349 mg of Al.

Category Antacid.

Storage Preserve in tightly closed containers, protected from light.

Preparation (1) Compound Bismuth Aluminate Capsules
(2) Compound Bismuth Aluminate Tablets

Compound Bismuth Aluminate Tablets

Compound Bismuth Aluminate Tablets contain not less than 79 mg and not more than 97 mg of

bismuth (Bi); not less than 30.6 mg and not more than 37.4 mg of aluminium (Al); not less than 37.3% and not more than 45.7% of the labelled amount of heavy magnesium carbonate calculated as magnesium oxide (MgO) in each tablet.

Formula	Bismuth Aluminate	200 g
	Heavy Magnesium Carbonate	400 g
	Sodium Bicarbonate	200 g
	Liquorice Extract	300 g
	Rhamnus Frangula	25 g
	Fennel Powder	10 g
	Excipient	sufficient
	To make	1000 tablets

Description Pale yellow to yellowish brown tablets.

Identification Heat gently about 1 g of the powdered tablets in a crucible, until it is thoroughly charred, cool, add 3 ml of nitric acid. Heat gently until nitric acid fume is no longer evolved, ignite until the incineration is complete. The residue complies with the following tests:

(1) Dissolve a quantity of the residue in 5 ml of dilute nitric acid, filter, to the filtrate add potassium iodide TS dropwise, a brownish-red precipitate is produced which is dissolved in an excess of potassium iodide TS.

(2) Dissolve a quantity of the residue in 5 ml of dilute hydrochloric acid, filter; to the filtrate add a few drops of sodium alizarin sulfonate IS; the precipitate becomes cherry red in colour.

(3) Dissolve a quantity of the residue in 3 ml of dilute hydrochloric acid, adjust the solution to neutral with ammonia TS, add 3 ml of ammonia-ammonium chloride (pH 10) BS, filter. Apply several drops of the filtrate to a white porcelain plate, add several drops of sodium hydroxide and 1-2 drops of 5% *p*-nitrobenzene azo-resorcinol solution; a blue precipitate is produced.

(4) To about 0.5 g of the powdered tablets add 5 ml of water and 3 ml of dilute sulfuric acid, it effervesces with the evolution of carbon dioxide, producing a white precipitate when passed into calcium hydroxide TS.

(5) To about 0.5 g of the powdered tablets add 10 ml dilute sulfuric acid boil for 2 minutes, filter while hot, extract the filtrate with 5 ml ether, separate the ether layer, add 2 ml of sodium hydroxide TS, shake, an orange-red colour is produced in the water layer.

(6) To about 1 g of the powdered tablets add 15 ml of methanol, warm gently for 30 minutes, filter. Examine the filtrate under ultraviolet light at 254 nm, a yellowish-green fluorescence is produced.

(7) To about 1 g of the powdered tablets, add 10 ml of ether, shake for 10 minutes and filter. Evaporate the ether extract to dryness in a porcelain evaporating dish, to the residue add 2 drops of 5% vanilline in a sulfuric acid solution (prepared freshly), a purple colour is produced.

(8) Dissolve a quantity of the residue in 3 ml of dilute hydrochloric acid, filter, the filtrate yields the reactions characteristic of sodium salts (Appendix III).

Other requirements Comply with the general requirement for tablets (Appendix I A), with the exception of disintegration test.

Assay *Bismuth* Weigh and powder 10 tablets. Weigh accurately a quantity of the powder equivalent to about 0.3 g of bismuth aluminate in a 50 ml crucible, heat gently until it is thoroughly charred, cool. Add 3 ml of nitric acid, heat gently until nitric acid fumes are no longer evolved, ignite until the incineration is complete and cool. Add 20 ml of nitric solution (3→10), transfer the residue into a 500 ml conical flask, cover with a small funnel, heat gently to

reflux until the residue is dissolved (the solution turns slightly turbid). Cool, add 200 ml of water, adjust the pH value to 1.0, add 5 drops of xylenol orange IS, titrate with disodium edetate (0.05 mol/L) VS until the colour of the solution turns from orange-red to lemon yellow. Each ml of disodium edetate (0.05 mol/L) VS is equivalent to 10.45 mg of Bi.

Aluminium To the solution after titration of bismuth add ammonia TS dropwise until a precipitate is just formed and redissolve it by adding dropwise dilute nitric acid (about pH 6). Add 15 ml of acetic acid-ammonium acetate BS (pH 6.0) and 50 ml of disodium edetate (0.05 mol/L) VS, accurately measured, heat to boil for 10 minutes, allow to cool, add 5 drops of xylenol orange IS and titrate with zinc (0.05 ml/L) VS until the colour turns from lemon yellow to orange-red. Perform a blank determination and make any necessary correction. Each ml of disodium edetate (0.05 mol/L) VS is equivalent to 1.349 mg of Al.

Magnesium oxide Weigh accurately a quantity of the above powdered tablets equivalent to about 0.4 g of magnesium carbonate, in a 50 ml of crucible, heat gently until it is thoroughly charred, cool and add 3 ml of nitric acid. Heat gently until nitric acid fumes are no longer evolved, ignite until the incineration is complete, allow to cool. Add 15 ml of dilute hydrochloric acid and transfer the residue into a 50 ml beaker, heat to boil, then allow to cool. Add 20 ml of water and 1 drop of methyl red IS, then add ammonia TS dropwise until the colour turns from red to yellow. Boil again for 5 minutes, filter while hot, wash the residue with 30 ml of warm 2% ammonium chloride solution. Combine the washings with the filtrate into a 100 ml volumetric flask, dilute to volume with water, mix well. Measure accurately 20 ml of the solution into a conical flask, add 20 ml of water, 5 ml each of ammonia-ammonium chloride BS (pH 10.0) and triethanolamine solution, (1→2), then add a small amount of eriochrome black T indicator, titrate with disodium edetate (0.005 mol/L) VS to blue colour. Each ml of disodium edetate (0.05 mol/L) VS is equivalent to 2.015 mg of MgO.

Category Antacid.

Storage Preserve in tightly closed containers, stored in a dry place.

Compound Bismuth Aluminate Capsules

Compound Bismuth Aluminate Capsules contain not less than 26.4 mg and not more than 32.2 mg of Bismuth Aluminate as bismuth (Bi); not less than 10.2 mg and not more than 12.5 mg of aluminate (Al); not less than 37.3% and not more than 45.7% of the labelled amount of heavy magnesium carbonate calculated as magnesium oxide (MgO) in each capsule.

Formula	Bismuth Aluminate	66.7 g
	Heavy Magnesium Carbonate	133.3 g
	Sodium Bicarbonate	66.7 g
	Powdered Liquorice Extract	100 g
	Rhamnus Frangula	8.3 g
	Fennel Powder	3.3 g
	Excipient	a quantity
	to make	1000 capsules

Description Hard capsules containing pale brown powder.

Identification Heat gently about 1 g of the contents of capsules in a crucible, until it is thoroughly charred, cool, add 3 ml of nitric acid. Heat gently until nitric acid fume is no longer evolved, ignite until the incineration is complete. The residue complies with the following tests:

(1) Dissolve a quantity of the residue in 5 ml of dilute nitric acid, filter, to the filtrate add potassium iodide TS dropwise, a brownish-red precipitate is produced which is dissolved in an excess of potassium iodide TS.

(2) Dissolve a quantity of the residue in 5 ml of dilute hydrochloric acid, filter; to the filtrate add ammonia TS until a white precipitate is produced, add a few drops of sodium alizarin sulfonate IS; the precipitate becomes cherry red in colour.

(3) Dissolve a quantity of the residue in 3 ml of dilute hydrochloric acid, adjust the solution to neutral with ammonia TS, add 3 ml of ammonia-ammonium chloride (pH 10) BS, filter. Apply several drops of the filtrate to a white porcelain plate, add several drops of sodium hydroxide and 1-2 drops of 5% *p*-nitrobenzene azo-resorcinol solution; a blue precipitate is produced.

(4) To about 0.5 g of the contents of capsules add 5 ml of water and 3 ml of dilute sulfuric acid, it effervesces with the evolution of carbon dioxide, producing a white precipitate when passed into calcium hydroxide TS.

(5) To about 0.5 g of the contents of capsules add 10 ml dilute sulfuric acid, boil for 2 minutes, filter while hot, extract the filtrate with 5 ml of ether, separate the ether layer, add 2 ml of sodium hydroxide TS, shake, an orange-red colour is produced in the water layer.

(6) To about 1 g of the contents of capsules add 15 ml of methanol, warm gently for 30 minutes, filter. Examine the filtrate under ultraviolet light at 254 nm, a yellowish-green fluorescence is produced.

(7) To about 1 g of the contents of capsules add 10 ml of ether, shake for 10 minutes and filter. Evaporate the ether extract to dryness in a porcelain evaporating dish, to the residue add 2 drops of 5% vaniline in a sulfuric acid solution (prepared freshly), a purple colour is produced.

(8) Dissolve a quantity of the residue in 3 ml of dilute hydrochloric acid, filter, the filtrate yields the reaction characteristic of sodium salts (Appendix III).

Other requirements Comply with the general requirements for capsules (Appendix I E).

Assay bismuth Mix the contents obtained in the test for weight variation of contents. Weigh accurately a quantity of the contents equivalent to about 0.3 g of bismuth aluminate in a 50 ml crucible, heat gently until it is thoroughly charred, cool. Add 3 ml of nitric acid, heat gently until nitric acid fumes are no longer evolved, ignite until the incineration is complete and cool. Add 20 ml of nitric solution (3→10), transfer the residue into a 500 ml conical flask, cover with a small funnel, heat gently to reflux until the residue is dissolved (the solution is slightly turbid). Cool, add 200 ml of water, adjust the pH value to 1.0, add 5 drops of xylenol orange IS, Titrate with disodium edetate (0.05 mol/L) VS until the colour of the solution turns from orange-red to lemon yellow. Each ml of disodium edetate (0.05 mol/L) VS is equivalent to 10.45 mg of Bi.

Aluminium To the solution after titration of bismuth add ammonis TS dropwise until a precipitate is just formed and redissolve it by adding dropwise dilute nitric acid (about pH 6). Add 15 ml of acetic acid-ammonium acetate BS (pH 6.0) and 50 ml of disodium edetate (0.05 mol/L), accurately measured, heat to boil for 10 minutes, allow to cool, add 5 drops of xylenol orange IS and titrate with zinc (0.05 mol/L) VS until the colour turns from lemon yellow to orange-red. Perform a blank determination and make any necessary correction. Each ml of disodium edetate (0.05

mol/L) VS is equivalent to 1.349 mg of Al.

Magnesium oxide Weigh accurately a quantity of the contents equivalent to about 0.4 g of heavy magnesium carbonate, in a 50 ml of crucible, heat gently until it is thoroughly charred, cool and add 3 ml of nitric acid. Heat gently until nitric acid fumes are no longer evolved, ignite until the incineration is complete, allow to cool. Add 15 ml of dilute hydrochloric acid and transfer the residue into a 50 ml beaker, heat to boil to dissolve the residue, then allow to cool. Add 20 ml of water and 1 drop of methyl red IS, then add ammonia TS dropwise until the colour turns from red to yellow. Boil again for 5 minutes, filter while hot, wash the residue with 30 ml of warm 2% ammonium chloride solution. Combine the washings with the filtrate into a 100 ml volumetric flask, dilute to volume with water, mix well. Measure accurately 20 ml of the solution into a conical flask, add 20 ml of water, 5 ml each of ammonia-ammonium chloride BS (pH 10.0) and triethanolamine solution, (1→2), then add a small amount of eriochrome black T indicator, titrate with disodium edetate (0.05 mol/L) VS until the colour turns to pure blue. Each ml of disodium edetate (0.05 mol/L) VS is equivalent to 2.015 mg of MgO.

Category Antacid.

Storage Preserve in tightly closed containers, stored in a dry place.

Bismuth Potassium Citrate

Bismuth Potassium Citrate is a bismuth complex of indefinite composition. It contains not less than 35.0% and not more than 38.5% of bismuth (Bi), calculated on the dried basis.

Description A white powder; taste saline; hygroscopic. Very soluble in water; very slightly soluble in ethanol.

Identification (1) Dissolve about 1 mg in 5 ml of water, add 2-3 drops of dilute sulfuric acid and several drops of thiourea solution (1→10), a deep yellow colour is produced.

(2) Dissolve about 0.1 g in 5 ml of water, add 3 drops of perchloric acid solution (1→10), a white turbidity or precipitate is produced which is insoluble in sodium hydroxide TS or concentrate ammonia solution.

(3) Dissolve about 10 mg in 0.2 ml of water, add 5 ml of a mixture of pyridine acetic anhydride (3:1), shake, a yellow to red or purplish red colour is produced.

Acidity or alkalinity Dissolve 0.60 g in 10 ml water, pH 6.0-8.0 (Appendix VI H)

Sulfate Dissolve 1.0 g in 20 ml of water, add 4 ml dilute hydrochloric acid, heat on water bath for 10 minutes, cool and filter. Divide the filtrate into two equal portions. To one portion add 5 ml of 25% barium chloride solution, mix well, allow to stand for 10 minutes, filter repeatedly until the filtrate is clear. Dilute with water to produce about 40 ml, add 2.0 ml of potassium sulfate standard solution, dilute with water to 50 ml, mix well, allow to stand for 10 minutes, use as reference solution. To another portion dilute with water to 40 ml, add 5 ml of 25% barium chloride solution, dilute with water to 50 ml, mix well, allow to stand for 10 minutes. Any opalescence produced is not more intense than that of the reference preparation (0.04%).

Nitrate Dissolve 0.50 g in 5 ml of water in a test tube, mix cautiously with 5 ml of sulfuric acid, cool, add 5 ml of

ferrous sulfate TS along the inner wall of the test tube, a brown ring is not developed immediately at the interface of the two layers.

Loss on drying When dried to constant weight at 105°C, loses not more than 5.0% of its weight (Appendix VIII L).

Copper Dissolve 0.20 g in 2 ml of water, add 2 ml of ammonium citrate solution (1→10), adjust the pH value to 8-9 with ammonia TS, add 5 ml of dilute ethanolic solution of 0.1% dicyclohexyl ketone oxalodihydrazone and dilute with water to 50 ml. Repeat the operation, using 0.50 ml IS prepare the reference solution. Any colour produced is not more intense than that of 0.50 ml of standard cupric sulfate solution (each ml is equivalent to 10 µg of Cu) (0.0025%).

Lead Ignite 1.0 g at 600°C until the incineration is complete, cool, add nitric acid dropwise to dissolve the residue, heat on a water bath to dryness, cool, add 5 ml of potassium hydroxide solution (1→6), heat to boil for 2 minutes, cool and filter. Wash the residue with a small amount of water, combine the filtrate and washings, adjust to pH 7 with acetic acid, dilute with water to 25 ml. Add 2 ml of dilute acetic acid and 10 ml of hydrogen sulfide TS, allow to stand for 10 minutes. Any colour produced is not more intense than that of a reference using 2.0 ml of lead standard solution operated in similar manner (0.002%).

Ammonia content Weigh accurately about 1 g, carry out the method for determination of nitrogen (Appendix VII D, method 1), beginning at the words "add cautiously 250 ml of water..." (but add 30 ml of 40% sodium hydroxide solution). Each ml of sulfuric acid (0.05 mol/L) VS is equivalent to 1.703 mg of NH₃. It contains not less than 2% and not more than 6% of ammonia.

Assay Dissolve about 0.5 g, accurately weighed, in 50 ml of water, add 3 ml of nitric acid solution (1→3) and 2 drops of xylenol orange IS, titrate with disodium edetate (0.05 mol/L) VS to pale yellow colour. Each ml of disodium edetate (0.05 mol/L) VS is equivalent to 10.45 mg of Bi.

Category anti-ulcerative.

Storage Preserve in tightly closed containers, protected from light, stored in a dry place.

Preparation (1) Bismuth Potassium Citrate Capsules
(2) Bismuth Potassium Citrate Granules
(3) Bismuth Potassium Citrate Tablets

Bismuth Potassium Citrate Capsules

Bismuth Potassium Citrate Capsules contain not less than 90.0% and not more than 110.0% of the labelled amount of bismuth (Bi).

Description Capsules containing white granules.

Identification To a quantity of the powdered granules equivalent to about 220 mg of bismuth add 50 ml of water, stir thoroughly to dissolve bismuth potassium citrate, and filter, comply with test (1)(2)(3) for Identification described under Bismuth Potassium Citrate, using the filtrate.

Other requirements Comply with the general requirements for capsules (Appendix I E).

Assay Weigh accurately a quantity of the mixed contents obtained in the test for weight variation of contents equivalent to about 200 mg of Bi, add 18 ml diluted nitric acid, shake thoroughly to dissolve bismuth potassium

citrate, add 50 ml of water, mix well, add 3 drops of xylenol orange IS, titrate with disodium edetate (0.05 mol/L) VS until the solution turns to yellow. Each ml of disodium edetate (0.05 mol/L) VS is equivalent to 10.45 mg of Bi.

Category As described under Bismuth Potassium Citrate.

Strength 0.3 g (equivalent to 110 mg of Bi)

Storage Preserve in tightly closed containers, stored in a dry place and protected from light.

Bismuth Potassium Citrate Granules

Bismuth Potassium Citrate Granules contain not less than 90.0% and not more than 110.0% of the labelled amount of bismuth (Bi).

Description White to pale yellow granules; taste, slightly sweet.

Identification To a quantity equivalent to about 220 mg of bismuth add 50 ml of water, stir thoroughly to dissolve bismuth potassium citrate and filter. Comply with test (1)(2)(3) for Identification described under Bismuth Potassium Citrate, using the filtrate.

Loss on drying When dried to constant weight at 105°C, loses not more than 5.0% of its weight (Appendix VIII L).

Other requirements Comply with the general requirements for granules (Appendix I N).

Assay Weigh accurately a quantity of the powdered contents obtained in the test for weight variation equivalent to about 180 mg of Bi, add 50 ml of water, shake thoroughly to dissolve bismuth potassium citrate. Add 5 ml of nitric acid solution (1→5) and 2 drops of xylenol orange IS, titrate with disodium edetate (0.05 mol/L) VS to yellow colour. Each ml of disodium edetate (0.05 mol/L) VS is equivalent to 10.45 mg of Bi.

Category As described under Bismuth Potassium Citrate.

Strength (1) 1.0 g (equivalent to 110 mg of Bi)
(2) 1.2 g (equivalent to 110 mg of Bi)

Storage Preserve in tightly closed containers, stored in a dry place and protected from light.

Bismuth Potassium Citrate Tablets

Bismuth Potassium Citrate Tablets contain not less than 90.0% and not more than 110.0% of the labelled amount of bismuth (Bi).

Description White tablets or film-coated tablets with white cores.

Identification To a quantity of the powdered tablets, equivalent to about 220 mg of Bi, add 50 ml of water, shake thoroughly to dissolve bismuth potassium citrate and filter. Complies with test (1)(2)(3) for Identification described under Bismuth Potassium Citrate, using the filtrate.

Other requirements Comply with the general requirements for tablets (Appendix I A).

Assay Weigh accurately and powder 10 tablets. Weigh accurately a quantity of the powder equivalent to about 180 mg of Bi, add 50 ml of water, shake thoroughly to dissolve bismuth potassium citrate. Add 5 ml of nitric acid solution

(1 → 5) and 2 drops of xylenol orange IS, titrate with disodium edetate (0.05 mol/L) VS to yellow colour. Each ml of disodium edetate (0.05 mol/L) VS is equivalent to 10.45 mg of Bi.

Category As described under Bismuth Potassium Citrate.

Strength 0.3 g (equivalent to 110 mg of Bi)

Storage Preserve in tightly closed containers, stored in cool place, protected from light.

Bismuth Subcarbonate

[5892-10-4]

Bismuth Subcarbonate is a basic bismuth salt of indefinite composition. It contains not less than 80.0% and not more than 82.5% of bismuth (Bi), calculated on the dried basis.

Description A white to slightly pale yellow powder; odourless; tasteless; deteriorated slowly on exposure to light.

Insoluble in water or ethanol.

Identification (1) To about 0.2 g add 2 ml of dilute hydrochloric acid, it dissolves with effervescence. Divide this solution to two equal parts. Dilute one part with water, a white precipitate is produced which changes to brown colour on adding sodium sulfide TS. Add 1 ml of 10% thiourea solution to the other part, a deep yellow colour is produced.

(2) Dissolve about 50 mg in 1 ml of nitric acid, add 10 ml of water. To 2 ml of this solution, add potassium iodide TS dropwise, a brownish-black precipitate is produced which is dissolved in an excess of potassium iodide TS to form a yellowish-orange solution.

Chloride Dissolve 0.20 g in 4 ml of nitric acid, add a quantity of water to produce 20 ml. Carry out the limit test for chlorides (Appendix VIII A) using accurately measured 5.0 ml. Any opalescence produced is not more pronounced than that of a reference using 7.0 ml of sodium chloride standard solution (0.14%).

Sulfate Dissolve 1.0 g in 2 ml of hydrochloric acid, pour into 40 ml of water, a lot of white precipitate is produced. Add ammonia TS dropwise until the solution is neutral to litmus paper, add water to 50 ml and mix well, filter. Carry out the limit test for sulfates (Appendix VIII B), using 25 ml of the filtrate. Any opalescence produced is not more pronounced than that of a reference using 1.0 ml of potassium sulfate standard solution (0.02%).

Nitrate To 0.10 g add 8 ml of water and 2 ml of indigo carmine TS, then add cautiously 10 ml of sulfuric acid. When effervescence is ceased, heat to boil and allow to stand for 1 minute; the blue colour of the solution is not discharged completely.

Loss on drying When dried to constant weight at 105°C, loses not more than 1.5% of its weight (Appendix VIII L).

Alkali and alkaline earth salts Boil 1.0 g with 20 ml of acetic acid-water (1:1) for 2 minutes, cool, filter and wash the residue with water. To the combined filtrate and washings, add 2 ml of dilute hydrochloric acid and pass hydrogen sulfide into the solution until no further precipitate is formed. Filter, add 5 drops of sulfuric acid to the filtrate, evaporate to dryness and ignite to constant weight; the residue weighs not more than 5 mg.

Copper Dissolve 1.0 g in 2 ml of hydrochloric acid, pour into 40 ml of water, a lot of white precipitate is produced, add water to 50 ml, mix well and filter. To 5 ml of the filtrate add ammonia TS dropwise until the solution is neutral to litmus paper, add 5 ml more, filter and wash the precipitate with two quantities of 5 ml each of water. To the combined filtrate and washings add 5 ml of sodium diethyldithiocarbamate TS and water to produce 50 ml. Any colour produced is not more intense than that of a reference solution prepared by mixing 0.5 ml of copper sulfate solution (measure accurately 2.5 ml of standard copper sulfate CS in an 100 ml volumetric flask, dilute to volume with water and mix well. Measure accurately 2.5 ml of the above solution into another 100 ml volumetric flask, dilute with water to volume and mix well. Each ml is equivalent to 10 µg of Cu), 5 ml of ammonia TS, 5 ml of sodium diethyl-dithiocarbamate TS and water to 50 ml (0.005%).

Silver Dissolve 1.0 g in 5 ml of nitric acid, add 15 ml of water and 2 drops of dilute hydrochloric acid, no turbidity is produced.

Lead Transfer separately two portions of 3.0 g into 50 ml of volumetric flask and dissolve in 10 ml of nitric acid; dilute the one portion with water to volume, mix well (test solution) and to another portion add 6 ml of standard lead solution and dilute with water to volume, mix well (reference solution). Carry out the method for atomic absorption spectrophotometry (Appendix IV D) and measure the absorbance of the two solution at 283.3 nm. It complies with the requirements.

Arsenic Dissolve 1.0 g in 5 ml of hydrochloric acid and 23 ml of water, carry out the limit test for arsenic (Appendix VIII J, method 1). Complies with the requirements (0.0002%).

Assay Dissolve about 0.2 g, accurately weighed, in 5 ml of nitric acid solution (3 → 10), add 100 ml of water and 3 drops of xylenol orange IS, titrate with disodium edetate (0.05 mol/L) VS to pale yellow colour. Each ml of disodium edetate (0.05 mol/L) VS is equivalent to 10.45 mg of Bi.

Category Antacid, astringent.

Storage Preserve in tightly closed containers, protected from light.

Preparation Bismuth Subcarbonate Tablets

Bismuth Subcarbonate Tablets

Bismuth Subcarbonate Tablets contain not less than 75.0% and not more than 85.0% of the labelled amount of bismuth subcarbonate calculated as bismuth (Bi).

Description White to slightly pale yellow tablets.

Identification To a quantity of the powdered tablets equivalent to about 0.3 g of bismuth subcarbonate add 3 ml of dilute hydrochloric acid, an effervescence takes place. Add 10 ml of water, filter, divide the filtrate into three parts; dilute part (1) with water; a white precipitate is produced which changes to brown colour on addition of sodium sulfide TS. To part (2) add 1 ml of 10% thiourea solution; a deep yellow colour is produced. To part (3) add potassium iodide TS, a brownish-black precipitate is produced which is dissolved in an excess of potassium iodide TS to form yellowish-orange solution.

Other requirements Comply with the general requirements for tablets (Appendix I A).

Assay Weigh accurately and powder 10 tablets. Weigh accurately a quantity of the powdered tablets equivalent to about 0.2 g of bismuth subcarbonate. Carry out the Assay described under Bismuth Subcarbonate, beginning at the words "dissolve in 5 ml of nitric acid solution (3→10)...". Each ml of disodium edetate (0.05 mol/L) VS is equivalent to 10.45 mg of Bi.

Category As described under Bismuth Subcarbonate.

Strength (1) 0.3 g (2) 0.5 g

Storage Preserve in tightly closed containers, protected from light and stored in a dry place.

Black Ferric Oxide

Fe_3O_4 231.53

Black Ferric Oxide contains not less than 96.0% of Fe_3O_4 , calculated on the dried basis.

Description A black powder; odourless; tasteless. Insoluble in water; freely soluble in boiling hydrochloric acid.

Identification Boil about 0.1 g with 5 ml of dilute hydrochloric acid, allow to cool, the solution yields the reactions characteristic of ferric salts (Appendix III).

Water soluble substances To 2.0 g add 100 ml of water, heat under reflux on a water bath for 2 hours and filter. Wash the residue with a quantity of water, evaporate the combined filtrate and washings to dryness in an evaporating dish previously dried to constant weight at 105°C, dry the residue to constant weight at 105°C; not more than 10 mg (0.5%).

Acid insoluble substances Dissolve 2.0 g in 25 ml of hydrochloric acid by heating in a water bath, add 100 ml of water, filter through a sintered glass crucible (No. 4) previously dried to constant weight at 105°C, wash the residue with hydrochloric acid solution (1→100) until the washings become colourless, then wash the residue with water until the washings give no reaction of chlorides, dry the residue to constant weight at 105°C; not more than 20 mg (1.0%).

Loss on ignition When dried to constant weight at 105°C, loses not more than 1.0% of its weight (Appendix VIII L).

Barium To 0.2 g add 5 ml of hydrochloric acid, heat until dissolved. Add 1 drop of hydrogen peroxide TS and 20 ml of 10% sodium hydroxide solution, filter, wash the residue with 10 ml of water. Combine the filtrate and washings, add 10 ml of sulfuric acid solution (2→10), no opalescence is produced.

Lead To 0.5 g add 10 ml of hydrochloric acid, heat until dissolved. Add 3 ml of nitric acid, boil for 1 minute, allow to cool. Extract with anhydrous ether for 4 times (30 ml, 20 ml, 20 ml and 20 ml), discard the ether layer. Heat the acid solution to expel the remaining ether, add ammonia TS to make the solution alkaline, add 1 ml of potassium cyanide TS and sufficient water to produce 50 ml. Add a few drops of sodium sulfide TS and mix well. Any colour produced is not more intense than that of a reference solution prepared in the same manner using 1.5 ml of lead standard solution (0.003%).

Arsenic To 0.2 g add 7 ml of hydrochloric acid, heat until dissolved. Add 21 ml of water, and add acid stannous

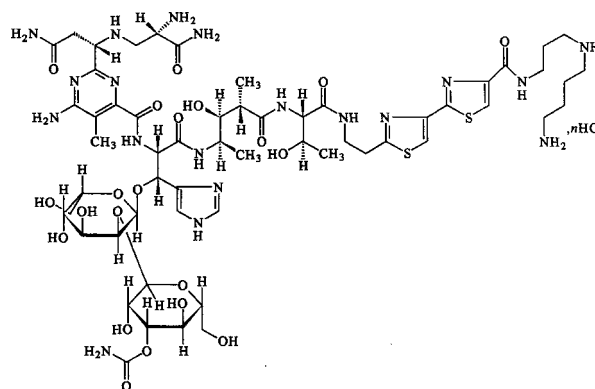
chloride TS dropwise until the yellow colour disappears. Carry out the limit test for arsenic (Appendix VIII J, method 1): not more than 0.001%.

Assay To about 0.15 g, accurately weighed, in a conical flask with stopper add 30 ml of hydrochloric acid solution (1→2), heat until dissolved. Continue to heat until the solution begins to boil. Add freshly prepared stannous chloride TS dropwise until the solution is just colourless. Then add 1 drop of freshly prepared stannous chloride TS in excess and 200 ml of water, allow to cool, add 4 ml of mercuric chloride TS, mix well, then add 3 ml of sulfuric acid and 3 ml of phosphoric acid. Add 6 drops of 0.2% diphenylamine sulfonic acid sodium IS, titrate with potassium dichromate (0.01667 mol/L) VS until a purple blue colour persists for 30 seconds. Each ml of potassium dichromate (0.01667 mol/L) VS is equivalent to 7.72 mg of Fe_3O_4 .

Category Pharmaceutical aid, colouring agent.

Storage Preserve in tightly closed containers.

Bleomycin A5 Hydrochloride for Injection



$\text{C}_{57}\text{H}_{89}\text{N}_{19}\text{O}_{21}\text{S}_2 \cdot n\text{HCl}$

Bleomycin A5 Hydrochloride for Injection is a sterile lyophilized powder of bleomycin A5 hydrochloride. It contains not less than 80.0% of bleomycin A5 hydrochloride, calculated on the dried basis. Each container contains not less than 85.0% and not more than 115.0% of the labelled amount of bleomycin A5 hydrochloride, calculated on the basis of the average weight of contents.

Description A white friable solid or amorphous solid; odourless or almost odourless; hygroscopic. Freely soluble in water or methanol; slightly soluble in ethanol; practically insoluble in acetone, chloroform or ether.

Identification (1) Carry out the method for high performance liquid chromatography as described under the Assay. The retention time of the principal peak of the substance being examined in the chromatogram is identical with that of Bleomycin A5 hydrochloride CRS.

(2) Dissolve 0.4 mg in 10 ml of water and add 0.05 ml of 3% copper sulfate solution, the light absorption of the resulting solution exhibits maxima at 242 nm and 291 nm (Appendix IV A).

(3) The aqueous solution yields the reactions characteristic of chlorides (Appendix III).

Acidity An aqueous solution of 4 mg per ml, pH 4.5-6.0 (Appendix VI H).

Clarity and colour of solution To each of 5 containers add water to produce solutions of 4 mg per ml, the solutions are clear and colourless; any opalescence produced is not more pronounced than that of reference suspension 1 (Appendix IX B); any colour produced is not more intense than that of reference solution Y₂ or YG₂ (Appendix IX A, method 1).

Loss on drying When dried in vacuum over phosphorous pentoxide to constant weight at 60°C, loses not more than 6.0% of its weight (Appendix VII L).

Copper Dissolve 15 mg, accurately weighed, in a 10 ml volumetric flask with 3 ml of hydrochloric acid solution (0.1 mol/L). Transfer 3 ml of standard copper solution [Weigh accurately 1.965 g of copper sulfate (CuSO₄ • 5H₂O) to a 1000 ml volumetric flask, dissolve in 0.1 mol/L hydrochloric acid solution and dilute to volume, mix well, Transfer accurately 5 ml to a 500 ml volumetric flask, add 0.1 mol/L hydrochloric acid to volume. Each ml of the solution is equivalent to 5 µg of copper.] to another 10 ml volumetric flask; add separately 0.4 ml of 3% acacia solution, mix well, followed with 2 ml of sodium diethyldithiocarbamate TS and dilute with 0.1 mol/L hydrochloric acid solution to volume as test solution and copper standard solution respectively. Measure the absorbances of the solutions at 450 nm (Appendix IV A), using 0.1 mol/L hydrochloric acid solution as the blank. Calculate the content of copper; not more than 0.1%.

Content uniformity To each of 10 containers add water to produce 200 ml respectively, and measure the absorbance of the resulting at 291 nm (Appendix IV A). Not more than one of the individual absorbance deviates from the average absorbance by more than ±15% and none deviates by more than ±20%.

Bacterial endotoxin Carry out the test for bacterial endotoxin (Appendix XI E); less than 25 EU per mg.

Sterility Complies with the test for sterility (Appendix XI H, membrane filtration method), dissolve each container in feasible solvent and dilute with 500 ml of 0.9% steril sodium chloride solution respectively.

Other requirements Complies with the general requirements for injections (Appendix I B).

Assay Carry out the method for high performance liquid chromatography (Appendix V D), using a column packed with octadecylsilane bonded silica gel and a mixture of sodium 1-pentane sulfonate solution (dissolve 0.96 g of sodium 1-pentane sulfonate and 1.86 g of disodium edetate in 0.08 mol/L acetic acid solution, dilute to 1000 ml and adjust to pH 4.3 with ammonia solution)-methanol-acetonitrile (76:16:8) as the mobile phase; wavelength of the detector is 254 nm and the number of theoretical plates of the column is not less than 700, calculated with reference to the peak of bleomycin A5.

Procedure Dissolve about 10 mg of the mixed contents obtained from the test for weight variation of contents, accurately weighed, in water and dilute to 10 ml, inject 10 µl into the column. Repeat the operation using bleomycin A5 hydrochloride CRS instead of the substance being examined, calculate the content of C₅₇H₈₉N₁₉O₂₁S₂ • nHCl with respect to the peak area obtained in the chromatogram by the external standard method.

Category Antineoplastic antibiotic.

Strength Calculated as Bleomycin A5 Hydrochloride
(1) 4 mg (2) 8 mg

Storage Preserve in tightly closed containers, stored in a

dry, cool and dark place.

Borax

Na₂B₄O₇ • 10H₂O 381.37

[1303-96-4]

Borax is sodium tetraborate. It contains not less than 99.0% and not more than 105.0% of Na₂B₄O₇ • 10H₂O.

Description Colourless, translucent crystals or a white crystalline powder; odourless; efflorescent; its aqueous solution exhibits an alkaline reaction.

Freely soluble in boiling water or glycerin; soluble in water; insoluble in ethanol.

Identification Its aqueous solution yields the reactions characteristic of sodium salts and borates (Appendix III).

Clarity of solution A solution of 0.5 g in 10 ml of water is clear. Any opalescence produced is not more pronounced than that of reference suspension 2 (Appendix IX B).

Chlorides Carry out the limit test for chlorides (Appendix VIII A), using 0.25 g. Any opalescence produced is not more pronounced than that of a reference using 5.0 ml of sodium chloride standard solution (0.02%).

Sulfates Carry out the limit test for sulfates (Appendix VIII B), using 0.50 g. Any opalescence produced is not more pronounced than that of a reference using 2.0 ml of potassium sulfate standard solution (0.04%).

Carbonates and bicarbonates Dissolve 0.25 g in 5 ml of water. Add hydrochloric acid, no effervescence is produced.

Calcium Dissolve 0.25 g in 10 ml of water, acidify with acetic acid, add 1.0 ml of ammonium exalate TS, allow to stand for 1 minute, add 5 ml of ethanol, mix well. Any opalescence produced after 15 minutes is not more pronounced than that of a reference solution prepared in the same manner, using 2.5 ml of calcium standard solution (weigh accurately 0.125 g of calcium carbonate, previously dried to constant weight at 105-110°C, to a 500 ml volumetric flask. Add 5 ml of water and 0.5 ml of hydrochloric acid to dissolve, it dilute with water to volume, mix well. Measure accurately 10 ml, dilute with water previous to use in a 100 ml volumetric flask to volume and mix well. Each ml is equivalent to 10 µg of Ca) (0.01%).

Iron Dissolve 1.0 g in 25 ml of water. Carry out the limit test for iron (Appendix VIII G). Any colour produced is not more intense than that of a reference using 3.0 ml of iron standard solution (0.003%).

Heavy metals Dissolve 1.0 g in 16 ml of water, add dropwise 1 mol/L hydrochloric acid solution until congo red TP turns to bluish-violet, add water to produce 25 ml. Carry out the limit test for heavy metals (Appendix VIII H, method 1); not more than 0.001%.

Assay Dissolve about 0.4 g, accurately weighed, in 25 ml of water, add 1 drop of 0.05% methyl orange IS and titrate with hydrochloric acid (0.1 mol/L) VS until the solution becomes reddish-orange, boil for 2 minutes, allow to cool. If the solution is yellow, continue the titration until the colour changes to reddish-orange. Add 80 ml of neutral glycerin [add 20 ml of water and 1 drop of phenolphthalein IS to 80 ml of glycerin, titrate with sodium hydroxide (0.1 mol/L) VS to a pink colour] and 8 drops of phenolphthalein IS, titrate with sodium hydroxide (0.1 mol/L) VS until the solution becomes pink. Each ml of sodium hydroxide (0.1 mol/L) VS is equivalent to 9.534 mg of Na₂B₄O₇ • 10H₂O.

Category Antiseptics.

Storage Preserve in tightly closed containers.

Boric Acid

H_3BO_3 61.83 [10043-35-3]

Boric Acid contains not less than 99.5% of H_3BO_3 .

Description Colourless or slightly pearly crystals or a white loose powder; unctuous on touching; odourless; its aqueous solution exhibits a weak acidic reaction. Freely soluble in boiling water, boiling ethanol or glycerin; soluble in water or ethanol.

Identification Its aqueous solution yields the reactions characteristic of borates (Appendix III).

Clarity of solution Dissolve 1.0 g in 25 ml of warm water, cool to room temperature. The solution is clear. Any opalescence produced is not more pronounced than that of reference suspension 1 (Appendix IX B).

Clarity of ethanolic solution Dissolve 1.0 g in 10 ml of boiling ethanol. The solution is clear. Any opalescence produced is not more pronounced than that of reference suspension 2 (Appendix IX B).

Chlorides Carry out the limit test for chlorides (Appendix VIII A), using 0.50 g. Any opalescence produced is not more pronounced than that of a reference using 5.0 ml of sodium chloride standard solution (0.01%).

Sulfates Carry out the limit test for sulfates (Appendix VIII B), using 0.50 g. Any opalescence produced is not more pronounced than that of a reference using 2.0 ml of potassium sulfate standard solution (0.04%).

Phosphates Dissolve 0.50 g in 15 ml of water, add 2 drops of saturated 2,4-dinitrophenol solution, add dropwise sulfuric acid solution (12→100) until the yellow colour disappears, dilute with water to 20 ml. Add 4 ml of sulfuric acid solution (12→100), 1 ml of 5% ammonium molybdate solution and 1.0 ml of *p*-methylaminophenol sulfate TS, mix well. Warm the solution in a water bath at 60°C for 10 minutes. Any colour produced is not more intense than that of a reference solution prepared in the same manner, using 5.0 ml of phosphate standard solution (weigh accurately 0.1430 g of potassium dihydrogen phosphate into a 1000 ml volumetric flask, add water to volume, mix well. Transfer 10 ml, accurately measured, to a 100 ml volumetric flask, dilute with water to volume, shake well. Each ml is equivalent to 10 µg of PO_4) (0.01%).

Calcium Dissolve 0.50 g in 10 ml of water, make alkaline with ammonia TS, then add 0.5 ml of ammonium oxalate, 5 ml of ethanol and sufficient water to produce 20 ml, mix well. Any opalescence produced is not more pronounced than that of a reference solution prepared in the same manner, using 5.0 ml of calcium standard solution described under Borax (0.01%).

Magnesium Dissolve by warming slightly 0.50 g in 8 ml of water, neutralize with 8% sodium hydroxide solution, add water to 10 ml and add 5 ml of sodium hydroxide, add 0.2 ml of 0.05% titan yellow IS, mix well. Any colour produced is not more intense than that of a reference solution prepared in the same manner, using 5.0 ml of magnesium standard solution (dissolve 16.58 mg of magnesium oxide, previously ignited to constant weight at 800°C, in 2.5 ml of hydrochloric acid and sufficient water to produce 1000 ml, mix well) (0.01%).

Iron Dissolve 1.0 g in 25 ml of water. Carry out the limit test for iron (Appendix VIII G). Any colour produced is not more intense than that of a reference using 1.0 ml of iron standard solution (0.001%).

Heavy metals Dissolve 1.0 g in 23 ml of water, add 2 ml of acetate BS (pH 3.5). Carry out the limit test for heavy metals (Appendix VIII H, method 1): not more than 0.001%.

Assay Weigh accurately about 0.50 g, add 5 g of mannitol and 25 ml of freshly boiled and cooled water, warm gently to dissolve, cool rapidly to room temperature. Add 3 drops of phenolphthalein IS, titrate with sodium hydroxide (0.5 mol/L) VS until the solution becomes pink. Each ml of sodium hydroxide (0.5 mol/L) VS is equivalent to 30.92 mg of H_3BO_3 .

Category Antiseptics.

Storage Preserve in tightly closed containers.

Preparation Boric Acid Ointment

Boric Acid Ointment

Boric Acid Ointment contains not less than 4.50% and not more than 5.50% of boric acid (H_3BO_3).

Description A pale yellow or yellow ointment.

Identification To about 0.5 g add 4 ml of water and heat on a water bath with stirring to dissolve boric acid, cool to room temperature. The aqueous solution yields the reactions characteristic of borates (Appendix III).

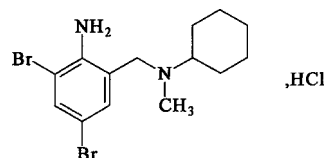
Other requirements Complies with the general requirements for ointments (Appendix I F).

Assay To about 2 g, accurately weighed, add 3 g of mannitol and 20 ml of freshly boiled and cooled water, heat on a water bath with stirring to dissolve boric acid, cool to room temperature. Add 3 drops of phenolphthalein IS and titrate with sodium hydroxide (0.1 mol/L) VS until the solution becomes pink. Each ml of sodium hydroxide (0.1 mol/L) VS is equivalent to 6.183 mg of H_3BO_3 .

Category As described under Boric Acid.

Storage Preserve in tightly closed containers.

Bromhexine Hydrochloride



$\text{C}_{14}\text{H}_{20}\text{Br}_2\text{N}_2 \cdot \text{HCl}$ 412.60 [611-75-6]

Bromhexine Hydrochloride is *N*-methyl-*N*-cyclohexylmethylamine-2-amino-3,5-dibromobenzyl hydrochloride. It contains not less than 98.5% of $\text{C}_{14}\text{H}_{20}\text{Br}_2\text{N}_2 \cdot \text{HCl}$, calculated on the dried basis.

Description A white or almost white crystalline powder; odourless; tasteless. Slightly soluble in ethanol or chloroform; very slightly soluble in water.

Specific absorbance Measure the absorbance of a solution of 20 µg per ml in ethanol at 249 nm (Appendix IV A), the value of A (1%, 1 cm) is 262-278.

Identification (1) The infrared absorption spectrum (Appendix IV C) is concordant with the reference spectrum of bromhexine hydrochloride (Appendix XVI).

(2) Dissolve 10 mg in 1 ml of ethanol by warming, the solution yields the reactions characteristic of primary aromatic amines (Appendix III).

(3) Take 50 mg, carry out the method for oxygen flask combustion (Appendix VII C), using 5 ml of 0.4% sodium hydroxide solution as the absorbing liquid. After the combustion is complete, neutralize it with dilute nitric acid. The solution yields the reactions characteristic of bromides (Appendix III).

(4) Dissolve 10 mg in 2 ml of ethanol by warming, the solution yields the reactions characteristic of chlorides (Appendix III).

Related substances Carry out the method for thin-layer chromatography (Appendix V B), using silica gel G as the coating substance and a mixture of chloroform-dehydrated ethanol (9:1) as the mobile phase. Apply separately to the plate 10 µl each of two solutions in methanol containing (1) 20 mg per ml and (2) 50 µg per ml. After developing and removal of the plate, dry it in air. Place the plate in a closed tank containing a freshly prepared mixture of 1.0 g of sodium nitrite and 10 ml of 5 mol/L hydrochloric acid solution and allow to stand for 1 minute. Remove the plate and immediately spray with 0.5% N-(1-naphthyl)-ethylene diamine dihydrochloride in methanol. Any spot other than the principal spot in the chromatogram obtained with solution (1) is not more intense than the principal spot obtained with solution (2).

Loss on drying When dried to constant weight at 105°C, loses not more than 0.5% of its weight (Appendix VIII L).

Residue on ignition Not more than 0.1% (Appendix VIII N), using 1.0 g.

Heavy metals Carry out the limit test for heavy metals (Appendix VIII H, method 2), using the residue obtained in the Residue on ignition; not more than 0.002%.

Assay To about 0.25 g, accurately weighed, add 20 ml of glacial acetic acid and warm gently to dissolve. Allow to cool, add 5 ml of mercuric acetate TS and one drop of crystal violet IS, until the colour changes to blue. Titrate with perchloric acid (0.1 mol/L) VS. Perform a blank determination and make any necessary correction. Each ml of perchloric acid (0.1 mol/L) VS is equivalent to 41.26 mg of $C_{14}H_{20}Br_2N_2 \cdot HCl$.

Category Expectorant.

Storage Preserve in tightly closed containers.

Preparation Bromhexine Hydrochloride Tablets

Bromhexine Hydrochloride Tablets

Bromhexine Hydrochloride Tablets contain not less than 93.0% and not more than 107.0% of the labelled amount of bromhexine hydrochloride ($C_{14}H_{20}Br_2N_2 \cdot HCl$).

Description White tablets.

Identification The light absorption of the solution obtained in the Assay exhibits maxima at 249 nm and 310 nm (Appendix IV A).

Related substances Weigh a quantity of powdered tablets equivalent to about 50 mg of bromhexine hydrochloride, add 5 ml of methanol, shake thoroughly, and centrifuge. Use the supernatant liquid as solution (1) and 1 ml of supernatant liquid diluted with methanol to 400 ml as solution (2). Apply separately to the plate 20 µl each of two solutions. Carry out the test for Related substances described under Bromhexine Hydrochloride. Any spot other than the principal spot in the chromatogram obtained with solution (1) is not more intense than the principal spot obtained with solution (2).

Content uniformity Comply with the requirements for content uniformity (Appendix X E). Triturate 1 tablet with ethanol in a mortar and transfer with ethanol to a 50 ml volumetric flask, slightly warm to make bromhexine hydrochloride dissolved, dilute with ethanol to volume, mix well and filter. Dilute 5 ml of successive filtrate with ethanol to 50 ml and mix well. Measure the absorbance of the resulting solution at 249 nm (Appendix IV A), calculate the content of $C_{14}H_{20}Br_2N_2 \cdot HCl$, taking 270 as the value of A (1%, 1 cm).

Other requirements Comply with the general requirements for tablets (Appendix I A).

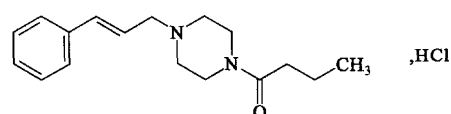
Assay Weigh accurately and powder 20 tablets. Weigh accurately a quantity of the powder equivalent to 20 mg of bromhexine hydrochloride to a 100 ml volumetric flask. Add 20 ml of ethanol, warm to dissolve, dilute with ethanol to volume and mix well. Filter, measure accurately 5 ml of the successive filtrate to a 50 ml volumetric flask, dilute with ethanol to volume, mix well. Measure the absorbance at 249 nm (Appendix IV A). Calculate the content of $C_{14}H_{20}Br_2N_2 \cdot HCl$, taking 270 as the value of A (1%, 1 cm).

Category As described under Bromhexine Hydrochloride.

Strength 8 mg

Storage Preserve in tightly closed containers.

Bucinnazine Hydrochloride



$C_{17}H_{24}N_2O \cdot HCl$ 308.85

Bucinnazine Hydrochloride is 1-*n*-butyryl-4-cinnamyl-piperazine hydrochloride. It contains not less than 99.0% of $C_{17}H_{24}N_2O \cdot HCl$, calculated on the dried basis.

Description White crystalline powder; odour, characteristic; taste, bitter.

Freely soluble in water or chloroform, soluble in ethanol, insoluble in benzene.

Melting range 204-208°C, with decomposition (Appendix VI C).

Identification (1) Dissolve about 50 mg in 1 ml of water, add bromine TS; the colour is faded.

(2) Dissolve about 50 mg in 2 ml of water, add silver nitrate TS; A white precipitate is produced.

(3) Dissolve about 50 mg in 1 ml of water, add several drops of 1% trinitrophenol TS; a yellow precipitate is produced.

(4) The infrared absorption spectrum (Appendix IV C) is

concordant with the reference spectrum of bucinnazine hydrochloride (Appendix XVI).

Clarity of solution Dissolve 1.0 g with 10 ml of water, the solution is clear.

Acidity The solution obtained in Clarity of solution has a pH value of 3.0-4.0 (Appendix VI H).

Loss on drying When dried to constant weight at 105°C, loses not more than 0.5% of its weight (Appendix VIII L).

Residue on ignition Not more than 0.1% (Appendix VIII N).

Assay Dissolve about 0.2 g, accurately weighed, in 10 ml of glacial acetic acid and 5 ml of mercuric acetate, add 2 drops of crystal violet IS and titrate with perchloric acid (0.1 mol/L) VS until the colour of the solution changes to blue. Perform a blank determination and make any necessary correction. Each ml of perchloric acid (0.1 mol/L) VS is equivalent to 30.89 mg of $C_{17}H_{24}N_2O \cdot HCl$.

Category Analgesic.

Storage Preserve in tightly closed containers, protected from light.

Preparation (1) Bucinnazine Hydrochloride Injection
(2) Bucinnazine Hydrochloride Tablets

Bucinnazine Hydrochloride Injection

Bucinnazine Hydrochloride Injection is a sterile solution of Bucinnazine Hydrochloride in Water for Injections. It contains not less than 93.0% and not more than 107.0% of the labelled amount of bucinnazine hydrochloride ($C_{17}H_{24}N_2O \cdot HCl$).

Description A clear, colourless liquid.

Identification Complies with the tests for Identification (1), (2) and (3) described under Bucinnazine Hydrochloride.

pH value 3.0-4.5 (Appendix VI H)

Other requirements Complies with the general requirements for injections (Appendix I B).

Assay Measure accurately a quantity equivalent to about 50 mg of bucinnazine hydrochloride into a 100 ml volumetric flask, dilute with 0.1 mol/L hydrochloric acid solution to volume, mix well. Measure accurately 2 ml to 200 ml volumetric flask, dilute with 0.1 mol/L hydrochloric acid solution to volume, mix well, carry out the method for spectrophotometry and measure the absorbance at 252 nm (Appendix IV A), calculate the content of $C_{17}H_{24}N_2O \cdot HCl$, taking 671 as the value of A (1%, 1 cm).

Category As described under Bucinnazine Hydrochloride.

Strength (1) 2 ml : 50 mg (2) 2 ml : 100 mg

Storage Preserve in well closed containers, protected from light.

Bucinnazine Hydrochloride Tablets

Bucinnazine Hydrochloride Tablets contain not less than 90.0% and not more than 110.0% of the labelled amount of bucinnazine hydrochloride ($C_{17}H_{24}N_2O \cdot HCl$).

Description White or almost white tablets.

Identification Dissolve a quantity of the powdered tablets equivalent to about 0.1 g of bucinnazine hydrochloride in 5 ml of water, shake to dissolve and filter. The filtrate complies with the tests for Identification (1), (2) and (3) described under Bucinnazine Hydrochloride.

Dissolution Comply with dissolution test (Appendix X C, method 1), using 900 ml of hydrochloric acid solution (9→1000) as the dissolution medium. Adjust the rotation speed at 75 rpm. Withdraw and filter 5 ml of the solution after 30 minutes, filter. Measure accurately 2 ml of the successive filtrate to a 100 ml volumetric flask, dilute with dissolution medium to volume, mix well. Measure the absorbance of the resulting solution at 252 nm (Appendix IV A) and calculate the dissolution of $C_{17}H_{24}N_2O \cdot HCl$, from each tablet taking 671 as the value of A (1%, 1 cm). The amount of the dissolution for each tablets is not less than 70% of the labelled amount.

Other requirements Comply with the general requirements for tablets (Appendix I A).

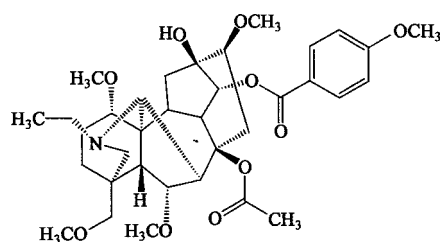
Assay Weigh accurately and powder 20 tablets. Dissolve a quantity, accurately weighed, equivalent to about 30 mg of Bucinnazine Hydrochloride in 0.1 mol/L hydrochloric acid solution in a 100 ml volumetric flask, dilute to volume, mix well and filter. Measure accurately 2 ml of the successive filtrate to a 100 ml volumetric flask, dilute with 0.1 mol/L hydrochloric acid solution to volume and mix well. Measure the absorbance of the resulting solution at 252 nm (Appendix IV A). Calculate the content of $C_{17}H_{24}N_2O \cdot HCl$, taking 671 as the value of A (1%, 1 cm).

Category As described under Bucinnazine Hydrochloride.

Strength 30 mg

Storage Preserve in tightly closed containers, stored in dry place.

Bulleyaconitine A



$C_{35}H_{49}NO_{10}$ 643.77

Bulleyaconitine A is (1 α ,6 α ,14 α ,16 β) Tetrahydro-8,13,14-triol-20-ethyl-1,6,16-trimethoxy-4-methoxy-8-acetyloxy-14-(4'-para-methoxybenzoate)-aconitane. It contains not less than 97.0% of Bulleyaconitine A, calculated on the dried basis.

Description White crystals or a crystalline powder. Freely soluble in ethanol, chloroform or ether; insoluble in water; very soluble in diluted hydrochloric acid or diluted sulfuric acid.

Melting range 160-165°C (Appendix VI C).

Identification (1) Dissolve about 10 mg in 0.1 mol/L hydrochloric acid solution, divide to two portions. Add a few drops of mercuric potassium iodide TS in one portion, a white precipitate is produced. Add a few drops of potassium

heptaiodobismuthate TS in another portion, an orange-red precipitate is produced.

(2) The retention time of principal peak of the substance being examined in the chromatogram obtained in the Assay is identical with that of bulleyaconitine A CRS.

(3) The infrared absorption spectrum (Appendix IV C) is concordant with the spectrum of bulleyaconitine A CRS.

Other alkaloids Carry out the method as described under Assay. Dissolve a quantity of the substance being examined, accurately weighed, in mobile phase to produce a solution of 0.2 mg per ml as the test solution and of 4 μg per ml as the reference solution. Inject 20 μl of the reference solution into the column. Adjust the attenuation so that the principal peak height in the chromatogram is about 10% of full scale of the chart. Inject separately 20 μl each of the test solution and the reference solution, accurately measured, into the column. Record the chromatogram for twice the retention time of principal peak. The sum of the areas of all peaks other than the principal peak in the chromatogram obtained with the test solution is not greater than the area of the principal peak in the chromatogram obtained with reference solution.

Loss on drying When dried in vacuum over phosphorous pentoxide to constant weight, loses not more than 0.5% of its weight (Appendix VIII L).

Residue solvent Methanol, chloroform and benzene Carry out the method for residue solvent (Appendix VIII P, method 2), using a capillary column coated with dimethylpolysiloxane as the stationary phase. Maintain the temperature of the column at 50°C for 2 min, then raise the temperature at a rate of 10°C per minute to 70°C and maintain at 70°C for 3 min, then raise the temperature at a rate of 20°C per minute to 200°C and maintain at 200°C for 3 minutes; maintain injection port temperature at 220°C and detector temperature at 280°C. Headspace sampling parameters; the temperature of equilibration is 80°C, and the time of equilibration is 10 minutes.

Procedure Dissolve a quantity of the substance to be examined, accurately weighed, in dimethylformamide to produce a solution of 0.1 g per ml as test solution. Dissolve a quantity of methanol, chloroform and benzene, accurately weighed respectively, in dimethylformamide to produce a solution containing methanol, chloroform, benzene of 300 μg , 6 μg and 0.2 μg as reference solution. Transfer separately 3 ml each of test solution and reference solution, accurately measured, into different headspace sample vials. Calculate the content of methanol, chloroform and benzene respectively with respect to the peak area obtained in the chromatogram by the external standard method.

Assay Carry out the method for high performance liquid chromatography (Appendix V D), using a column packed with octadecylsilane bonded silica gel and mixture of 0.2% triethylamine solution (adjust to pH 3.1 ± 0.1 with phosphoric acid)-acetonitrile as the mobile phase. Detection wavelength is 260 nm and the number of theoretical plates of the column is not less than 3000, calculated with reference to the peak of bulleyaconitine A.

Procedure Dissolve about 20 mg, accurately weighed, in mobile phase in a 100 ml volumetric flask and dilute to volume with the same solvent and mix well. Transfer 5 ml of the solution into a 50 ml volumetric flask, accurately measured, dilute with mobile phase to volume and mix well, inject 20 μl of the solution into the column, accurately measured. Repeat the operation, using bulleyaconitine A CRS instead of the substance being examined. Calculate the content of $\text{C}_{35}\text{H}_{49}\text{NO}_{10}$ with respect to the peak area obtained in the chromatogram by the external standard method.

Category Anti-inflammatory, analgesic agent.

Storage Stored in dry and cool place, protected from light.

Preparation (1) Bulleyaconitine A Oral Solution
(2) Bulleyaconitine A Tablets

Bulleyaconitine A Oral Solution

Bulleyaconitine A Oral Solution contains not less than 90.0% and not more than 110.0% of the labelled amount of Bulleyaconitine A ($\text{C}_{35}\text{H}_{49}\text{NO}_{10}$).

Description A pale yellow, clear liquid; taste, sweet; slightly sour and slight numb.

Identification (1) To 40 ml, adjust pH to 9-10 by adding 0.5 mol/L sodium carbonate solution, extract the solution twice with 40 ml of ethyl ether. Evaporate the extracts to dryness on a water bath, the residue complies with the test for Identification (1) described under Bulleyaconitine A.
(2) The retention time of principal peak of the substance being examined in the chromatogram obtained in the Assay is identical with that of bulleyaconitine A CRS.

Relative density Not less than 1.050 (Appendix VI A).

pH value 4.0-6.0 (Appendix VI H).

Other requirements Complies with the general requirements for oral solution (Appendix I O).

Assay Dilute an accurately measured quantity of the substance being examined with mobile phase to produce a solution of 20 μg per ml. Carry out the Assay as described under Bulleyaconitine A, beginning at the words "inject 20 μl into the column...", calculate the content of $\text{C}_{35}\text{H}_{49}\text{NO}_{10}$.

Category As described under Bulleyaconitine A.

Strength 10 ml : 0.4 mg

Storage Preserve in tightly closed containers, protected from light.

Bulleyaconitine A Tablets

Bulleyaconitine A Tablets contain not less than 90.0% and not more than 110.0% of the labelled amount of Bulleyaconitine A ($\text{C}_{35}\text{H}_{49}\text{NO}_{10}$).

Description White tablets.

Identification (1) To a quantity of powdered tablets equivalent to about 1 mg of bulleyaconitine A, add 10 ml of 0.1 mol/L hydrochloric acid solution, shake to dissolve bulleyaconitine A and filter. Divide the filtrate to two portions. Add a few drops of mercuric potassium iodide TS in one portion, a white precipitate is produced. Add a few drops of potassium iodobismuthate TS in another portion, an orange-red precipitate is produced.

(2) The retention time of principal peak of the substance being examined in the chromatogram obtained in the Assay is identical with that of bulleyaconitine A CRS.

Content uniformity Comply with the requirements for content uniformity (Appendix X E). Dissolve 1 tablet in a 25 ml volumetric flask with mobile phase. Carry out the method as described under Assay, beginning at the words "ultrasonicate for 15 minutes to dissolve bulleyaconitine A...", and calculate the content of $\text{C}_{35}\text{H}_{49}\text{NO}_{10}$.

Dissolution Comply with the requirements for dissolution test (Appendix X C, method 3), using 100 ml of 0.1 mol/L hydrochloric acid solution as the dissolution medium, adjust the rotational speed of the paddle to 100 rpm. Withdraw the solution after exactly 20 minutes and filter. Carry out the procedure described under Assay, inject 20 μ l of the successive filtrate into the column, and record the chromatogram. Dissolve a quantity of bulleyaconitine A CRS, accurately weighed, in mobile phase to produce a solution of about 4 μ g per ml, repeat the operation. Calculate the dissolution of $C_{35}H_{49}NO_{10}$ from each tablet, not less than 80% of the labelled amount is dissolved.

Other requirements Comply with the general requirements for tablets (Appendix I A).

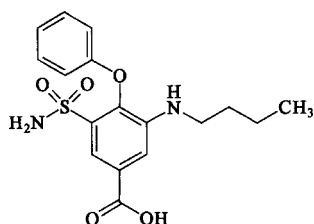
Assay Weigh and powder 20 tablets. Transfer an accurately weighed quantity of the powder equivalent to about 2 mg of bulleyaconitine A into a 100 ml volumetric flask, add a quantity of mobile phase, ultrasonicate for 15 minutes to dissolve bulleyaconitine A, dilute with mobile phase to volume, shake well. Filter and use the successive filtrate as the test solution. Carry out the Assay as described under Bulleyaconitine A, beginning at the words "inject 20 μ l into the column...", calculate the content of $C_{35}H_{49}NO_{10}$.

Category As described under Bulleyaconitine A.

Strength 0.4 mg

Storage Stored in dry and cool place, protected from light.

Bumetanide



$C_{17}H_{20}N_2O_5S$ 364.42

[28395-03-1]

Bumetanide is 5-butylamino-4-phenoxy-benzonic-3-aminosulfonyl. It contains not less than 98.5% of $C_{17}H_{20}N_2O_5S$, calculated on the dried basis.

Description A white crystal or crystalline powder; odourless; taste, slightly bitter. Soluble in ethanol; slightly soluble in chloroform; insoluble in water.

Melting range 231-235°C (Appendix VI C).

Identification (1) Dissolve 1 mg in 2 ml of dehydrated ethanol, examine under ultraviolet light (365 nm), a violet fluorescence is produced.

(2) To 5 mg add 1 drop of alkaline sodium formate solution (dissolve 5 g of sodium formate and 6 g of sodium hydroxide in 100 ml of water), evaporate the mixture to dryness over a small flame. Heat gently until the residue is charred. Allow to cool and acidify with 0.5 ml of sulfuric acid solution (1→2), add 0.5 ml of water, and filter. To the filtrate add 1 drop of potassium ferricyanide TS, a blue colour is produced.

(3) The infrared absorption spectrum (Appendix IV C) is concordant with the reference spectrum of bumetanide (Appendix XVI).

Clarity and colour of alkaline solution A solution of 50 mg in

10 ml of potassium hydroxide solution (to 1 ml of potassium hydroxide TS add 9 ml of water) is clear and colourless; any opalescence produced is not more pronounced than that of standard suspension 1 (Appendix IX B); any colour produced is not more intense than that of reference solution OY₁ (Appendix IX A, method 1).

Chloride To 0.25 g add 25 ml of water, shake thoroughly for 10 minutes and filter, carry out the limit test for chlorides (Appendix VIII A), any opalescence produced is not more pronounced than that of a reference using 5.0 ml of sodium chloride standard solution (0.02%).

Aromatic primary amine Dissolve 40 mg in ethanol in a 10 ml volumetric flask, dilute with ethanol to volume, mix well. Transfer accurately 1 ml to another 10 ml volumetric flask, add 3 ml of hydrochloric acid solution (9→100) and 0.5 ml of 4% sodium nitrite solution, mix well and allow to stand for 2 minutes. Add 1 ml of 10% ammonium sulfamate solution, mix well, allow to stand for 5 minutes. Add 0.5 ml of 2% N-(1-naphthyl)-ethylene-diamine dihydrochloride solution in dilute ethanol, mix well, allow to stand for 2 minutes, dilute with water to volume, mix well. The absorbance of the resulting solution at 518 nm is not greater than 0.19 (Appendix IV B).

Related substances Protected from light throughout the procedure. Carry out the method for thin-layer chromatography (Appendix V B), using silica gel GF₂₅₄ as the coating substance and a mixture of chloroform-glacial acetic acid-cyclohexane-methanol (32:4:4:1) as the mobile phase. Apply separately to the plate 10 μ l each of two solutions in dehydrated ethanol containing (1) 10 mg per ml and (2) 50 μ g per ml of the substance being examined. After developing and removal of the plate, dry it in a current of air and examine under ultraviolet light (254 nm). No spot other than the principal spot obtained with solution (1) is more intense than the principal spot obtained with solution (2).

Loss on drying When dried to constant weight at 105°C, loses not more than 0.5% of its weight (Appendix VIII L).

Residue on ignition Not more than 0.1% (Appendix VIII N), using 1.0 g.

Heavy metals Carry out the test for heavy metals (Appendix VIII H, method 2), using the residue obtained in the test for Residue on ignition; not more than 0.001%.

Arsenic Mix 1.0 g with 1.0 g of calcium hydroxide, add a small quantity of water, dry it in air. Heat gently until it is thoroughly charred, and then ignite at 500-600°C until the incineration is complete. Allow it to cool, dissolve in 8 ml of hydrochloric acid and 20 ml of water. Carry out the limit test for arsenic (Appendix VIII J, method 1); not more than 0.0002%.

Assay Dissolve about 0.1 g, accurately weighed, in 25 ml of neutralized ethanol (neutral to cresol red IS), add 3-4 drops of cresol red IS. Titrate with sodium hydroxide (0.01 mol/L) VS until a red colour is produced. Each ml of sodium hydroxide (0.01 mol/L) VS is equivalent to 3.644 mg of $C_{17}H_{20}N_2O_5S$.

Category Diuretic.

Storage Preserve in tightly closed containers, protected from light.

Preparation (1) Bumetanide Injection
(2) Bumetanide Tablets

Bumetanide Injection

Bumetanide Injection is a sterile solution of bumetanide and sodium hydroxide in Water for Injection. It contains not less than 90.0% and not more than 110.0% of the labelled amount of bumetanide ($C_{17}H_{20}N_2O_5S$).

Description A clear, colourless liquid.

Identification (1) Examine under ultraviolet light (365 nm), a violet fluorescence is exhibited. (2) To 8 ml add 1 ml of dilute sulfuric acid, a white precipitate is produced, filter and wash the precipitate with water. Dissolve the precipitate in 2 ml of dehydrated ethanol, add 1 ml of 1% potassium iodate solution and 1 ml of potassium iodide TS, a yellow colour is produced.

pH value 6.5-8.5 (Appendix VI H).

Other requirements Complies with the general requirements for injections (Appendix I B).

Assay Transfer accurately 5 ml to a 25 ml volumetric flask, dilute with phosphate BS (pH 7.4) to volume, mix well. Measure the absorbance of the solution at 328 nm (Appendix IV A). Calculate the content of $C_{17}H_{20}N_2O_5S$, taking 98.5 as the value of A (1%, 1 cm).

Category As described under Bumetanide.

Strength 2 ml : 0.5 mg

Storage Preserve in well closed containers, protected from light.

Bumetanide Tablets

Bumetanide Tablets contain not less than 90.0% and not more than 110.0% of the labelled amount of bumetanide ($C_{17}H_{20}N_2O_5S$).

Description white tablets.

Identification To 10 powdered tablets add 10 ml of dehydrated ethanol, shake to dissolve bumetanide and filter. The filtrate complies with tests (1) and (2) for Identification described under Bumetanide.

Content uniformity Comply with the requirements (Appendix X E). Place 1 tablet in a 25 ml volumetric flask. Carry out the procedure described under Assay, beginning at the words "add a quantity of phosphate BS (pH 7.4)...". Calculate the contents of $C_{17}H_{20}N_2O_5S$.

Dissolution Carry out the dissolution test (Appendix X C, method 1), using 900 ml of phosphate BS (pH 7.8-8.0) as dissolution medium and adjust rotational speed of the basket to 100 rpm. Withdraw 25 ml of the solution after exactly 30 minutes and filter, take the successive filtrate as test solution. Dissolve a quantity of bumetanide CRS in phosphate BS (pH 7.8-8.0) and dilute to produce a solution of 1.2 µg per ml. Measure the fluorescence of two solutions (Appendix X E) at an excitation wavelength at 264 nm and an emission wavelength at 420 nm, calculate the dissolution of $C_{17}H_{20}N_2O_5S$, not less than 80% of the labelled amount is dissolved.

Other requirements Comply with the general requirements for tablets (Appendix I A).

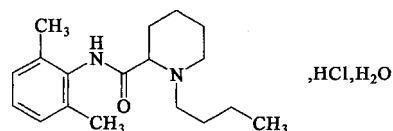
Assay Weigh accurately and powder 20 tablets. Transfer an accurately weighed quantity of the powder, equivalent to about 2 mg of bumetanide, to a 50 ml volumetric flask, add a quantity of phosphate BS (pH 7.4), shake for 30 minutes to dissolve bumetanide, dilute with phosphate BS (pH 7.4) to volume. Mix well, filter and measure the absorbance of the successive filtrate at 328 nm (Appendix IV A). Calculate the content of $C_{17}H_{20}N_2O_5S$, taking 98.5 as the value of A (1%, 1 cm).

Category As described under Bumetanide.

Strength 1 mg

Storage Preserve in tightly closed containers, protected from light.

Bupivacaine Hydrochloride



$C_{18}H_{28}N_2O \cdot HCl \cdot H_2O$ 342.91 [14252-80-3]

Bupivacaine Hydrochloride is 1-butyl-N-(2,6-dimethyl-phenyl)-2-piperidinecarboxamide monohydrochloride monohydrate. It contains not less than 98.5% of $C_{18}H_{28}N_2O \cdot HCl$, calculated on the dried basis.

Description A white, crystalline powder; odourless; taste, bitter.

Freely soluble in ethanol; soluble in water; slightly soluble in chloroform; practically insoluble in ether.

Identification (1) Dissolve about 0.15 g in 10 ml of water, add 15 ml of trinitrophenol TS, a yellow precipitate is formed. Filter, wash the precipitate with a small amount of water, then wash with methanol and ether, dry at 105°C, it melt at about 194°C (Appendix VI C).

(2) The light absorption of a solution of about 0.40 mg per ml in 0.01 mol/L hydrochloric acid solution exhibits maxima at 263 nm and 271 nm; the absorbance is about 0.53-0.58 and 0.43-0.48, respectively (Appendix IV A).

(3) The infrared absorption spectrum (Appendix IV C) is concordant with the reference spectrum of bupivacaine hydrochloride (Appendix XVI).

(4) The aqueous solution yields the reactions characteristic of chlorides (Appendix III).

Acidity Dissolve 0.10 g in 10 ml of water, pH 4.5-6.0 (Appendix VI H).

Related substances Carry out the method for thin-layer chromatography (Appendix V B), using silica gel G as the coating substance and 95% ethanol as the mobile phase. Apply separately to the plate 10 µl each of two solutions in methanol containing (1) 10 mg per ml, (2) 0.10 mg per ml of the substance being examined. After developing and removal of the plate, dry it in air, visualize with iodine vapour. Any spot other than the principal spot in the chromatogram obtained with solution (1) is not more intense than the principal spot in the chromatogram obtained with solution (2).

Loss on drying When dried to constant weight at 105°C, loses 4.5%-6.0% of its weight (Appendix VIII L).

Residue on ignition Not more than 0.1%, using 1.0 g

(Appendix VIII N).

Copper Dissolve 0.25 g in 10 ml of water, add 0.25 ml of 0.05 mol/L disodium edetate solution, mix well, and allow to stand for 2 minutes. Add 0.20 g of citric acid, 1.0 ml of ammonia TS and 1.0 ml of sodium diethyldithiocarbamate TS, mix well. Add 5 ml of carbon tetrachloride and shake for 2 minutes. The colour of the carbon tetrachloride layer is not more intense than that of 10 ml of reference solution, obtained by diluting 3.0 ml of copper standard solution (10 µg of Cu per ml) with water to 400 ml and treated in similar manner (0.0003%).

Iron To the residue obtained in the test for Residue on ignition add 2 ml hydrochloric acid, evaporate to dryness on a water bath. Dissolve the residue in 4 ml of dilute hydrochloric acid by heating, add 30 ml of water and 50 mg of ammonium persulfate. Carry out the limit test for iron (Appendix VIII G), the colour produced is not more intense than that of 1.0 ml of iron standard solution treated in a similar manner (0.001%).

Assay Dissolve about 0.2 g, accurately weighed, in 20 ml of glacial acetic acid and 5 ml of mercuric acetate TS, add 5 drops of naphtholbenzene IS. Titrate with perchloric acid (0.1 mol/L) VS until the solution becomes green. Perform a blank determination and make any necessary correction. Each ml of perchloric acid (0.1 mol/L) VS is equivalent to 32.49 mg of $C_{18}H_{28}N_2O \cdot HCl$.

Category Local anesthetic agent.

Storage Preserve in tightly closed containers, protected from light.

Preparation Bupivacaine Hydrochloride Injection

Bupivacaine Hydrochloride Injection

Bupivacaine Hydrochloride Injection is a sterile solution of Bupivacaine Hydrochloride in Water for Injection. It contains not less than 90.0% and not more than 110.0% of the labelled amount of bupivacaine hydrochloride ($C_{18}H_{28}N_2O \cdot HCl$).

Description A clear, colourless or almost colourless liquid.

Identification (1) A quantity equivalent to about 50 mg of bupivacaine hydrochloride complies with test (1) for Identification described under Bupivacaine Hydrochloride. (2) The light absorption of a solution of 0.4 mg per ml in 0.01 mol/L hydrochloric acid exhibits maxima at 263 nm and 271 nm (Appendix IV A).

pH value 4.0-6.5 (Appendix VI H).

Related substances Evaporate a quantity equivalent to about 20 mg of bupivacaine hydrochloride to dryness on a water bath and cool. Carry out the test for Related substances described under Bupivacaine Hydrochloride, the result complies with the requirement.

Other requirements Complies with the general requirements for injections (Appendix I B).

Assay Mix thoroughly an accurately measured quantity, equivalent to about 25 mg of bupivacaine hydrochloride with 15 g of chromatographic kieselguhr and 0.5 ml of a 10% sodium hydroxide solution. Transfer the mixture to a sintered glass funnel or a chromatographic tube, extract with 7 quantities, each 20 ml, of gently warm chloroform until the extraction is completed. Transfer the combined extracts to a 250 ml conical flask, evaporate to almost dryness, add

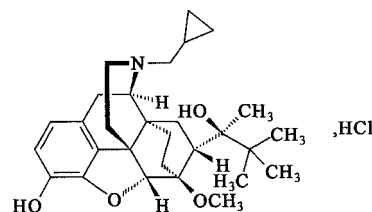
40 ml of glacial acetic acid and 5 drops of naphtholbenzene IS. Titrate with perchloric acid (0.02 mol/L) VS until the solution becomes green. Perform a blank determination and make any necessary correction. Each ml of perchloric acid (0.02 mol/L) VS is equivalent to 6.498 mg of $C_{18}H_{28}N_2O \cdot HCl$.

Category As described under Bupivacaine Hydrochloride.

Strength (1) 5 ml:12.5 mg (2) 5 ml:25 mg
(3) 5 ml:37.5 mg

Storage Preserve in well closed containers, protected from light.

Buprenorphine Hydrochloride



$C_{29}H_{41}NO_4 \cdot HCl$ 504.11

[53152-21-9]

Buprenorphine Hydrochloride is 21-cyclopropyl-7α-[(S)-1-hydroxy-1, 2, 2-trimethylpropyl]-6, 14-endo-ethano-6,7,8,14-tetrahydrooripavine hydrochloride. It contains not less than 99.0% of $C_{29}H_{41}NO_4 \cdot HCl$, calculated on the dried basis.

Description A white crystalline powder; odourless. Soluble in alcohol; sparingly soluble in chloroform; very slightly soluble in water.

Specific optical rotation -95° to -101° , in a solution of 5 mg per ml in ethanol (Appendix VI E).

Identification (1) Dissolve about 2 mg in 5 ml of water, add a few drops of bromine TS, a yellow precipitate is produced immediately.

(2) The light absorption of the solution of 0.16 mg per ml in water exhibits a maximum at 286 nm (Appendix IV A).

(3) The infrared absorption spectrum (Appendix IV C) is concordant with the reference spectrum of buprenorphine hydrochloride (Appendix XVI).

(4) The aqueous solution yields the reactions characteristic of chlorides (Appendix III).

Acidity Dissolve 8 mg in 25 ml of water, pH 5.0-7.0 (Appendix VI H).

Clarity of solution Dissolve about 8 mg in 25 ml of water, the solution is clear.

Related substances Carry out the method for thin-layer chromatography (Appendix V B), using a suspension of silica gel G in 0.1 mol/L sodium hydroxide solution to coat the plate and use a mixture of chloroform-methanol (15:1) as the mobile phase. Apply separately to the plate 10 µl of each of two solutions in ethanol containing (1) 10 mg per ml, (2) 0.01 mg per ml of the substance being examined. After developing and removal of the plate, dry it in air and expose it to iodine vapour. Any spot other than the principal spot obtained with solution (1) is not more intense than the principal spot obtained with solution (2).

Loss on drying When dried to constant weight in vacuum over phosphorous pentoxide, loses not more than 0.5% of its weight (Appendix VIII L).

Assay Dissolve about 0.12 g, accurately weighed, in a mixture of 2 ml of mercuric acetate TS and 30 ml of glacial acetic acid, add 1 drop of crystal violet IS. Titrate with perchloric acid (0.02 mol/L) VS until the colour changes to blue. Perform a blank determination and make any necessary correction. Each ml of perchloric acid (0.02 mol/L) VS is equivalent to 10.08 mg of $C_{29}H_{41}NO_4 \cdot HCl$.

Category Analgesic.

Storage Preserve in tightly closed container, protected from light.

Preparation (1) Buprenorphine Hydrochloride Injection
(2) Buprenorphine Hydrochloride Sublingual Tablets

Buprenorphine Hydrochloride Injection

Buprenorphine Hydrochloride Injection is a sterile solution of Buprenorphine Hydrochloride and Glucose in Water for Injection. It contains not less than 90.0% and not more than 110.0% of the labelled amount of buprenorphine hydrochloride ($C_{29}H_{41}NO_4 \cdot HCl$).

Description A clear, colourless liquid.

Identification (1) To 1 ml add a few drops of bromine TS, a yellow precipitate is produced.

(2) The light absorption of the injection exhibits a maximum at 286 nm (Appendix IV A).

(3) Acidify 1 ml of the injection with dilute nitric acid and add silver nitrate TS; a white opalescence is formed which is soluble in ammonia TS.

pH value 3.0-5.5 (Appendix VI H).

Other requirements Complies with the general requirements for injections (Appendix I B)

Assay Carry out the method for high performance liquid chromatography (Appendix V D), using a column packed with octadecylsilane bonded silica gel and a mixture of methanol-acetonitrile-2% solution of ammonium acetate-acetic acid (60 : 10 : 40 : 5) as the mobile phase. Detection wavelength is 286 nm and the number of theoretical plates of the column is not less than 1000, calculated with reference to the peak of buprenorphine hydrochloride.

Procedure Dilute an accurately measured quantity of the injection equivalent to about 0.6 mg of buprenorphine hydrochloride in a 25 ml volumetric flask with mobile phase to volume, mix well. Inject 50 μ l of the resulting solution into the column, record the chromatogram and measure the peak areas. Dissolve 15 mg of buprenorphine hydrochloride CRS, accurately weighed, in methanol in a 50 ml volumetric flask, and dilute to volume, mix well. Transfer 2.0 ml of this solution, accurately weighed, into a 25 ml volumetric flask, dilute with mobile phase to volume and mix well, use the resulting solution as reference solution. Repeat the operation, using the reference solution instead of the test solution. Calculate the content of $C_{29}H_{41}NO_4 \cdot HCl$ with respect to the peak area obtained in the chromatogram by the external standard method.

Category As described under Buprenorphine Hydrochloride.

Strength (1) 1 ml:0.15 mg (2) 1 ml:0.3 mg

Storage Preserve in well closed container, protected from light.

Buprenorphine Hydrochloride Sublingual Tablets

Buprenorphine Hydrochloride Sublingual Tablets contain not less than 90.0% and not more than 110.0% of the labelled amount of buprenorphine hydrochloride ($C_{29}H_{41}NO_4 \cdot HCl$).

Description White tablets.

Identification (1) To 10 powdered tablets add 8 ml of ethanol, shake to dissolve buprenorphine hydrochloride. Filter, evaporate the filtrate to dryness, dissolve the residue in 2 ml of 5% solution of hydrochloric acid, add 1 drop of potassium iodobismuthate TS, a reddish-brown precipitate is produced.

(2) The retention time of principal peak of the substance being examined in the chromatogram obtained in the Assay is identical with that of buprenorphine hydrochloride CRS.

(3) To 10 tablets add 10 ml of water and 1 drop of nitric acid, shake to dissolve, filter. To the filtrate add 2 drops of silver nitrate TS, a white opalescence is produced.

Content uniformity Comply with the requirements (Appendix X E). Transfer 1 powdered tablet with 5 ml (for strength 0.4 mg) or 2 ml (for strength 0.2 mg) water to 25 ml (for strength 0.4 mg) or 10 ml (for strength 0.2 mg) volumetric flask. Add 5 ml methanol to volume, mix well. Proceed as described under the Assay, beginning at the words "ultrasonic for 10 minutes..."

Other requirements Comply with the general requirements for sublingual tablets (Appendix I A).

Assay Carry out the method for high performance liquid chromatography (Appendix V D), using a column packed with octadecylsilane bonded silica gel and a mixture of methanol-acetonitrile-2% solution of ammonium acetate-acetic acid (60 : 10 : 40 : 5) as the mobile phase. Detection wavelength is 286 nm and the number of theoretical plates of the column is not less than 1000, calculated with reference to the peak of buprenorphine hydrochloride.

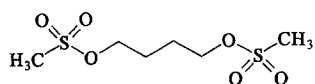
Procedure Weigh accurately and powder 20 tablets. Weigh accurately a quantity of the powder equivalent to about 0.4 mg of buprenorphine hydrochloride in a 25 ml volumetric flask, add 5 ml of water and 5 ml of methanol. Shake thoroughly and ultrasonic for 10 minutes, dilute with the mobile phase to volume and mix well. Inject 50 μ l of the successive filtrate into the column, record the chromatogram and measure the peak areas. Dissolve 10 mg of buprenorphine hydrochloride CRS, accurately measured, in methanol in a 50 ml volumetric flask and dilute to volume, mix well. Transfer 4.0 ml of this solution, accurately measured, to a 50 ml volumetric flask, dilute with mobile phase to volume and mix well, use the resulting solution as reference solution. Repeat the operation, using the reference solution instead of the test solution. Calculate the content of $C_{29}H_{41}NO_4 \cdot HCl$ with respect to the peak area obtained in the chromatogram by the external standard method.

Category As described under Buprenorphine Hydrochloride.

Strength (1) 0.2 mg (2) 0.4 mg

Storage Preserve in tightly closed containers, protected from light.

Busulfan



$C_6H_{14}O_6S_2$ 246.29

[55-98-1]

Busulfan is 1,4-butanediol dimethanesulfonate. It contains not less than 98.5% of $C_6H_{14}O_6S_2$, calculated on the dried basis.

Description A white crystalline powder; almost odourless. Soluble in acetone; slightly soluble in water or ethanol.

Melting range 114-118°C (Appendix VI C).

Identification (1) Fuse 0.1 g with 0.1 g of potassium nitrate and 0.25 g of potassium hydroxide and cool. Dissolve it in 5 ml of water, acidify with dilute hydrochloric acid and add a few drops of barium chloride TS; a white precipitate is produced.

(2) Dissolve 0.1 g in 10 ml of water and 5 ml of sodium hydroxide TS by heating; a characteristic odour is perceptible. Cool, to one half of the solution add 1 drop of potassium permanganate TS, the colour of the solution changes from purple to blue, then to emerald-green. Acidify the remainder with dilute sulfuric acid and add 1 drop of potassium permanganate TS, the purple colour is changeless.

(3) The infrared absorption spectrum (Appendix IV C) is concordant with the reference spectrum of busulfan (Appendix XVI).

Acidity Dissolve 0.20 g in 50 ml of dehydrated ethanol (neutral to methyl red IS) by warming, add 3 drops of methyl red IS and titrate with sodium hydroxide (0.1 mol/L) VS, not more than 0.05 ml is required.

Loss on drying When dried in vacuum over phosphorous pentoxide to constant weight, loses not more than 0.5% of its weight (Appendix VIII L).

Residue on ignition Not more than 0.1% (Appendix VIII N).

Assay Transfer about 0.2 g, accurately weighed, to a 200 ml conical flask, add 40 ml water, boil gently under reflux for 30 minutes and cool. Add a few drops of phenolphthalein IS, titrate with sodium hydroxide (0.1 mol/L) VS. Each ml of sodium hydroxide (0.1 mol/L) VS equivalent to 12.32 mg of $C_6H_{14}O_6S_2$.

Category Antineoplastic.

Storage Preserve in tightly closed containers.

Preparation Busulfan Tablets

dryness; the residue has a melting range of 113-118°C (Appendix VI C).

Other requirements Comply with the general requirements for tablets (Appendix I A).

Assay Triturate carefully 20 tablets (2 mg) or 80 tablets (0.5 mg) in a mortar. Transfer all powder to a beaker by washing with 20 ml of acetone. Warm and stir, allow to stand, filter the supernatant liquid into a conical flask using a wad of absorbent cotton moistened with acetone. Extract the residue with three 20 ml portions of acetone, filter the extracts into the same conical flask and evaporate the combined filtrates on a water bath to expel. Boil the residue with 30 ml of water under reflux for 30 minutes, cool, add a few drops of phenolphthalein IS, titrate with sodium hydroxide (0.05 mol/L) VS. Each ml of sodium hydroxide (0.05 mol/L) VS is equivalent to 6.158 mg of $C_6H_{14}O_6S_2$.

Category As described under Busulfan.

Strength (1) 0.5 mg (2) 2 mg

Storage Preserve in tightly closed containers, stored in a dry place.

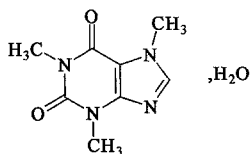
Busulfan Tablets

Busulfan Tablets contain not less than 90.0% and not more than 110.0% of the labelled amount of busulfan ($C_6H_{14}O_6S_2$).

Description Sugar-coated tablets with white cores.

Identification To a quantity of the powdered tablets equivalent to about 5 mg of busulfan add 25 ml of acetone, shake to dissolve busulfan, filter and evaporate the filtrate to

Caffeine



$C_8H_{10}N_4O_2 \cdot H_2O$ 212.21

[5743-12-4]

Caffeine is 3,7-dihydro-1,3,7-trimethyl-1*H*-purine-2,6-dione monohydrate. It contains not less than 98.5% of $C_8H_{10}N_4O_2$, calculated on the dried basis.

Description Silky, white or faintly yellowish-green needle crystals; odourless; taste, bitter; efflorescent. Freely soluble in hot water or chloroform; sparingly soluble in water, ethanol or acetone; very slightly soluble in ether.

Melting point 235-238°C (Appendix VI C).

Identification (1) To 10 mg add 1 ml of hydrochloric acid and 0.1 g of potassium chlorate, evaporate on a water bath to dryness, the residue reacts with ammonia vapour to produce a purple colour, which disappears on the addition of a few drops of sodium hydroxide TS.

(2) To 5 ml of a saturated water solution add 5 drops of iodine TS, the solution remains clear; add 3 drops of dilute hydrochloric acid to the solution, a brownish-red precipitate is produced which is soluble in a slight excess of sodium hydroxide TS.

(3) The infrared absorption spectrum (Appendix IV C) is concordant with the reference spectrum of caffeine (Appendix XVI).

Clarity of solution Boil 1.0 g in 50 ml of water, allow to cool, the solution is clear.

Related substances Carry out the method for thin-layer chromatography (Appendix V B), using silica gel GF₂₅₄ as the coating substance and a mixture of *n*-butanol-acetone-chloroform-concentrated ammonia solution (40 : 30 : 30 : 10) as the mobile phase. Apply separately to the plate 10 µl each of two solutions in chloroform-methanol (3 : 2) containing (1) 20 mg per ml and (2) 0.10 mg per ml of the substance being examined. After developing and removal of the plate, allow it to dry in air, examine under ultraviolet light (254 nm). Any spot other than the principal spot in the chromatogram obtained with solution (1) is not more intense than the principal spot obtained with solution (2).

Loss on drying When dried at 105°C to constant weight, loses not more than 8.5% of its weight or not more than 0.5% of the weight of anhydrous caffeine (Appendix VIII L).

Residue on ignition Not more than 0.1% (Appendix VIII N).

Heavy metals Dissolve 0.5 g in 20 ml of water with heating, cool, add 2 ml of acetate BS (pH 3.5) and sufficient water to produce 25 ml, filter, if necessary. Carry out the limit test for heavy metals (Appendix VIII H, method 1); not more than 0.001%.

Assay Dissolve about 0.15 g, accurately weighed, in 25 ml of a mixture of acetic anhydride-glacial acetic acid (5 : 1) by gently warming, cool, add 1 drop of crystal violet IS, titrate with perchloric acid (0.1 mol/L) VS until the colour changes to yellow. Perform a blank determination and make any necessary collection. Each ml of perchloric acid (0.1

mol/L) VS is equivalent to 19.42 mg of $C_8H_{10}N_4O_2$.

Category Central stimulant.

Storage Preserve in tightly closed containers.

Caffeine and Sodium Benzoate Injection

Caffeine and Sodium Benzoate Injection is a sterile solution of anhydrous Caffeine and Sodium Benzoate in Water for Injection. It contains not less than 93.0% and not more than 107.0% of the labelled amount of anhydrous caffeine ($C_8H_{10}N_4O_2$) and sodium benzoate ($C_7H_5NaO_2$).

Description A clear, colourless liquid.

Identification (1) Evaporate 1 ml with 1 ml of hydrochloric acid and 0.1 g of potassium chlorate on a water bath to dryness, the residue reacts with ammonia vapour to produce a purple colour which disappears on the addition of a few drops of sodium hydroxide TS.

(2) Evaporate a quantity to dryness and ignite, the residue yields the flame reaction of sodium salts (Appendix III).

(3) Yields the reactions characteristic of benzoates (Appendix III).

pH value 7.5-8.5 (Appendix VI H).

Other requirements Complies with the general requirements for injections (Appendix I B).

Assay Measure accurately 5 ml into a 50 ml volumetric flask, dilute with water to volume and mix well, carry out the assay as follows.

Caffeine Measure accurately 10 ml of the above solution into a 100 ml volumetric flask, add 20 ml of water and 10 ml of dilute sulfuric acid, add accurately 50 ml of iodine (0.05 mol/L) VS, dilute with water to volume and mix well, allow to stand in a dark place for 15 minutes. Filter with a dry filter paper, titrate 50 ml of the successive filtrate, accurately measured, with sodium thiosulfate (0.1 mol/L) VS, add 2 ml of starch IS towards the end of titration, continue the titration until the blue colour disappears. Perform a blank determination and make any necessary correction. Each ml of iodine (0.05 mol/L) VS is equivalent to 4.855 mg of $C_8H_{10}N_4O_2$.

Sodium benzoate Measure accurately 10 ml of the above solution, add 15 ml of water, 25 ml of ether and 1 drop of methyl orange IS, titrate with hydrochloric acid (0.1 mol/L) VS with constant-shaking until the reddish-orange colour in the aqueous layer persists. Each ml of hydrochloric acid (0.1 mol/L) VS is equivalent to 14.41 mg of $C_7H_5NaO_2$.

Category Central stimulant.

Strength (1) 1 ml : 0.12 g anhydrous caffeine and 0.13 g sodium benzoate
(2) 2 ml : 0.24 g anhydrous caffeine and 0.26 g sodium benzoate

Storage Preserve in well closed containers, protected from light.

Calcitonin (Salmon) Injection

Calcitonin (Salmon) Injection is a sterile solution

of Calcitonin (salmon) in Water for Injections. It contains not less than 90.0% and not more than 115.0% of the labelled amount of calcitonin (salmon) ($C_{145}H_{240}N_{44}O_{48}S_2$).

Description A clear, colourless liquid.

Identification The retention time of the principal peak of calcitonin salmon in the substance being examined in the chromatogram obtained in the Assay is identical with that of the principal peak of calcitonin (salmon) CRS in the chromatogram of the reference solution.

H value 3.9-4.5 (Appendix VI H).

Related substances In the chromatogram obtained in the Assay the area of any peak corresponding to calcitonin C is not greater than 7% and the sum of the areas of any peaks, other than the principal peak and the peak of calcitonin C is not greater than 5.0% of the total area of all the peaks by the peak area normalisation method.

Undue toxicity Complies with the test for Undue toxicity (Appendix XI C), injected subcutaneously.

Bacterial endotoxin Carry out the test for bacterial endotoxin (Appendix XI E); less than 0.5 EU per μg of the calcitonin (salmon).

Other requirements Complies with the general requirements for injections (Appendix I B).

Assay Carry out the method for high performance liquid chromatography (Appendix V D), using a column packed with octadecylsilane bonded silica gel, a mixture of 0.402% tetramethylammonium hydroxide pentahydrate solution-acetonitrile (9 : 1) (adjust the pH to 2.5 with phosphoric acid) as the mobile phase A, and a mixture of 0.363% tetramethylammonium hydroxide pentahydrate solution-acetonitrile (2 : 3) (adjust the pH to 2.5 with phosphoric acid) as the mobile phase B. Perform the gradient elution using the following gradient programme and detection wavelength is 220 nm.

Time(min)	Mobile phase A(%)	Mobile phase B(%)
0	65	35
21	43	57
21.01	65	35
30	65	35

Heat the reference solution at 75°C for 15 hours and cool. Inject 200 μl into the column, the resolution factor between the peaks of calcitonin C (the largest peak to elute after the injection buffer salts and before the principal peak with a relative retention to that of calcitonin (salmon) of between 0.5 and 0.8) and calcitonin (salmon) is more than 3.0.

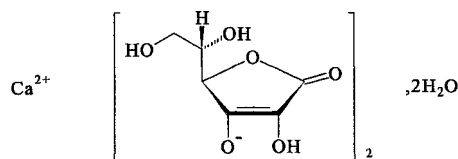
Procedure Inject 200 μl of the injection being examined into the column and record the chromatogram. Dissolve a quantity of calcitonin (salmon) CRS, accurately weighed, in water to produce a reference solution containing about 10 μg per ml. Repeat the operation, using the reference solution instead of the injection being examined. Calculate the content of $C_{145}H_{240}N_{44}O_{48}S_2$ with respect to the peak area obtained in the chromatogram by the external standard method.

Category Medicine for treating osteoporosis.

Strength 1 ml : 10 μg

Storage Preserve in well closed containers, protected from light and stored at a temperature of 2°C to 8°C.

Calcium Ascorbate



$C_{12}H_{14}CaO_{12} \cdot 2H_2O$ 426.35

Calcium Ascorbate is Calcium salt of L-Ascorbic acid dihydrate. It contains not less than 98.0% of $C_{12}H_{14}CaO_{12} \cdot 2H_2O$.

Description A white to pale yellow crystalline powder; odourless.

Soluble in water, slightly soluble in ethanol, insoluble in ether.

Specific optical rotation +95.0° to +97.0°, in a solution of about 0.10 g per ml in water (Appendix VI E).

Identification (1) To 5 ml of aqueous solution (1→10) add 1 to 2 drops of sodium dichloroindophenol TS, the colour of the solution disappears.

(2) The infrared absorption spectrum (Appendix IV C) is concordant with the reference spectrum of Calcium ascorbate (Appendix XVI).

(3) The aqueous solution yields the reactions characteristic of calcium salts (Appendix III).

Acidity or alkalinity Dissolve 2.0 g in 20 ml of water, pH value is 6.8-7.4 (Appendix VI H).

Oxalate Dissolve 1.0 g in 10 ml of water, add 2 drops of glacial acetic acid and 5 ml of 10% calcium oxalate solution, allow to stand for 5 minutes, the solution is still clear.

Loss on drying When dried at 105°C for 2 hours, loses not more than 0.1% of its weight (Appendix VIII L), using 3 g.

Residue on ignition Not less than 30.0% and not more than 33.0% (Appendix VIII N).

Heavy metals Dissolve 1.0 g in a quantity of water, add 2 ml of acetate BS (pH 3.5), dilute with water to 25 ml. Carry out the limit test for heavy metals (Appendix VIII H, method 1); not more than 0.001%.

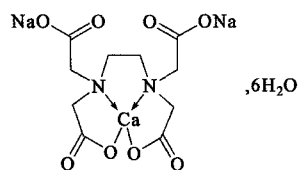
Arsenic Dissolve 0.67 g in 23 ml of water, add 5 ml of hydrochloric acid, carry out the limit test for arsenic (Appendix VIII J, method 1); not more than 0.0003%.

Assay Dissolve about 0.2 g, accurately weighed, in 50 ml of water, add 1.5 ml of starch IS. Titrate with iodine (0.05 mol/L) VS until a blue colour persist for at least 30 seconds. Each ml of iodine (0.05 mol/L) VS is equivalent to 10.66 mg of $C_{12}H_{14}CaO_{12} \cdot 2H_2O$.

Category Vitamin.

Storage Preserve in tightly closed vacuum containers, protected from light.

Calcium Disodium Edetate



$\text{C}_{10}\text{H}_{12}\text{CaN}_2\text{Na}_2\text{O}_8 \cdot 6\text{H}_2\text{O}$ 482.38 [23411-34-9]

Calcium Disodium Edetate is disodium [(ethylenedinitrilo) tetraacetato] calciate (2-) hexhydrate. It contains not less than 97.0% and not more than 102.0% of $\text{C}_{10}\text{H}_{12}\text{CaN}_2\text{Na}_2\text{O}_8$, calculated on the anhydrous basis.

Description A white crystalline or granule powder; odourless; tasteless; hygroscopic. Freely soluble in water; insoluble in ethanol or ether.

Identification (1) To 5 ml of water add 2 drops of ammonium thiocyanate TS and 2 drops of ferric chloride TS; a deep red colour is produced and it disappears upon shaking with about 50 mg of calcium disodium edetate. (2) To the aqueous solution (1 → 20) add ammonium oxalate TS; a white precipitate is produced which is soluble in hydrochloric acid but insoluble in acetic acid. (3) Yields the reactions characteristic of sodium salts (Appendix III).

Clarity of solution Dissolve 0.1 g in 50 ml of water, the solution is clear.

Chloride Carry out the limit test for chloride (Appendix VIII A), using 1.0 g. Any opalescence produced is not more pronounced than that of a reference solution using 7.0 ml of sodium chloride standard solution (0.07%).

Sulfate Carry out the limit test for sulfate (Appendix VIII B), using 0.5 g. Any opalescence produced is not more pronounced than that of a reference solution using 5.0 ml of potassium sulfate standard solution (0.1%).

Water Not more than 25% (Appendix VIII M, method 1 A).

Iron Ignite 0.1 g until charred, cool. Add 25 ml of water and filter. Carry out the limit test for iron (Appendix VIII G), using the resulting solution. Any colour produced is not more intense than that of a reference solution using 4 ml of iron standard solution (0.04%).

Assay To about 0.6 g, accurately weighed, add 75 ml of water and shake to dissolve. Add 25 ml of dilute acetic acid and 1 ml of diphenylcarbazide IS. Titrate slowly with mercuric nitrate (0.05 mol/L) VS until the solution becomes purple. Perform a blank determination and make any necessary correction. Each ml of mercuric nitrate (0.05 mol/L) VS is equivalent to 18.72 mg of $\text{C}_{10}\text{H}_{12}\text{CaN}_2\text{Na}_2\text{O}_8$.

Category Heavy metal antidote.

Storage Preserve in tightly closed containers.

Preparation Calcium Disodium Edetate Injection

Calcium Disodium Edetate Injection

Calcium Disodium Edetate Injection is a sterile solution of Calcium Disodium Edetate in Water for

Injection. It contains not less than 90.0% and not more than 110.0% of the labelled amount of calcium disodium edetate ($\text{C}_{10}\text{H}_{12}\text{CaN}_2\text{Na}_2\text{O}_8$).

Description A clear, colourless liquid.

Identification Complies with the tests for Identification described under Calcium Disodium Edetate.

pH Value 6.5-8.0 (Appendix VI H).

Pyrogens Complies with the test for pyrogens (Appendix XI D), using 2 ml per kg of rabbit's weight, injected slowly.

Other requirements Complies with the general requirements for injections (Appendix I B).

Assay Measure accurately a quantity equivalent to about 0.6 g of calcium disodium edetate. Carry out the Assay described under Calcium Disodium Edetate. Each ml of mercuric nitrate (0.05 mol/L) VS is equivalent to 18.72 mg of $\text{C}_{10}\text{H}_{12}\text{CaN}_2\text{Na}_2\text{O}_8$.

Category As described under Calcium Disodium Edetate.

Strength 5 ml : 1 g

Storage Preserve in tightly closed containers, protected from light.

Calcium Carbonate

CaCO_3 100.09 [471-34-1]

Calcium Carbonate contains not less than 98.5% of CaCO_3 , calculated on the dried basis.

Description A white fine crystalline powder; odourless; tasteless.

Practically insoluble in water; insoluble in ethanol; slightly soluble in the water containing ammonium salts or carbon dioxide; soluble in dilute acetic acid, dilute hydrochloric acid or dilute nitric acid with effervescence.

Identification The aqueous solution yields the reactions characteristic of calcium salts and carbonates. (Appendix III)

Acid-insoluble substances Mix 2.0 g with 10 ml of water, add dilute hydrochloric acid dropwise and shake gently until the effervescence is ceased, then add 90 ml of water and filter. Wash the residue with water until the washing shows no chloride. Dry and ignited to constant weight, the residue weighs not more than 0.2% of its weight.

Loss on drying When dried to constant weight at 105°C, loses not more than 1.0% of its weight (Appendix VIII L).

Barium Mix 2.0 g with 10 ml of water, add dilute hydrochloric acid dropwise to dissolve. Dilute with water to 100 ml. Dip a platinum wire in the resulting solution, it does not impart a green colour in a nonluminous flame.

Magnesium and alkali salts Dissolve 1.0 g in 20 ml of water and 10 ml of dilute hydrochloric acid, add 1 drop of methyl red IS, boil. Add ammonia TS dropwise to neutralize, add an excess of ammonium oxalate TS to precipitate the calcium completely. Heat on a water bath for 1 hour and allow to cool. Dilute with water to 100 ml, mix well and filter. To 50 ml of the filtrate add 0.5 ml of sulfuric acid, evaporate to dryness and ignited to constant weight, the residue weighs not more than 1.0% of its weight.

Iron Dissolve 0.12 g in 2 ml of dilute hydrochloric acid and dilute with water to 25 ml, carry out the limit test for iron (Appendix VIII G), Any colour produced is not more intense

than that of a reference solution prepared in the same manner using 5.0 ml of iron standard solution (0.04%).

Heavy metals Mix 0.50 g with 5 ml of water, add 4 ml of dilute hydrochloric acid, boil for 5 minutes and allow to cool. Filter and wash the filter with a small quantity of water. Combine the filtrate and washing, add 1 drop of phenolphthalein IS then add dropwise ammonia TS until the solution becomes light red. Add 2 ml of dilute acetic acid and sufficient water to 25 ml, add 0.5 g of ascorbic acid. Carry out the limit test for heavy metals (Appendix VIII H, method 1); not more than 0.003%.

Arsenic Dissolve 0.50 g in 6 ml of hydrochloric acid and 22 ml of water. Carry out the limit test for arsenic (Appendix VIII J, method 1); not more than 0.0004%.

Assay Dissolve about 1 g, accurately weighed, in a 250 ml volumetric flask, moisten with a small quantity of water, in dilute hydrochloric acid, dilute with water to volume and mix well. Measure accurately 25 ml to a conical flask, add 25 ml of water and 5 ml of potassium hydroxide solution (1→10), adjust the pH value to exceeding 12. Add a small quantity of calcon indicator mixture. Titrate the solution with disodium edetate (0.05 mol/L) VS until the colour turns from purple to pure blue. Each ml of disodium edetate (0.05 mol/L) VS is equivalent to 5.005 mg of CaCO_3 .

Category Calcium replenisher, antacid.

Storage Preserve in tightly closed containers.

Preparation (1) Calcium Carbonate Chewable Tablets
(2) Calcium Carbonate Granules

Calcium Carbonate Chewable Tablets

Calcium Carbonate Chewable Tablets contain not less than 93.0% and not more than 107.0% of the labelled amount of calcium (Ca).

Description White or coloured tablets, aromatic.

Identification (1) Moisten the substance being examined with hydrochloric acid on a platinum wire, it imparts a brick red colour to a nonluminous flame.

(2) To a quantity of powdered tablets, equivalent to about 0.25 g of calcium, add 15 ml of dilute hydrochloric acid, shake thoroughly and filter. Add 2 drops of methyl red IS to the filtrate, neutralize with ammonia TS, and then acidify with dilute hydrochloric acid. Add ammonium oxalate TS, a white precipitate is formed which is soluble in hydrochloric acid but insoluble in acetic acid.

(3) Add dilute hydrochloric acid to a quantity of powdered tablets, it effervesces with the evolution of carbon dioxide, forming a white precipitate when lead in calcium hydroxide TS immediately.

Other requirements Comply with the general requirements for tablets (Appendix I A).

Assay Weigh accurately and powder 10 tablets. Weigh accurately a quantity of the powder, equivalent to about 0.03 g of calcium, to a crucible, heat gently until it is thoroughly charred, and then ignite at 700-800°C for about 2 hours. Cool to room temperature and moisten the residue with a small quantity of water, add 5 ml of dilute hydrochloric acid, heat gently to dissolve the residue, transfer the solution with 70 ml of water in portions to a flask, adjust to pH 5-6 with sodium hydroxide TS. Add 2 ml of tartaric acid solution (1→5), 5 ml of triethanolamine solution (3→100), 15 ml of sodium hydroxide TS and a small quantity of calcon indicator mixture to the solution. Titrate the solution with

disodium edetate (0.05 mol/L) VS until the colour turns from purple to pure blue. Each ml of disodium edetate (0.05 mol/L) VS is equivalent to 2.004 mg of Ca.

Category Calcium replenisher.

Strength (1) 0.5 g (2) 0.125 g (calculated on Ca)

Storage Preserve in tightly closed containers, stored in a dry place.

Calcium Carbonate Granules

Calcium Carbonate Granules contain not less than 93.0% and not more than 107.0% of the labelled amount of calcium (Ca).

Description White or coloured granules.

Identification (1) Moisten the substance being examined with hydrochloric acid on a platinum wire, it imparts a brick red colour to a nonluminous flame.

(2) To a quantity of powdered granules, equivalent to about 0.25 g of calcium, add 15 ml of dilute hydrochloric acid, shake thoroughly and filter. Add 2 drops of methyl red IS to the filtrate, neutralize with ammonia TS, and then acidify with dilute hydrochloric acid. Add ammonium oxalate TS, a white precipitate is produced which is soluble in hydrochloric acid but insoluble in acetic acid.

(3) Add dilute hydrochloric acid to a quantity of granules, it effervesces with the evolution of carbon dioxide, producing a white precipitate when lead in calcium hydroxide TS immediately.

Loss on drying When dried to constant weight at 105°C, loses not more than 5.0% of its weight (Appendix VIII L).

Other requirements Comply with the general requirements for granules (Appendix I N) except Loss on drying and Dispersion.

Assay Weigh accurately a quantity of the mixed contents equivalent to about 0.03 g of calcium obtained under the test for weight variation of contents. to a crucible, heat gently until it is thoroughly charred, and then ignite at 700-800°C for about 2 hours. Cool to room temperature and moisten the residue with a small quantity of water, add 5 ml of dilute hydrochloric acid, heat gently to dissolve the residue, transfer the solution with 70 ml of water in portions to a flask, adjust to pH 5-6 with sodium hydroxide TS. Add 2 ml of tartaric acid solution (1→5), 5 ml of triethanolamine solution (3→100), 15 ml of sodium hydroxide TS and a small quantity of calcon indicator mixture to the solution. Titrate the solution with disodium edetate (0.05 mol/L) VS until the colour changes from purple to pure blue. Each ml of disodium edetate (0.05 mol/L) VS is equivalent to 2.004 mg of Ca.

Category Calcium replenisher.

Strength 0.25 g (calculated on Ca)

Storage Preserve in tightly closed containers, stored in a dry place.

Calcium Chloride

$\text{CaCl}_2 \cdot 2\text{H}_2\text{O}$ 147.02

[10035-04-8]

Calcium Chloride contains not less than 97.0% and not more than 103.0% of $\text{CaCl}_2 \cdot 2\text{H}_2\text{O}$.

Description White, hard solids or granules; odourless; taste, slightly bitter; very hygroscopic. Very soluble in water; freely soluble in ethanol.

Identification The aqueous solution yields the reactions characteristic of calcium salts (Appendix III) and chlorides (Appendix III).

Acidity or alkalinity Dissolve 3.0 g in 20 ml of water, add 2 drops of phenolphthalein IS. If the solution is pink, the colour is discharged on adding 0.30 ml of hydrochloric acid (0.02 mol/L) VS. If the solution is colourless, it produces pink by adding 0.10 ml of sodium hydroxide (0.02 mol/L) VS.

Clarity of solution A solution of 1.0 g in 10 ml of water is clear. Any opalescence produced is not more pronounced than that of reference suspension 1 (Appendix IX B).

Sulfates Carry out the limit test for sulfates (Appendix VIII B), using 1.0 g. Any opalescence produced is not more pronounced than that of a reference using 2.0 ml of potassium sulfate standard solution (0.02%).

Barium Dissolve 2.0 g in 20 ml of water and filter. Divide the filtrate into 2 equal parts. To one part add 5 ml of freshly prepared calcium sulfate TS, to the other part add 5 ml of water, allow to stand for 1 hour. The solutions are equal in clarity.

Aluminium, Iron and Phosphate Dissolve 1.0 g in 20 ml of water, add 2 drops of dilute hydrochloric acid and 1 drop of phenolphthalein IS. Add dropwise ammoniated ammonium chloride TS until a pink colour is produced. No turbidity or precipitate is produced when boiling.

Magnesium and Alkali metals Dissolve 1.0 g in 40 ml of water, add 0.5 g of ammonium chloride and heat the solution to boil. Add an excess of ammonium oxalate TS to precipitate calcium completely and heat on a water bath for 1 hour. Cool to room temperature, dilute with water to 100 ml, stir well and filter. To 50 ml of the filtrate add 0.5 ml of sulfuric acid, evaporate to dryness and ignite to constant weight. The residue does not exceed 5 mg.

Heavy metals Dissolve 2.0 g in 2 ml of acetate BS (pH 3.5) and a quantity of water to produce 25 ml. Carry out the limit test for heavy metals (Appendix VIII H, method 1): not more than 0.001%.

Arsenic Dissolve 1.0 g in 5 ml of hydrochloric acid and 23 ml of water. Carry out the limit test for arsenic (Appendix VIII J, method 1): not more than 0.0002%.

Assay Add 10 ml of water to a weighing bottle and weigh accurately. Add about 1.5 g of the substance being examined and weigh again accurately. Transfer the solution to a 100 ml volumetric flask, dilute with water to volume and mix well. Measure accurately 10 ml of the solution to a conical flask, add 90 ml of water, 15 ml of sodium hydroxide TS and about 0.1 g of calcon indicator mixture, titrate with disodium edetate (0.05 mol/L) VS until the colour changes from purplish-red to pure blue. Each ml of disodium edetate (0.05 mol/L) VS is equivalent to 7.351 mg of $\text{CaCl}_2 \cdot 2\text{H}_2\text{O}$.

Category Calcium replenisher.

Storage Preserve in tightly closed containers, stored in a dry place.

Preparation Calcium Chloride Injection

Calcium Chloride Injection

Calcium Chloride Injection is a sterile solution of Calcium Chloride in Water for Injection. It contains not less than 95.0% and not more than 105.0% of the labelled amount of calcium chloride ($\text{CaCl}_2 \cdot 2\text{H}_2\text{O}$).

Description A clear, colourless liquid.

Identification Yields the reactions characteristic of calcium salts and chlorides (Appendix III).

pH value 4.5-6.5 (Appendix VI H).

Bacterial endotoxin Carry out the test for bacterial endotoxin (Appendix XI E); less than 0.2 Eu per ml.

Other requirements Complies with the general requirements for injections (Appendix I B).

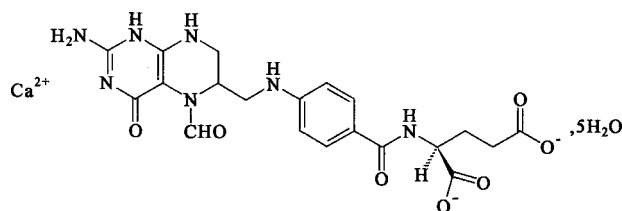
Assay Measure accurately a quantity equivalent to 0.15 g of calcium chloride into a conical flask, add a quantity of water to produce 10 ml. Carry out the Assay described under calcium chloride, beginning at the words "add 90 ml of water". Each ml of disodium edetate (0.05 mol/L) VS is equivalent to 7.351 mg of $\text{CaCl}_2 \cdot 2\text{H}_2\text{O}$.

Category As described under Calcium Chloride.

Strength (1) 10 ml : 0.3 g (2) 10 ml : 0.5 g
(3) 20 ml : 0.6 g (4) 20 ml : 1 g

Storage Preserve in well closed containers.

Calcium Folate



$\text{C}_{20}\text{H}_{21}\text{CaN}_7\text{O}_7 \cdot 5\text{H}_2\text{O}$ 601.61

[1492-18-8]

Calcium Folate is calcium *N*-[*p*-[[[(6*RS*)-2-amino-5-formyl-5,6,7,8-tetrahydro-4-hydroxy-6-pteridyl] methyl] amino] benzoyl]-*L*-glutamate, pentahydrate. It contains not less than 95.0% and not more than 105.0% of $\text{C}_{20}\text{H}_{21}\text{CaN}_7\text{O}_7$, calculated on the anhydrous basis.

Description Almost white to slightly yellow crystals or an amorphous powder; odourless. Soluble in water, practically insoluble in ethanol or ether; freely soluble in 0.1 mol/L sodium hydroxide solution.

Identification (1) The retention time of principal peak of the substance being examined in the chromatogram obtained in the Assay is identical with that of calcium folinate CRS.

(2) The light absorption of the solution of 10 μg per ml in 0.1 mol/L sodium hydroxide solution exhibits a maximum at 282 nm and a minimum at 241 nm (Appendix IV A).

(3) The aqueous solution yields the reactions characteristic of calcium salts (Appendix III).

Related substances Dissolve a quantity of the substance being examined in water to produce solutions of 1 mg per ml (solution 1) and 10 µg per ml (solution 2). Carry out the method as described under the Assay. Inject 20 µl of solution (2) into the column, adjust the attenuation so that the principal peak height in the chromatogram is about 10% of the full scale of the chart. Inject separately 20 µl of above two solutions, and record the chromatogram for three times the retention time of the principal peak. The sum of the areas of all peaks other than the principal peak in the chromatogram obtained with solution (1) is not greater than 2.5 times of area of the principal peak in the chromatogram obtained with solution (2).

Water Not more than 16.0% (Appendix VIII M, method 1 A).

Heavy metals Carry out the limit test for heavy metals (Appendix VIII H, method 2), using 0.40 g; not more than 0.005%.

Assay Carry out the method for high performance liquid chromatograph (Appendix V D), using a column packed with octadecylsilane bonded silica gel and a mixture as the mobile phase prepared as follows: mix 220 ml of methanol and 780 ml of a solution containing 8.0 ml of 10% tetrabutylammonium hydroxide solution and 2.2 g of disodium hydrogen phosphate previously adjusted to pH 7.8 with phosphoric acid. Detection wavelength is 280 nm and the column is maintained at 40°C. The number of the theoretical plates of the column is not less than 1000, calculated with reference to the peak of calcium folinate.

Dissolve an accurately weighed quantity in water to produce a solution of about 0.1 mg per ml. Inject 10 µl of solution into the column. Repeat the operation, using calcium folinate CRS instead of the substance being examined, calculate the content of $C_{20}H_{21}CaN_7O_7$ with respect to the peak area obtained in the chromatogram by the external standard method.

Category Antidote, Antianemic.

Storage Preserve in hermetically sealed containers, protected from light and stored in a cool place.

Preparation (1) Calcium Folate Capsules
(2) Calcium Folate for Injection
(3) Calcium Folate Tablets

Calcium Folate Capsules

Calcium Folate Capsules contain not less than 90.0% and not more than 110.0% of the labelled amount of folic acid ($C_{20}H_{23}N_7O_7$).

Description Capsules containing almost white to yellow granules or powder.

Identification (1) The retention time of principal peak of the substance being examined in the chromatogram obtained in the Assay is identical with that of calcium folinate CRS.

(2) Weigh a quantity of the contents of the capsules with 0.1 mol/L sodium hydroxide solution to produce a solution of about 10 µg per ml, filter. The light absorption of the filtrate exhibits a maximum at 282 nm, and minimum at 241 nm. (Appendix IV A).

(3) Weigh a quantity of the contents of the capsules, equivalent to about 15 mg of folic acid, with 4 ml of water to dissolve calcium folinate, shake and filter. The filtrate yields the reactions characteristic of calcium salts (Appendix III).

Related substances Carry out the method as described under Assay. Weigh a quantity of the contents of the capsules with water to produce a solution of 1 mg per ml and filter, using the successive filtrate as the test solution. Dilute the filtrate, accurately measured, with water to produce a solution of 10 µg per ml as the reference solution. Inject 20 µl of the reference solution into the column, adjust the attenuation so that the principal peak height in the chromatogram is about 10% of full scale of the chart. Inject separately 20 µl each of the test solution and the reference solution into the column, and record the chromatogram for three times the retention time of the principal peak. The sum of the areas of all the peaks other than the principal peak are not greater than 2.5 times of area of the principal peak in the chromatogram obtained with the reference solution.

Dissolution Carry out the dissolution test (Appendix X C, method 1), using 900 ml of water as the dissolution medium and adjust the rotational speed of the basket to 100 rpm. Withdraw the solution at 30 minutes and filter. Dilute an accurately measured quantity of the successive filtrate with 0.2 mol/L sodium hydroxide solution to produce a solution of 10 µg of folic acid per ml. Measure the absorbance of the resulting solution at 282 nm (Appendix IV A). Calculate the dissolution of $C_{20}H_{21}CaN_7O_7$ from each capsule, taking 575 as the value of A (1%, 1 cm) and multiply the result by 0.9256. Not less than 75% of the labelled amount is dissolved.

Other requirements Comply with the general requirements for capsules (Appendix I E).

Assay Triturate the mixed contents obtained under the test for weight variation of contents. Weigh accurately a quantity of the powder equivalent to about 20 mg of folic acid into a 200 ml volumetric flask, add a quantity of water and shake to dissolve calcium folinate, dilute with water to volume, shake thoroughly and filter. Measure accurately a quantity of the successive filtrate and carry out the Assay as described under Calcium Folate, and multiply the result by 0.9256.

Category As described under Calcium Folate.

Strength 25 mg (calculated as folic acid)

Storage Preserve in tightly closed containers, protected from light.

Calcium Folate for Injection

Calcium Folate for Injection is a sterile lyophilized preparation of calcium folinate. It contains not less than 85.0% and not more than 115.0% of the labelled amount of folic acid ($C_{20}H_{23}N_7O_7$).

Description An almost white to yellow friable mass or powder.

Identification (1) The retention time of principal peak of the substance being examined in the chromatogram obtained in the Assay is identical with that of calcium folinate CRS.

(2) The light absorption of the solution of 10 µg per ml in 0.1 mol/L sodium hydroxide solution exhibits a maximum at 282 nm and a minimum at 241 nm (Appendix IV A).

(3) Dissolve a quantity equivalent to about 15 mg of folic acid in 4 ml of water with shaking, filter, the filtrate yields the reactions characteristic of calcium salts (Appendix III).

Acidity or alkalinity An aqueous solution of 1 mg per ml, pH 6.5-8.5 (Appendix VI H).

Content uniformity Complies with the requirements for content uniformity (Appendix X E). Dissolve the content of one container in 0.1 mol/L sodium hydroxide solution to produce a solution of 10 µg per ml (for strength 3 mg or 5 mg). Measure the absorbance of the solution at 282 nm (Appendix IV A), calculate the content of $C_{20}H_{21}CaN_7O_7$, taking 575 as the value of A (1%, 1 cm), and multiply the result by 0.9256.

Related substances Dissolve a quantity of the content in water to produce a solution of about 1 mg per ml (solution 1), measure accurately 1 ml, dilute with water to 100 ml volumetric flask and mix well (solution 2). Carry out the method described under the Assay. Inject 20 µl of solution (2) into the column, adjust the attenuation so that the principal peak height in the chromatogram is about 10% of the full scale of the chart. Inject separately 20 µl of above two solutions, and record the chromatogram for three times the retention time of the principal peak. The sum of the areas of all peaks other than the principal peak in the chromatogram obtained with solution (1) is not greater than 2.5 times the area of the principal peak in the chromatogram obtained with solution (2).

Water Not more than 16.0% (Appendix VIII M, method 1 A).

Pyrogens Complies with the test for pyrogens (Appendix XI D), using 2 ml of a solution of 5.6 mg per ml in Sodium Chloride Injection per kg of rabbit's weight.

Other requirements Complies with the general requirements for injections (Appendix I B).

Assay Dissolve contents of 10 containers (for strength 3 mg or 5 mg) or 5 containers (for strength 25 mg, 30 mg, 50 mg or 100 mg) in water to produce a solution of 0.1 mg per ml. Carry out the Assay described under Calcium Folate, and multiply the result by 0.9256.

Category As described under Calcium Folate.

Strength (1) 3 mg (2) 5 mg (3) 15 mg (4) 25 mg (5) 30 mg (6) 50 mg (7) 100 mg (Calculated as folic acid)

Storage Preserve in well closed containers, protected from light.

Calcium Folate Tablets

Calcium Folate Tablets contain not less than 90.0% and not more than 110.0% of the labelled amount of folic acid ($C_{20}H_{23}N_7O_7$).

Description almost white to yellow tablets.

Identification (1) The retention time of principal peak of the substance being examined in the chromatogram obtained in the Assay is identical with that of calcium folinate CRS.

(2) Weigh a quantity of the powdered tablets with 0.1 mol/L sodium hydroxide solution to produce a solution of about 10 µg per ml, filter. The light absorption of the filtrate exhibits a maximum at 282 nm, and a minimum at 241 nm (Appendix IV A).

(3) Weigh a quantity of the powdered tablets, equivalent to about 15 mg of folic acid, with 4 ml of water to dissolve, filter. The filtrate yields the reaction characteristic of calcium salts (Appendix III).

Related substances Carry out the method described under Assay. Weigh a quantity of finely powdered tablets with water to produce a solution of 1 mg per ml and filter, using

the successive filtrate as the test solution. Dilute the filtrate, accurately measured, with water to produce a solution of 10 µg per ml as the reference solution. Inject 20 µl of the reference solution into the column. Adjust the attenuation so that the principal peak height in the chromatogram is about 10% of full scale of the chart. Inject separately 20 µl each of the test solution and the reference solution into the column, and record the chromatogram for three times the retention time of the principal peak. The sum of the areas of all peaks other than the principal peak is not greater than 2.5 times of area of the principal peak in the chromatogram obtained with the reference solution.

Dissolution Carry out the dissolution test (Appendix X C, method 1), using 900 ml of water as the dissolution medium and adjust the rotational speed of the basket to 100 rpm. Withdraw the solution at 30 minutes and filter. Dilute a quantity of the successive filtrate with 0.2 mol/L sodium hydroxide solution to produce a solution of 10 µg of folic acid per ml. Measure the absorbance of the resulting solution at 282 nm (Appendix IV A). Calculate the dissolution of $C_{20}H_{21}CaN_7O_7$ from each tablet, taking 575 as the value of A (1%, 1 cm), and multiply the result by 0.9256. Not less than 75% of the labelled amount is dissolved.

Other requirements Comply with the general requirements for tablets (Appendix I A).

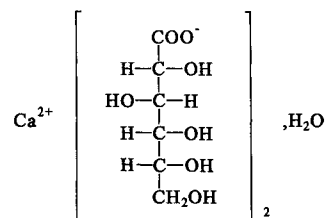
Assay Weigh accurately and powder 20 tablets. Weigh accurately a quantity of the powder equivalent to about 20 mg of folic acid into a 200 ml volumetric flask, add a quantity of water and shake to dissolve calcium folinate, dilute with water to volume, shake thoroughly and filter. Measure accurately a quantity of the successive filtrate and carry out the Assay as described under calcium folinate, and multiply the result by 0.9256.

Category As described under Calcium Folate.

Strength (1) 15 mg (2) 25 mg (calculated as folic acid)

Storage Preserve in tightly closed containers, protected from light.

Calcium Gluconate



$C_{12}H_{22}CaO_{14} \cdot H_2O$ 448.40

[12569-38-9]

Calcium Gluconate is the calcium salt of D-Gluconic acid, monohydrate. It contains not less than 99.0% and not more than 104.0% of $C_{12}H_{22}CaO_{14} \cdot H_2O$.

Description A white granular powder; odourless; tasteless. Freely soluble in boiling water; slowly soluble in water; insoluble in dehydrated ethanol, chloroform or ether.

Identification (1) Dissolve about 0.5 g in 5 ml of water by warming, add 0.7 ml of glacial acetic acid and 1 ml of freshly distilled phenylhydrazine, heat on a water bath for 30 minutes and cool to room temperature. Scratch the inner surface of the test tube with a glass rod, yellow crystals are formed gradually.

(2) Dissolve about 0.1 g in 5 ml of water, add 1 drop of ferric chloride TS; an intense yellow colour is produced.

(3) The infrared absorption spectrum (Appendix IV C) is concordant with the reference spectrum of calcium gluconate (Appendix XVI).

(4) The aqueous solution yields the reactions characteristic of calcium salts (Appendix III).

Clarity of solution Boil 4.0 g with 40 ml of water; a clear solution is obtained (for injection).

Chloride Carry out the limit test for chlorides (Appendix VIII A), using 0.10 g. Any opalescence produced is not more pronounced than that of a reference using 5.0 ml of sodium chloride standard solution (0.05%).

Sulfate Carry out the limit test for sulfates (Appendix VIII B), using 0.50 g. Any opalescence produced is not more pronounced than that of a reference using 5.0 of potassium sulfate standard solution (0.1%).

Sucrose or reducing sugars Dissolve 0.50 g in 10 ml of hot water, add 2 ml of dilute hydrochloric acid, boil for 2 minutes and cool to room temperature. Add 5 ml of sodium carbonate TS, allow to stand for 5 minutes, dilute with water to 20 ml and filter. To 5 ml of the filtrate, add 2 ml of alkaline cupric tartrate TS, and boil for 1 minute; no red precipitate is produced immediately.

Magnesium and alkali metals Dissolve 1.0 g in 40 ml of water, add 0.5 g of ammonium chloride, boil, add an excess of ammonium oxalate TS to precipitate the calcium salt completely. Heat on a water bath for 1 hour and cool to room temperature. Dilute with water to 100 ml, mix well and filter. To 50 ml of the filtrate, add 0.5 ml of sulfuric acid, evaporate to dryness and ignite to constant weight, the residue weighs not more than 5 mg.

Heavy metals Dissolve 1.0 g in 2 ml of 1 mol/L hydrochloric acid solution and sufficient water to produce 25 ml by warming. Cool to room temperature, carry out the limit test for heavy metals (Appendix VIII H, method 1); not more than 0.0015%.

Arsenic Dissolve 1.0 g in 5 ml of hydrochloric acid and 23 ml of water, carry out the limit test for arsenic (Appendix VIII J, method 1); not more than 0.0002%.

Assay Dissolve 0.5 g, accurately weighed, in 100 ml of water by warming, add 15 ml of sodium hydroxide TS, and 0.1 g of calcon indicator mixture. Titrate the solution with disodium edetate (0.05 mol/L) VS until the colour changes from violet to pure blue. Each ml of disodium edetate (0.05 mol/L) VS is equivalent to 22.42 mg of $C_{12}H_{22}CaO_{14} \cdot H_2O$.

Category Calcium replenisher.

Storage Preserve in tightly closed containers.

Preparation (1) Calcium Gluconate Buccal Tablets
(2) Calcium Gluconate Injection
(3) Calcium Gluconate Oral Solution
(4) Calcium Gluconate Tablets

Calcium Gluconate Buccal Tablets

Calcium Gluconate Buccal Tablets contain not less than 95.0% and not more than 105.0% of the labelled amount of calcium gluconate ($C_{12}H_{22}CaO_{14} \cdot H_2O$).

Description White or coloured tablets; odour, aromatic;

taste, sweet.

Identification To a quantity of the powdered tablets, equivalent to about 1 g of calcium gluconate, add 10 ml of warm water, shake and filter. The filtrate complies with the tests (1), (2) and (4) for Identification described under Calcium Gluconate.

Other requirements Comply with the general requirements for tablets (Appendix I A), except the disintegration test.

Assay Carry out the assay described under Calcium Gluconate Tablets.

Category As described under Calcium Gluconate.

Strength (1) 0.1 g (2) 0.15 g (3) 0.2 g

Storage Preserve in tightly closed containers, stored in dry place.

Calcium Gluconate Injection

Calcium Gluconate Injection is a sterile solution of Calcium Gluconate in Water for Injection. It contains not less than 97.0% and not more than 107.0% of the labelled amount of $C_{12}H_{22}CaO_{14} \cdot H_2O$.

Calcium salt or other suitable substance may be added as a stabilizing agent. But the amount of Ca added does not exceed 5% of that equivalent to the content of calcium gluconate.

Description A clear, colourless liquid.

Identification Complies with the tests (1), (2) and (4) for Identification described under Calcium Gluconate.

pH value 4.0-7.5 (Appendix VI H).

Pyrogens Complies with the test for pyrogens (Appendix XI D), using 2 ml per kg of the rabbit's weight.

Other requirements Complies with the general requirements for injections (Appendix I B).

Assay Measure accurately a volume equivalent to 0.5 g of calcium gluconate to a conical flask, add water to produce 100 ml. Carry out the Assay described under Calcium Gluconate, beginning at the words "add 15 ml of sodium hydroxide TS...". Each ml of disodium edetate (0.05 mol/L) VS is equivalent to 22.42 mg of $C_{12}H_{22}CaO_{14} \cdot H_2O$.

Category As described under Calcium Gluconate.

Strength (1) 10 ml : 0.5 g (2) 10 ml : 1 g

Storage Preserve in well closed containers.

Calcium Gluconate Oral Solution

Calcium Gluconate Oral Solution contains not less than 9.00% and not more than 10.50% (g/ml) of the labelled amount of calcium gluconate ($C_{12}H_{22}CaO_{14} \cdot H_2O$).

Description A colourless to pale yellow liquid or viscous liquid with aromatic odour; taste, sweet.

Identification Complies with the tests (1), (2) and (4) for Identification described under Calcium Gluconate.

Clarity of solution Dilute 10 ml with water to 50 ml, the

solution is clear.

Relative density 1.10 to 1.15 (Appendix VI A) (That without saccharide need not check this item).

pH value 4.0-7.5 (Appendix VI H).

Other requirements Complies with the general requirements for oral solutions (Appendix I O).

Assay Measure accurately 5.0 ml to a conical flask, dilute with water to 100 ml. Add 15 ml of sodium hydroxide TS, and 0.1 g of calcon indicator mixture. Titrate with disodium edetate (0.05 mol/L) VS until the colour changes from violet to pure blue. Each ml of disodium edetate (0.05 mol/L) VS is equivalent to 22.42 mg of $C_{12}H_{22}CaO_{14} \cdot H_2O$.

Category As described under Calcium Gluconate.

Strength 10%

Storage Preserve in tightly closed containers.

Calcium Gluconate Tablets

Calcium Gluconate Tablets contain not less than 95.0% and not more than 105.0% of the labelled amount of calcium gluconate ($C_{12}H_{22}CaO_{14} \cdot H_2O$).

Description White tablets.

Identification Shake a quantity of the powdered tablets equivalent to 1 g of calcium gluconate with 10 ml of warm water and filter. The filtrate complies with the tests (1), (2) and (4) for Identification described under Calcium Gluconate.

Dissolution Carry out the dissolution test (Appendix X C, method 2), using 900 ml of water as the dissolution medium, adjust the rotational speed of the paddle to 50 rpm. Withdraw 10 ml of the solution at 45 minutes and filter, using the successive filtrate (for 0.1 g per tablet) or dilute 2 ml of the successive filtrate, accurately measured, into a 10 ml volumetric flask and dilute with water to volume, mix well (for 0.5 g per tablet) as the test solution. Carry out the method for atomic absorption spectrophotometry (Appendix IV D, method 1), measure the absorbance of the test solution at 422.7 nm. Dissolve a quantity of calcium gluconate CRS, accurately weighed, in water to produce a solution of about 0.1 mg per ml. Repeat the operation using calcium gluconate CRS instead of the substance being examined. Calculate the dissolution of $C_{12}H_{22}CaO_{14} \cdot H_2O$ from each tablet. Not less than 75% of the labelled amount is dissolved.

Other requirements Comply with the general requirements for tablets (Appendix I A).

Assay Weigh accurately and powder 20 tablets. Weigh accurately a quantity of the powder equivalent to about 1 g of calcium gluconate, dissolve in about 50 ml of water by warming. Cool to room temperature, transfer to a 100 ml volumetric flask, dilute with water to volume and mix well and filter. Measure accurately 25 ml of the successive filtrate and add 75 ml of water. Complete the Assay described under Calcium Gluconate, beginning at the words "add 15 ml of sodium hydroxide TS...". Each ml of disodium edetate (0.05 mol/L) VS is equivalent to 22.42 mg of $C_{12}H_{22}CaO_{14} \cdot H_2O$.

Category As described under Calcium Gluconate.

Strength (1) 0.1 g (2) 0.5 g

Storage Preserve in tightly closed containers.

Calcium Hydrogen Phosphate

$CaHPO_4 \cdot 2H_2O$ 172.09

[7789-77-7]

Calcium Hydrogen Phosphate contains not less than 98.0% and not more than 105.0% of $CaHPO_4 \cdot 2H_2O$.

Description A white powder; odourless; tasteless. Insoluble in water or ethanol; freely soluble in dilute hydrochloric acid or dilute nitric acid.

Identification The acidic aqueous solution yields the reactions characteristic of calcium salts and phosphates (Appendix III).

Fluorides Place 2.0 g together with 5 ml of perchloric acid, 15 ml of water and a few glass beads in a 50 ml volumetric distilling flask connected with a condenser. The flask is also equipped with a stopper with 2 holes. Insert a thermometer and a dropping funnel, filled with water and connected to a capillary tube through each hole, both of which extend into the liquid surface, heat until the temperature reaches 135°C with a small flame, receiving the distillate under the surface of 10 ml of water, and then maintain at 135°C to 140°C by adding water in dropwise from the funnel. Continue the distillation until 70 ml of the distillate has been collected. Rinse the condenser with water, and dilute the distillate to 100 ml, mix well and use 50 ml of the solution as the test solution. Dilute 15 ml of sodium fluoride standard solution [dissolve 0.2210 g, accurately weighed, of sodium fluoride dried previously to constant weight at 105°C, with water in a 100 ml volumetric flask and dilute with water to volume, mix well; measure accurately 10 ml to a 1000 ml volumetric flask, dilute with water to volume and mix well before use. Each ml of the standard solution contains 10 µg of fluorine (F)], with water to 50 ml, use as standard solution. Add 1.5 ml of sodium alizarinsulfonate IS to the test solution and the standard solution, and add sodium hydroxide (0.05 mol/L) VS dropwise until the solutions become faintly pink. Then add to each solution 5 ml of hydrochloric acid (0.02 mol/L) VS. Titrate with a 0.025% solution of thorium nitrate to pink colour. The titration volume (ml) consumed for the test solution is not more than that for the standard solution (0.015%).

Chlorides Dissolve 0.20 g in 10 ml of water and 2 ml of nitric acid with gentle heating, cool, carry out the limit test for chlorides (Appendix VIII A). Any opalescence produced is not more pronounced than that of a reference using 10.0 ml of sodium chloride standard solution (0.05%).

Sulfates Dissolve 1.0 g in a quantity of dilute hydrochloric acid, dilute with water to 100 ml, mix well and filter. To 20 ml of the filtrate add 5 ml of water, carry out the limit test for sulfates (Appendix VIII B). Any opalescence produced is not more pronounced than that of a reference using 4 ml of potassium sulfate standard solution (0.2%).

Carbonates Mix 1.0 g with 5 ml of water and add 2 ml of hydrochloric acid, no effervescence is produced.

Insoluble substances in hydrochloric acid Heat to dissolve 5.0 g in a mixture of 10 ml of hydrochloric acid and 40 ml of water and dilute with water to 100 ml. Filter and wash any residue with water until the washing does not give a reaction for chloride, and dry the residue at 105°C for 1 hour. The weight of the residue does not exceed 5 mg.

Loss on ignition Ignite it at 600°C to constant weight, loses

24.5%-26.5% of its weight, using 1.0 g.

Barium Heat 0.50 g with 10 ml of water and add hydrochloric acid dropwise with stirring until no more dissolves. Filter and to the filtrate add 2 ml of potassium sulfate TS, no turbidity is produced within 10 minutes.

Heavy metals Dissolve 1.0 g in 3 ml of dilute hydrochloric acid with heating, dilute with water to 50 ml and filter. Carry out the limit test for heavy metals (Appendix VIII H, method 1) with 25 ml of filtrate; not more than 0.003%.

Arsenic Dissolve 0.50 g in 5 ml of hydrochloric acid (1→25) solution. Carry out the limit test for arsenic (Appendix VIII J, method 1); not more than 0.001%.

Assay Dissolve 0.6 g, accurately weighed, in 10 ml of dilute hydrochloric acid with heating, cool, transfer to a 100 ml volumetric flask, dilute with water to volume and mix well. To 10 ml of the solution, accurately measured, add 50 ml of water, adjusted to neutral by ammonia test solution, and 25 ml, accurately measured, of disodium edetate (0.05 mol/L) VS, heat for a few minutes. Allow it to cool, add 10 ml of ammonia-ammonium chloride BS (pH 10.0) and a small amount of eriochrome black T indicator mixture. Titrate with zinc (0.05 mol/L) VS until the solution turns to reddish-violet. Each ml of disodium edetate (0.05 mol/L) VS is equivalent to 8.605 mg of $\text{CaHPO}_4 \cdot 2\text{H}_2\text{O}$.

Category Calcium replenisher.

Storage Preserve in tightly closed containers.

Preparation calcium Hydrogen Phosphate Tablets

Calcium Hydrogen Phosphate Tablets

Calcium Hydrogen Phosphate Tablets contain not less than 92.5% and not more than 107.5% of the labelled amount of calcium hydrogen phosphate ($\text{CaHPO}_4 \cdot 2\text{H}_2\text{O}$).

Description White tablets.

Identification Dissolve a quantity of the powdered tablets, equivalent to about 1 g of calcium hydrogen phosphate, with 5 ml of dilute hydrochloric acid and 10 ml of water by heating, cool and filter. The filtrate yields the reactions characteristic of phosphates and calcium salts (Appendix III).

Other requirements Comply with the general requirements for tablets (Appendix I A), except disintegration test.

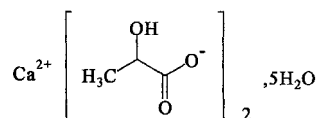
Assay Weigh and powder 20 tablets. Dissolve a quantity equivalent to about 0.6 g of calcium hydrogen phosphate, accurately weighed, in 10 ml of dilute hydrochloric acid by heating. Cool, transfer to a 100 ml volumetric flask, dilute with water to volume and mix well and filter. Measure accurately 10 ml of the successive filtrate, add 50 ml of water, adjusted to neutral by ammonia test solution, and 25 ml of disodium edetate (0.05 mol/L) VS, heat for a few minutes. Cool, add 10 ml of ammonia-ammonium chloride BS (pH 10.0) and a few drops of eriochrome black T indicator mixture, titrate with zinc (0.05 mol/L) VS until the solution turns to purplish red. Perform a blank determination and make any necessary correction. Each ml of disodium edetate (0.05 mol/L) VS is equivalent to 8.605 mg of $\text{CaHPO}_4 \cdot 2\text{H}_2\text{O}$.

Category As described under Calcium Hydrogen Phosphate.

Strength 0.3 g

Storage Preserve in tightly closed containers.

Calcium Lactate



$\text{C}_6\text{H}_{10}\text{CaO}_6 \cdot 5\text{H}_2\text{O}$ 308.30 [41372-22-9]

Calcium Lactate is 2-hydroxy-propanoic acid, calcium salt (2 : 1) pentahydrate. It contains not less than 98.0% and not more than 103.0% of $\text{C}_6\text{H}_{10}\text{CaO}_6 \cdot 5\text{H}_2\text{O}$.

Description A white or almost white crystalline or granular powder; almost odourless; slightly efflorescent. Freely soluble in hot water; soluble in water; practically insoluble in ethanol, chloroform or ether.

Identification (1) The infrared absorption spectrum (Appendix IV C) is concordant with the reference spectrum of calcium lactate (Appendix XVI).

(2) The aqueous solution yields the reactions characteristic of calcium salts and lactates (Appendix III).

Acidity Dissolve 1.0 g in 20 ml of freshly boiled warm water, allow to cool to room temperature, add 2 drops of phenolphthalein IS, not more than 0.50 ml of sodium hydroxide (0.1 mol/L) VS is required to change the colour of the solution to pink.

Chlorides Carry out the limit test for chlorides (Appendix VIII A), using 0.10 g. Any opalescence produced is not more pronounced than that of a reference using 5.0 ml of sodium chloride standard solution (0.05%).

Sulfates Carry out the limit test for sulfates (Appendix VIII B), using 0.40 g. Any opalescence produced is not more pronounced than that of a reference using 3.0 ml of potassium sulfate standard solution (0.075%).

Bariums Dissolve 1.0 g in 20 ml of water, divide the solution into two equal parts, use one of them as the reference solution; to the other one add 1 ml of calcium sulfate TS, allow to stand for 15 minutes. Any opalescence produced is not more pronounced than that of the reference solution.

Iron Dissolve 0.50 g in 25 ml of water by heating in a water bath, allow to cool to room temperature. Carry out the limit test for iron (Appendix VIII G). Any colour produced is not more intense than that of a reference using 2.5 ml of iron standard solution (0.005%).

Heavy metals Heat gently to dissolve 1.0 g in 15 ml of water and 2 ml of acetate BS (pH 3.5), allow to cool to room temperature, add a quantity of water to produce 25 ml. Carry out the limit test for heavy metals (Appendix VIII H, method 1); not more than 0.001%.

Arsenic Dissolve 1.0 g in 5 ml of hydrochloric acid and 23 ml of water. Carry out the limit test for arsenic (Appendix VIII J, method 1); not more than 0.0002%.

Assay Weigh accurately about 0.3 g, heat to dissolve in 100 ml of water, allow to cool to room temperature, add 15 ml of sodium hydroxide TS and about 0.1 g of calcon indicator mixture. Titrate with disodium edetate (0.05 mol/L) VS until the colour changes from purple red to pure blue. Each ml of disodium edetate (0.05 mol/L) VS is equivalent to 15.42 mg of $\text{C}_6\text{H}_{10}\text{CaO}_6 \cdot 5\text{H}_2\text{O}$.

Category Calcium replenisher.

Storage Preserve in tightly closed containers.

Preparation Calcium Lactate Tablets

Calcium Lactate Tablets

Calcium Lactate Tablets contain not less than 95.0% and not more than 105.0% of the labelled amount of calcium lactate ($\text{C}_6\text{H}_{10}\text{CaO}_6 \cdot 5\text{H}_2\text{O}$).

Description White tablets.

Identification Dissolve a quantity of the powdered tablets equivalent to 1 g of calcium lactate in 20 ml of water with heating, filter, the filtrate yields the reactions characteristic of calcium salts and lactates (Appendix III).

Other requirements Comply with the general requirements for tablets (Appendix I A), but the disintegration time is not more than 20 minutes.

Assay Weigh accurately and powder 10 tablets. Dissolve an accurately weighed quantity of the powder equivalent to about 0.3 g of calcium lactate in 100 ml of water with heating, allow to cool to room temperature, carry out the Assay described under Calcium Lactate, beginning at the words "add 15 ml of sodium hydroxide TS...". Each ml of disodium edetate (0.05 mol/L) VS is equivalent to 15.42 mg of $\text{C}_6\text{H}_{10}\text{CaO}_6 \cdot 5\text{H}_2\text{O}$.

Category As described under Calcium Lactate.

Strength (1) 0.25 g (2) 0.3 g (3) 0.5 g

Storage Preserve in tightly closed containers.

(3) The infrared absorption spectrum (Appendix IV C) is concordant with the reference spectrum of calcium pantothenate (Appendix XV).

(4) The aqueous solution yields the reactions characteristic of calcium salts (Appendix III).

Clarity and colour of solution Dissolve 1.0 g in 20 ml of water, the resulting solution is clear and colourless.

Loss on drying When dried to constant weight at 105°C, loses not more than 5.0% of its weight (Appendix VIII L).

Heavy metals Dissolve 1.0 g in a quantity of water, add 1.0 ml of hydrochloric acid solution (9→100), add water to produce 25 ml. Carry out the limit test for heavy metals (Appendix VIII H, method 1); not more than 0.002%.

Assay Calcium Dissolve about 0.5 g, accurately weighed, in 100 ml of water, add 15 ml of sodium hydroxide TS and 0.1 g of calcon indicator mixture. Titrate with disodium edetate (0.05 mol/L) VS until the solution colour changes from purple red to pure blue. Each ml of disodium edetate (0.05 mol/L) VS is equivalent to 2.004 mg of Ca.

Nitrogen Weigh accurately about 0.5 g, carry out the determination of nitrogen (Appendix VII D, method 1). Each ml of sulfuric acid (0.05 mol/L) VS is equivalent to 1.401 mg of N.

Category Vitamin.

Storage Preserve in tightly closed containers, stored in a dry place.

Preparation Calcium Pantothenate Tablets

Calcium Pantothenate Tablets

Calcium Pantothenate Tablets contain not less than 93.0% and not more than 107.0% of the labelled amount of calcium pantothenate ($\text{C}_{18}\text{H}_{32}\text{CaN}_2\text{O}_{10}$).

Description White tablets.

Identification (1) To a quantity of powdered tablets equivalent to about 50 mg of calcium pantothenate add 5 ml of sodium hydroxide TS, shake and filter, to the filtrate add 1 drop of cupric sulfate TS, a deep blue colour is produced.

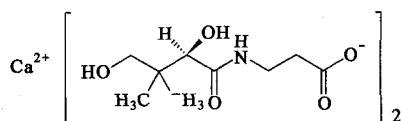
(2) To a quantity of powdered tablets equivalent to about 50 mg of calcium pantothenate add 5 ml of sodium hydroxide TS, heat to boil for 1 minute and allow to cool to room temperature. Add 5 ml of 1 mol/L hydrochloric acid solution and 2 drops of ferric chloride TS, a yellow colour is produced.

(3) Shake a quantity of powdered tablets with water and filter, the filtrate yields the reactions characteristic of calcium salts (Appendix III).

Other requirements Comply with the general requirements for tablets (Appendix I A).

Assay Weigh accurately and powder 150 tablets. Triturate an accurately weighed quantity of the powder equivalent to about 0.3 g of calcium pantothenate, add 25 ml of water, shake vigorously to dissolve the calcium pantothenate, filter and wash with 20 ml of water each for 5 times, combine the washings and filtrate, add 10 ml of ammonia-ammonium chloride BS, add 1 drop of dilute magnesium sulfate TS and a small amount of eriochrome black T indicator mixture, titrate with disodium edetate (0.05 mol/L) VS, until the colour changes from purple red to pure blue. Perform a blank determination and make any necessary correction. Each ml of disodium edetate (0.05 mol/L) VS is equivalent to 23.83 mg of $\text{C}_{18}\text{H}_{32}\text{CaN}_2\text{O}_{10}$.

Calcium Pantothenate



$\text{C}_{18}\text{H}_{32}\text{CaN}_2\text{O}_{10}$ 476.54

[135-08-6]

Calcium Pantothenate is (*R*)-*N*-(2,4-dihydroxy-3,3-dimethyl-1-oxobutyl)-3-alanine, calcium salt (2 : 1). It contains 8.20%-8.60% of calcium (Ca) and 5.70%-6.00% of nitrogen (N), calculated on the dried basis.

Description A white powder; odourless; taste, slightly bitter; hygroscopic. The aqueous solution yields a neutral or weakly alkaline reaction. Freely soluble in water; very slightly soluble in ethanol; practically insoluble in chloroform or ether.

Specific optical rotation +25° to +28.5°, in a solution of 50 mg per ml in water (Appendix VI E).

Identification (1) Shake about 50 mg with 5 ml of sodium hydroxide TS, add 2 drops of cupric sulfate TS; a bluish-violet colour is produced.

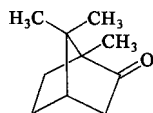
(2) Shake about 50 mg with 5 ml of sodium hydroxide TS, boil for 1 minute and cool to room temperature. Add 1 drop of phenolphthalein IS, then add dropwise hydrochloric acid solution (9→100) until the pink colour disappears, add further 0.5 ml of hydrochloric acid solution (9→100) and 2 drops of ferric chloride TS; a bright yellow colour is produced.

Category As described under Calcium Pantothenate.

Strength (1) 5 mg (2) 10 mg

Storage Preserve in tightly closed containers, stored in a dry place and protected from light.

Camphor



$C_{10}H_{16}O$ 152.24

[76-22-2]

Camphor is 1,7,7-trimethyl-bicycol [2.2.1] heptane-2-one. It is extracted from *Cinnamomum camphora* (L.) Nees and Eberm (natural camphor) or prepared by chemical synthesis (synthetic camphor).

Description A white crystalline powder or colourless translucent crumbly mass. Readily pulverized in the presence of a little ethanol, chloroform or ether; odour, characteristic, hot at first, then cool and refreshing; volatilized easily at room temperature; burns with black smoke and a bright flame.

Very soluble in chloroform; freely soluble in ethanol, ether, fatty oil or volatile oil; very slightly soluble in water.

Melting range Transfer a quantity to a thin-walled capillary tube, 2.0-2.5 mm in diameter, sealed at one end. Carry out the determination of melting point (Appendix VI C); Natural camphor melts at 176-181°C; synthetic camphor melts at 174-179°C.

Specific optical rotation +41° to +44° (natural) or -1.5° to +1.5° (synthetic), in a solution of 0.1 g per ml in ethanol (Appendix VI E).

Identification (1) Dissolve a quantity in ethanol to produce a solution of 2.5 mg per ml. Measure the absorbance within the range of 230-350 nm (Appendix IV A). It exhibits a maximum at 289 nm, the absorbance is about 0.53.

(2) The infrared absorption spectrum (Appendix IV C) is concordant with the reference spectrum of camphor (Appendix XVI).

Non-volatile matter Heat 2.0 g at 100°C to volatilize the camphor completely and dried to constant weight. It leaves not more than 1 mg of residue.

Water Dissolve 1.0 g in 10 ml of petroleum ether. The solution is clear.

Category Skin-irritant.

Storage Preserve in tightly closed containers.

Compound Camphor Tincture

Compound Camphor Tincture contains not less than 0.425 mg and not more than 0.575 mg of morphine ($C_{17}H_{19}NO_3$) per ml.

Formula	Camphor	3 g
	Opium Tincture	50 ml
	Benzoate	5 g
	Anise oil	3 ml

Ethanol (56%)

a quantity

To make

1000 ml

Processing Dissolve benzoate, camphor and anise oil with 900 ml of 56% ethanol solution, add slowly opium tincture and a quantity of 56% ethanol solution to produce 1000 ml, mix well and filter.

Description A yellowish-brown liquid; odour, aromatic similar to camphor and anise oil; taste, sweet and pungent.

Identification To 10 ml add a quantity of ammonia TS to adjust pH to about 9. Extract with two portions of a mixture of chloroform-isopropanol (3 : 1), each of 20 ml, filter the combined extracts through anhydrous sodium sulfate, evaporate in vacuum the successive filtrate to dryness, dissolve the residue in 0.3 ml of methanol as the test solution. Dissolve a quantity of morphine CRS in methanol to produce a solution containing 1 mg per ml as the reference solution. Carry out the thin-layer chromatography (Appendix V B), using silica gel G as the coating substance and a mixture of ethyl acetate-methanol-concentrated ammonia solution (17 : 2 : 1) as the mobile phase. Apply separately to the plate 10 µl of each of the above two solutions. After developing and removal of the plate, dry it in air and spray with dilute potassium iodobismuthate TS. The principal spot in the chromatogram obtained with the test solution corresponds in colour and position to the principal spot obtained with the reference solution.

Ethanol content 52%-60% (Appendix VII E)

Other requirements Complies with the general requirements for tinctures (Appendix I C).

Assay Carry out the method for high performance liquid chromatography (Appendix V D), using a column packed with octadecylsilane bonded silica gel and a mixture of 0.05 mol/L potassium dihydrogen phosphate solution-0.0025 mol/L sodium heptanesulfonate solution-acetonitrile (2 : 2 : 1) as the mobile phase. Detection wavelength is 220 nm and the number of the theoretical plates of the column is not less than 1000, calculated with reference to the peak of morphine.

System suitability test of solid phase extraction column Using a solid phase extraction column packed with octadecylsilane bonded silica gel. Carry out the test as described under the Procedure. Transfer 1 ml of a solution in 5% acetic acid solution containing 0.25 mg of morphine CRS per ml, accurately measured, to the column pretreated, collect the eluate into a 5 ml volumetric flask to volume and mix well. Respectively inject 10 µl of the eluate and the reference solution as described under the Procedure into the column, record the chromatogram. The ratio of the peak area of morphine obtained in the chromatogram of the eluate to that of the reference solution is not less than 0.97 and not more than 1.03.

Procedure Wash a solid phase extraction column with 15 ml of a mixture of methanol-water (3 : 1) and 5 ml of water in sequence, then wash the column with the ammonia solution of pH value about 9 (add drops of ammonia TS to a quantity of water until the pH value is about 9) until the pH value of the eluate is about 9. Place one bottle being examined in an ultrasonic bath for 10 minutes and mix well. Measure accurately 5 ml into a conical flask with stopper, evaporate to dryness, add accurately 10 ml of 5% acetic acid solution, Place in an ultrasonic bath for 10 minutes to dissolve morphine, allow to cool to room temperature and filter. Measure accurately 1 ml of the successive filtrate to the above washed column, adjust the solution in the column to pH 9 with drops of ammonia TS (defined the quantity of ammonia TS using another same volume of the successive filtrate

previously), mix well, rinse with 20 ml of water to make the drips neutral after no solvent drips. Elute with 5% acetic acid solution containing 20% methanol, collect the eluate into a 5 ml volumetric flask to volume and mix well. Inject 10 μ l of the eluate into the column, record the peak areas correspondingly obtained in the chromatogram. Repeat the operation, using a solution in 5% acetic acid solution containing 20% methanol, containing 0.05 mg of morphine CRS per ml instead of the eluate. Calculate the content of $C_{17}H_{19}NO_3$ with respect to the peak areas obtained in the chromatogram by the external standard method.

Category Antitussive, analgetic and antidiarrheal.

Storage Preserve in tightly closed containers, stored in cool and dry place and protected from light.

Capreomycin Sulfate

[1405-37-4]

Capreomycin Sulfate has a potency of not less than 830 Capreomycin Units per mg, calculated on the dried basis.

Description White or almost white powder; odourless; hygroscopic. Freely soluble in water; practically insoluble in ethanol, chloroform or ether.

Specific optical rotation -26° to -36° , in a solution of 10 mg per ml in water (Appendix VI E).

Identification (1) Carry out the method for thin-layer chromatography (Appendix V B), using silica gel GF₂₅₄ as the coating substance and a mixture of 10% ammonium acetate solution-10% ammonium hydroxide solution-acetone (9 : 1 : 10) as the mobile phase. Apply separately to the plate 3 μ l each of two solutions containing (1) 20 mg per ml of the substance being examined and (2) 20 mg per ml of capreomycin sulfate CRS. After developing and removal of the plate, dry it in air and examine under an ultraviolet light (254 nm). The colour and position of the two principal spots in the chromatogram obtained with solution (1) is correspond to the two principal spots obtained with solution (2).

(2) Carry out the method described under capreomycin I, using two solutions in water containing (1) 0.12 mg of the substance being examined per ml and (2) 0.12 mg of capreomycin sulfate CRS per ml. The retention time of principal peak of capreomycin sulfate in the chromatogram of solution (1) is identical with that of principal peaks of capreomycin sulfate in the chromatogram of solution (2).

(3) The light absorption of a solution of 20 μ g per ml in hydrochloric acid solution (9 \rightarrow 1000) exhibits a maximum at 269 nm (Appendix IV A).

(4) The light absorption of a solution of 20 μ g per ml in 0.4% sodium hydroxide solution exhibits a maximum at 287 nm (Appendix IV A).

(5) The aqueous solution yields the reactions characteristic of sulfates (Appendix III).

Tests (1) (3) and (4) may be omitted if tests (2) and (5) are carried out. Test (2) may be omitted if tests (1), (3), (4) and (5) are carried out.

Acidity or alkalinity An aqueous solution of 30 mg per ml, pH 5.0-7.5 (Appendix VI H).

Clarity and colour of solution Dissolve 5 portions each of 0.6 g in 5 ml of water respectively the solutions are clear and colourless; any opalescence produced is not more pronounced than that of reference suspension II (Appendix IX B); any

colour produced is not more intense than that of reference solution Y₅ (Appendix IX A, method 1).

Capreomycin I Carry out the method for high performance liquid chromatography (Appendix V D), using a column packed with octadecylsilane bonded silica gel and a mixture of 0.016 mol/L sodium hexanesulfonate solution-methanol-acetonitrile-glacial acetic acid (60 : 25 : 25 : 2) as mobile phase. Detection wavelength is 254 nm and the number of theoretical plates of the column is not less 1000, calculated with reference to peak area of Capreomycin I. The relative retention time of the Capreomycin II peak to that of Capreomycin I is about 0.6-0.7 and the resolution of factor between the peaks of Capreomycin I and Capreomycin II complies with the related requirements.

Procedure Dissolve a quantity, accurately weighed, in water to produce a solution of 0.12 mg per ml, inject 10 μ l into the column and record the chromatogram. The peak area of Capreomycin I is not less than 90% of the sum of the peak areas of Capreomycin I and Capreomycin II.

Loss on drying When dried to constant weight at 105°C, loses not more than 6.0% of its weight (Appendix VIII L).

Residue on ignition Not more than 3.0% (Appendix VIII N).

Bacterial endotoxins Carry out the method (Appendix XI E). It contains not more than 0.3 EU per mg.

Sterility Complies with the test for sterility (Appendix XI H, membrane filtration method), using not less than 500 ml of 0.9% sterile sodium chloride solution.

Assay Weigh accurately a quantity and add phosphate BS (pH 7.8-8.0) to produce a solution of about 1000 Units per ml, carry out the microbiological assay of antibiotics (Appendix XI A). 1000 Capreomycin Units are equivalent to 1 mg of Capreomycin.

Category Antibiotic Antituberculous.

Storage Preserve in hermetically sealed containers, stored in a cool and dry place.

Preparation Capreomycin Sulfate for Injection

Capreomycin Sulfate for Injection

Capreomycin Sulfate for Injection is a sterile powder of capreomycin sulfate. It has a potency of not less than 830 capreomycin Units per mg, calculated on the dried basis. It contains not less than 90.0% and not more than 110.0% of the labelled amount of capreomycin, calculated on the basis of the average weight of contents.

Description A white or almost white powder.

Identification Complies with the tests for Identification described under Capreomycin Sulfate.

Clarity and colour of solution To each of 5 containers add water to produce solutions of 0.1 g per ml, the solutions are clear and colourless; any opalescence produced is not more pronounced than that of the reference suspension II (Appendix IX B); any colour produced is not more intense than that of the reference solution Y₅ (Appendix IX A, method 1).

Acidity or alkalinity, Capreomycin I, Loss on drying, Residue on ignition, Bacterial endotoxins and sterility Complies with the corresponding requirement described under Capreomycin Sulfate.

Other requirements Complies with the general requirements for injections (Appendix I B).

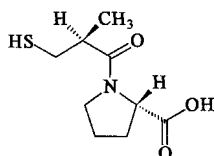
Assay Carry out the Assay described under Capreomycin Sulfate, using an accurately weighed quantity of the mixed contents obtained under the test for weight variation of the contents.

Category As described under Capreomycin Sulfate.

Strength 0.5 g (500000 Units)

Storage Preserve in well closed containers, stored in a cool and dry place.

Captopril



$C_9H_{15}NO_3S$ 217.29

[62571-86-2]

Captopril is 1-[(2S)-3-mercapto-2-methyl-1-oxopropyl]-L-proline. It contains not less than 97.5% of $C_9H_{15}NO_3S$, calculated on the dried basis.

Description a white or almost white crystalline powder; odour characteristic, alliaceous; taste, saline. Freely soluble in methanol, ethanol or chloroform; soluble in water.

Melting range 104-110°C (Appendix VI C).

Specific optical rotation -126° to -132° , in a solution of 20 mg per ml in ethanol (Appendix VI E).

Identification (1) Dissolve 25 mg in 2 ml of ethanol, add a quantity of sodium nitrate crystals and 10 drops of dilute sulfuric acid, shake, a red colour is produced.

(2) The infrared absorption spectrum (Appendix IV C) is concordant with the reference spectrum of captopril (Appendix XVI).

Captopril disulfide Protect from light throughout the procedure. Dissolve a quantity in methanol to produce a solution of 2 mg per ml (solution 1) (freshly prepared). Dissolve a quantity of captopril CRS in methanol to produce a solution of 30 μ g per ml (solution 2). Dissolve a quantity of captopril CRS and captopril disulfide CRS in methanol to produce a solution of 10 μ g per ml respectively (solution 3). Carry out the method for high performance liquid chromatography (Appendix V D), using a column packed with octadecylsilane bonded silica gel and a mixture of 9% tetrahydrofuran solution in methanol-0.05% phosphoric acid solution (33 : 67) as the mobile phase. The wavelength of the detection is 220 nm. Inject 20 μ l of solution (3) into the column, adjust the attenuation so that the peak height of captopril in the chromatogram is 50% of full scale of the chart, the relative retention time for captopril is 1.0 and for captopril disulfide is about 3.2. Inject accurately 20 μ l of solution (1) and solution (2), into the column respectively and record the chromatogram. The area of the peak of captopril disulfide in the chromatogram obtained with solution (1) is not greater than the area of the principal peak in the chromatogram obtained with solution (2).

Sulfate Carry out the limit test for sulfates (Appendix VIII B), using 1.0 g. Any opalescence produced is not more pronounced than that of a reference using 5.0 ml of potassium sulfate standard solution (0.05%).

Loss on drying When dried in vacuum over phosphorous pentoxide to constant weight at 60°C, loses not more than 0.5% of its weight (Appendix VIII L).

Residue on ignition Not more than 0.1% (Appendix VIII N), using 2.0 g.

Heavy metals To the residue obtained in the test for Residue on ignition add 1 ml of nitric acid, evaporate to dryness and expel completely the nitrogen oxide vapor. Add 2 ml of hydrochloric acid and evaporate to dryness on a water bath. Add 5 ml of water and evaporate to dryness again. Dissolve the residue in a mixture of 15 ml of water and 4 ml of sodium acetate BS (pH 3.5) by warming, dilute with water to 50 ml and mix well. Carry out the limit test for heavy metals (Appendix VIII H, method 1), using 25 ml of the resulting solution; not more than 0.002%.

Zinc Transfer the remaining 25 ml of the solution obtained in the test for Heavy metals to a 50 ml Nessler cylinder, add 4 ml of hydrochloric acid solution (1 \rightarrow 2) and 3 ml of potassium ferrous TS, dilute with water to volume and mix well. Any opalescence produced is not more pronounced than that of a reference using 3.0 ml of zinc standard solution (dissolve 44 mg, weighed accurately, of zinc sulfate in water in a 100 ml volumetric flask, dilute with water to volume and mix well; measure accurately 10 ml to another 100 ml volumetric flask, dilute with water to volume and mix well. Each ml is equivalent to 10 μ g of Zn) prepared in the same manner (0.003%).

Assay Dissolve about 0.3 g, weighed accurately, in 100 ml of water with shaking, add 10 ml of dilute sulfuric acid, 1.0 g of potassium iodide and 2 ml of starch TS. Titrate with potassium iodate (0.01667 mol/L) VS until a pale blue colour appears and persists for 30 seconds. Perform a blank determination and make any necessary correction. Each ml of potassium iodate (0.01667 mol/L) VS is equivalent to 21.73 mg of $C_9H_{15}NO_3S$.

Category Antihypertensive.

Storage Preserve in tightly closed containers, protected from light.

Preparation Captopril Tablets

Captopril Tablets

Captopril Tablets contain not less than 90.0% and not more than 110.0% of the labelled amount of captopril ($C_9H_{15}NO_3S$).

Description White or almost white tablets or sugar coated or film coated tablets with white or almost white core.

Identification Dissolve a quantity of the powdered tablets equivalent to about 50 mg of captopril in ethanol and filter. The filtrate complies with test (1) for Identification described under Captopril.

Captopril disulfide Protect from light throughout the procedure. To a quantity of the powdered tablets, weighed accurately, equivalent to about 25 mg of captopril in a 50 ml volumetric flask, add a quantity of the mobile phase and ultrasonicate it for 15 minutes. Cool to room temperature, dilute to volume with the mobile phase and mix well. Filter, using the successive filtrate as the test solution (use it within 8 hours). To a quantity of captopril CRS add methanol to produce a solution of 0.1 mg per ml (solution 1). To a quantity of captopril disulfide CRS add methanol to produce a solution of 0.5 mg per ml (solution 2). Transfer 1 ml of solution (1) and 3 ml of solution (2) to a 100 ml

volumetric flask, dilute to volume with the mobile phase and mix well, using the resulting solution as reference solution. Carry out the method for high performance liquid chromatography (Appendix V D), using a column packed with octadecylsilane bonded silica gel and a mixture of 0.01 mol/L disodium hydrogen phosphate solution-methanol-acetonitrile (70 : 25 : 5) as the mobile phase, adjust pH to 3.0 ± 0.05 with phosphoric acid. Detection wavelength is 215 nm, maintain the temperature of the column at 60°C and the flow rate 1.5 ml per minute. Inject accurately 50 μ l of the reference solution into the column, adjust the attenuation so that the peak height of captopril disulfide in the chromatogram is about 50% of full scale of the chart, the relative retention time for captopril is 1.0 and for captopril disulfate is about 3.4. Inject accurately 50 μ l of the test solution and the reference solution into the column respectively and record the chromatogram. The area of the peak of captopril disulfide in the chromatogram obtained with the test solution is not greater than the area of the principal peak in the chromatogram obtained with the reference solution.

Dissolution Carry out the dissolution test (Appendix X C, method 3), using 250 ml of water as the dissolution medium, adjust the rotational speed of the paddle to 75 rpm. Withdraw the solution at 20 minutes (45 minutes, if the tablets are sugar coated) and filter, transfer the successive filtrate as the test solution. Dissolve an accurately weighed quantity of captopril CRS in water and dilute to produce a solution with the same concentration as the test solution as the reference solution. Carry out the method for the Test described under captopril disulfide, inject accurately measured 20 μ l each of the resulting solutions into the column and record the chromatogram, calculate the dissolution of $C_9H_{15}NO_3S$ from each tablet. Not less than 80% of the labelled amount is dissolved.

Other requirements Comply with the general requirements for tablets (Appendix I A).

Assay Weigh accurately and powder 50 tablets (25 mg) or 100 tablets (12.5 mg) with sugar coating removed. Weigh accurately a quantity of the powdered tablets equivalent to about 0.45 g of captopril, add 100 ml of water and shake for 30 minutes to dissolve captopril. Carry out the Assay described under Captopril, beginning at the words "add 10 ml of dilute sulfuric acid...". Each ml of potassium iodate (0.01667 mol/L) VS is equivalent to 21.73 mg of $C_9H_{15}NO_3S$.

Category As described under Captopril.

Strength (1) 12.5 mg (2) 25 mg

Storage Preserve in tightly closed containers, protected from light.

Compound Captopril Tablets

Compound Captopril Tablets contain not less than 9.0 mg and not more than 11.0 mg of captopril ($C_9H_{15}NO_3S$), and not less than 5.4 mg and not more than 6.6 mg of hydrochlorothiazide ($C_7H_8ClN_3O_4S_2$) in each tablet.

Formula	Captopril	10 g
	Hydrochlorothiazide	6 g
	Excipient	a quantity
	To make	1000 tablets

Description White or almost white tablets.

Identification (1) Shake thoroughly 1 powdered tablet with 5 ml of water, add a quantity of alkaline sodium nitroprusside TS, a purple colour is produced.

(2) Shake thoroughly 3 powdered tablets with 15 ml of water to dissolve captopril, filter. Dry the residul and put into a test-tube, add 10 ml of sodium hydroxide TS shake to dissolve hydrochlorothiazide. Filter, boil 3 ml of the filtrate for 5 minutes and allow to cool to room temperature. Add 5 ml of chromotropic acid TS and heat on a water bath, a bluish violet colour is produced.

Content uniformity Comply with the requirements (Appendix X E).

Captopril To 1 tablet in a conical flask with stopper add 50 ml of water and shake vigorously for about 30 minutes to dissolve captopril. Add 5 ml of diluted sulfuric acid, then add 0.5 g of potassium iodide and 2 ml of starch IS, titrate with potassium iodate (0.001667 mol/L) VS until the colour changes to pale blue lasting for 30 seconds. Perform a blank determination and make any necessary correction. Each ml of potassium iodate (0.001667 mol/L) VS is equivalent to 2.173 mg of $C_9H_{15}NO_3S$.

Hydrochlorothiazide Place 1 tablet in a 250 ml volumetric flask, proceed as described under Hydrochlorothiazide in Assay beginning at the words "add a quantity of warmed hydrochloric acid solution (dilute 24 ml of dilute hydrochloric acid with water to 1000 ml)...", calculate the content of $C_7H_8ClN_3O_4S_2$.

Dissolution Hydrochlorothiazide Carry out the dissolution test (Appendix X C, method 1), using 1000 ml of hydrochloric acid solution (dilute 24 ml of dilute hydrochloric acid with water to 1000 ml) as the dissolution medium, adjust the rotational speed of the basket to 150 rpm. Withdraw 10 ml of the solution at 30 minutes and filter. Measure the absorbance of the successive filtrate at 272 nm (Appendix IV A). Calculate the dissolution of $C_7H_8ClN_3O_4S_2$ from each tablet, taking 640 as the value of A (1%, 1 cm); not less than 60% of the labelled amount is dissolved.

Other requirements Comply with the general requirements for tablets (Appendix I A).

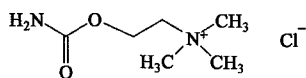
Assay Captopril Weigh accurately and powder 70 tablets. To an accurately weighed quantity of the powdered tablets equivalent to about 0.3 g of captopril in a conical flask with stopper add 100 ml of water, shake for 30 minutes to dissolve captopril. Add 10 ml of diluted sulfuric acid, 1 g of potassium iodide and 2 ml of starch IS, titrate with potassium iodate (0.01667 mol/L) VS until the colour changes to pale blue lasting for 30 seconds. Perform a blank determination and make any necessary correction. Each ml of potassium iodate (0.01667 mol/L) VS is equivalent to 21.73 mg of $C_9H_{15}NO_3S$.

Hydrochlorothiazide To an accurately weighed quantity of the above powdered tablets equivalent to about 12 mg of hydrochlorothiazide in a 500 ml volumetric flask add a quantity of warmed hydrochloric acid solution (dilute 24 ml of diluted hydrochloric acid with water to 1000 ml), shake for 30 minutes, allow to cool and dilute to volume, mix well and filter. Transfer 10 ml of the successive filtrate, accurately measured, to a 25 ml volumetric flask, dilute to volume and mix well. Measure the absorbance of the resulting solution at 272 nm (Appendix IV A), calculate the content of $C_7H_8ClN_3O_4S_2$, taking 640 as the value of A (1%, 1 cm).

Category Antihypertensive.

Storage Preserve in tightly closed containers, stored in a dry place at a temperature below 30°C and protected from light.

Carbachol



$C_6H_{15}ClN_2O_2$ 182.65

Carbachol is 2-[(Aminocarbonyl)oxy]-N, N, N-tri-methylethanaminium chloride. It contains not less than 99.0% of $C_6H_{15}ClN_2O_2$, calculated on the dried basis.

Description A white crystals; hygroscopic. Very soluble in water; sparingly soluble in ethanol; practically insoluble in chloroform and ether.

Melting range 200–204°C, with decomposition (Appendix VI C).

Identification (1) To about 50 mg, add 10 ml of ethanolic potassium hydroxide solution, heat gently to boil for 1–2 minutes, a white precipitate and ammonia odour are produced. Discard the supernatant liquid and add a few drops of 3 mol/L hydrochloric acid solution. Bubble is produced.

(2) The infrared absorption spectrum (Appendix IV C) is concordant with the reference spectrum of carbachol (Appendix XVI).

(3) Yield the reactions characteristic of chlorides (Appendix III).

Loss on drying When dried to constant weight at 105°C, loses not more than 2.0% of its weight (Appendix VIII L).

Residue on ignition Not more than 0.1% (Appendix VIII N).

Assay Dissolve about 0.15 g, accurately weighed, in 10 ml of glacial acetic acid and 10 ml of perchloric acid TS, add 2 drops of crystal violet IS, titrate with perchloric acid (0.1 mol/L) VS until the colour change to blue. Perform a blank determination and make any necessary correction. Each ml of perchloric acid (0.1 mol/L) VS is equivalent to 18.27 mg of $C_6H_{15}ClN_2O_2$.

Category M choline receptor excitomotor.

Storage Preserve in well closed containers.

Preparation Carbachol Injection

Carbachol Injection

Carbachol Injection is a sterile solution of Carbachol in Water for Injection. It contains not less than 90.0% and not more than 115.0% of the labelled amount of carbachol ($C_6H_{15}ClN_2O_2$).

Description A clear, colourless liquid.

Identification To 5 ml, add 1 ml of 1 mol/L sodium hydroxide solution and 2 ml of 0.2% hexanitrodiphenylamine, mix well. Add 15 ml of dichloromethane, shake for 1 minute, allow to separate, an amber colour is produced in dichloromethane layer.

pH value 5.5–7.5 (Appendix VI H).

Other requirements Complies with the general requirements for injections (Appendix I B)

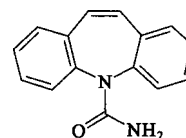
Assay Take the injection as test solution. Dissolve a quantity of carbachol CRS, accurately weighed, in water to produce a solution of 0.1 mg per ml as the reference solution. Transfer 2 ml each of the test solution and the reference solution, accurately measured, to two 50 ml iodine flasks, add 1.0 ml of 0.1 mol/L hydrochloric acid solution, mix well, add 4.0 ml of sodium hypochlorite TS (dilute one volume of sodium hypochlorite solution to 15 volumes with water, allow to stand for 30 minutes, mix with equal volume of 1 mol/L sodium hydroxide solution. Prepared before use), wash the inner wall with water, mix well, allow to stand for 15 minutes (accurately), add 2.0 ml of 0.5% phenol solution, wash the inner wall with a quantity of water, mix well. Stand for 5 minutes. Add 2.0 ml of 3.5 mol/L hydrochloric acid solution, wash the inner wall with 0.1 mol/L hydrochloric acid solution and acidify the solution obviously, mix well. Add 1.0 ml of 0.3% potassium iodide solution, mix well, allow to stand for 5 minutes. Add 3.0 ml of starch IS, mix well. Transfer separately the above solutions in 50 ml volumetric flask, wash the iodine flask with a quantity of water, transfer the washings to the same volumetric flask, dilute with water to volume, mix well. Measure the absorbance at 590 nm (Appendix IV A). Calculate the content of $C_6H_{15}ClN_2O_2$.

Category As described under Carbachol.

Strength 1 ml : 0.1 mg

Storage Preserve in well closed containers.

Carbamazepine



$C_{15}H_{12}N_2O$ 236.27

[298-64-4]

Carbamazepine is 5H-dibenz [b, f] azepine-5-carboxamide. It contains not less than 97.0% and not more than 103.0% of $C_{15}H_{12}N_2O$, calculated on the dried basis.

Description A white or almost white crystalline powder; almost odourless.

Freely soluble in chloroform; sparingly soluble in ethanol; practically insoluble in ether or water.

Melting range 189–193°C (Appendix VI C).

Identification (1) Heat 0.1 g with 2 ml of nitric acid in a water bath, an orange-red colour is produced.

(2) The light absorption of a solution of 10 µg per ml in ethanol exhibits maxima at 238 nm and 285 nm (Appendix IV A), the absorbance at 285 nm is 0.47–0.51.

(3) The infrared absorption spectrum (Appendix IV C) is concordant with the reference spectrum of carbamazepine (Appendix XVI).

Acidity or alkalinity Stir 1.0 g in 20 ml of freshly boiled and cooled water for 15 minutes, filter. Add 1 drop of phenolphthalein IS to 10 ml of the successive filtrate and titrate with sodium hydroxide (0.01 mol/L) VS, not more than 0.50 ml is required. Then titrate with hydrochloric acid (0.01 mol/L) VS, using 3 drops of methyl red IS as indicator, not more than 1.0 ml is required.

Chlorides Boil 1.0 g in 100 ml of water, boil, cool to room

temperature and filter. Carry out the limit test for chlorides (Appendix VIII A), using 50 ml of the successive filtrate. Any opalescence produced is not more pronounced than that of a reference using 7.0 ml of sodium chloride standard solution (0.014%).

Related substances Carry out the method for thin-layer chromatography (Appendix V B), using silica gel G as the coating substance and a mixture of chloroform-cyclohexane-methanol (5 : 4 : 1) as the mobile phase. Apply separately to the plate 10 μ l each of two solutions of the substance being examined in chloroform containing (1) 25 mg per ml and (2) 0.25 mg per ml. After developing and removal of the plate, dry it in air. Spray with a 0.5% solution of potassium dichromate in 20% (ml/ml) sulfuric acid, dry it in air and examine under ultraviolet light (365 nm). Any spot other than the principal spot in the chromatogram obtained with solution (1) is not more intense than the principal spot obtained with solution (2).

Loss on drying When dried at 105°C for 2 hours, loses not more than 0.5% of its weight (Appendix VIII L).

Residue on ignition Not more than 0.1% (Appendix VIII N).

Assay Dissolve an accurately weighed quantity in ethanol to produce a solution of about 10 μ g per ml and measure the absorbance at 285 nm (Appendix V H). Repeat the operation using carbamazepine CRS instead of the substance being examined and calculate the content of $C_{15}H_{12}N_2O$.

Category Anticonvulsant and analgesic agent.

Storage Preserve in tightly closed containers, protected from light.

Preparation (1) Carbamazepine Capsules
(2) Carbamazepine Tablets

Carbamazepine Capsules

Carbamazepine Capsules contain not less than 90.0% and not more than 110.0% of the labelled amount of carbamazepine ($C_{15}H_{12}N_2O$).

Identification The contents of carbamazepine capsules comply with tests (1) and (2) for Identification described under Carbamazepine.

Dissolution Carry out the dissolution test (Appendix X C, method 1), using 24 ml of dilute hydrochloric acid diluted with water to 1000 ml as the dissolution medium, adjust the rotational speed of the paddle to 150 rpm. Withdraw 10 ml of the solution at 60 minutes and filter. Dilute an accurately measured quantity of the successive filtrate with the dissolution medium to produce a solution containing 6-15 μ g of carbamazepine per ml and measure the absorbance at 285 nm (Appendix IV A). Calculate the dissolution of $C_{15}H_{12}N_2O$ from each capsule, taking 518 as the value of A (1%, 1 cm); not less than 65% of the labelled amount is dissolved.

Other requirements Comply with the general requirements for capsules (Appendix I E).

Assay Weigh accurately a quantity of the mixed contents obtained in the test for weight variation, equivalent to about 50 mg of carbamazepine. Carry out the Assay described under Carbamazepine tablets, beginning at the words "in a 50 ml volumetric flask".

Category As described under Carbamazepine.

Strength 0.2 g

Storage Preserve in tightly closed containers, protected from light.

Carbamazepine Tablets

Carbamazepine Tablets contain not less than 90.0% and not more than 110.0% of the labelled amount of carbamazepine ($C_{15}H_{12}N_2O$).

Description White tablets.

Identification Comply with tests (1) and (2) for Identification described under Carbamazepine, using a quantity of powdered tablets.

Dissolution Carry out the dissolution test (Appendix X C, method 2), using 24 ml of dilute hydrochloric acid diluted with water to 1000 ml as the dissolution medium, adjust the rotational speed of the paddle to 150 rpm. Withdraw 10 ml of the solution at 60 minutes and filter. Dilute an accurately measured quantity of the successive filtrate, with the dissolution medium to produce a solution containing 6-15 μ g of carbamazepine per ml and measure the absorbance at 285 nm (Appendix IV A). Calculate the dissolution of $C_{15}H_{12}N_2O$ from each tablet, taking 518 as the value of A (1%, 1 cm), not less than 65% of the labelled amount is dissolved.

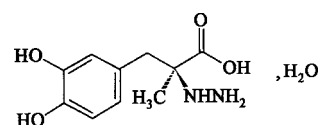
Other requirements Comply with the general requirements for tablets (Appendix I A).

Assay Weigh accurately and powder 20 tablets. Weigh accurately a quantity of the powder equivalent to about 50 mg of carbamazepine in a 50 ml volumetric flask and add about 40 ml of ethanol. Heat in a water bath with shaking to dissolve carbamazepine, cool. Add ethanol to volume, mix well and filter with a dry filter paper. Measure accurately 2 ml of successive filtrate into 200 ml volumetric flask and dilute above solution with the hydrochloric acid dilute 24 ml of dilute hydrochloride acid solution to 1000 ml with water to the volume, mix well. Measure the absorbance at 285 nm (Appendix IV A) and calculate the content of $C_{15}H_{12}N_2O$, taking 518 as the value of A (1%, 1 cm).

Category, Storage As described under Carbamazepine.

Strength (1) 0.1 g (2) 0.2 g

Carbidopa



$C_{10}H_{14}N_2O_4 \cdot H_2O$ 244.25

Carbidopa is benzenepropanoic acid, α -hydrazino-3,4-dihydroxy- α -methyl-mono-hydrate, (S)-. It contains not less than 99.0% of $C_{10}H_{14}N_2O_4$, calculated on the anhydrous basis.

Description A white or almost white crystalline powder; almost odourless.

Slightly soluble in water or methanol, practically insoluble in ethanol or chloroform; freely soluble in dilute hydrochloric acid.

Specific optical rotation -21.0° to -23.5° , in a solution of 10 mg per ml in aluminium trichloride solution (Dissolve 40

g of aluminium trichloride and dilute to 60 ml, shake, add 0.5 g of active carbon if any colour produced, stir for 10 minutes, filter, adjust the pH value to 1.5 with 10% sodium hydroxide solution, by shaking in a heat water bath and allow to cool to room temperature (Appendix VI E).

Specific absorbance Measure the absorbance of a solution of 50 µg per ml in 0.1 mol/L hydrochloric acid solution at 281 nm (Appendix IV A), the value of A (1%, 1 cm) is 117-129.

Identification The infrared absorption spectrum (Appendix IV C) is concordant with the reference spectrum of Carbidopa (Appendix XVI).

Related substances Carry out the method for thin-layer chromatography (Appendix V B), using silica gel G as the coating substance and a mixture of butanol-toluene-butanone-pyridine-glacial acetic acid water (1 : 3 : 3 : 1 : 1.5 : 0.8) as the mobile phase. Apply separately to the plate 10 µl of each of four solutions in 1% hydrochloric acid methanol solution containing (1) 10 mg per ml, (2) 50 µg per ml, (3) 100 µg per ml and (4) 150 µg per ml of the substance being examined. After developing and removal of the plate, dry it in air and expose in iodine vapour for 15 minutes. The number of the spots apart from principal spot obtained with solution (1) is not more than 2. Any secondary spot in the chromatogram obtained with the solution (1) is not more intense than the principal spots obtained with solutions (2), (3) and (4), the total amount of impurities does not exceed 2.0%.

Water 6.9%-7.9% (Appendix VIII M, method 1 A).

Residue on ignition Not more than 0.1% (Appendix VIII N), using 1.0 g.

Heavy metals Carry out the limit test for heavy metals (Appendix VIII H, method 2), using the residue obtained in the test for Residue on ignition; not more than 0.001%.

Assay Dissolve 0.25 g of the substance being examined, accurately weighed, with exact 15 ml of perchloric acid (0.1 mol/L) VS. Add 15 ml of acetic anhydride and 2 drops of crystal violet IS. Titrate with sodium acetate (0.1 mol/L) VS until green colour is produced. Perform a blank determination and make any necessary correction. Each ml of perchloric acid (0.1 mol/L) VS is equivalent to 22.62 mg $C_{10}H_{14}N_2O_4$.

Category Decarboxylase inhibitor.

Storage Preserve in tightly closed container, protected from light.

Preparation Carbidopa Tablets

Carbidopa Tablets

Carbidopa Tablets contain not less than 90.0% and not more than 110.0% of the labelled amount of anhydrous carbidopa ($C_{10}H_{14}N_2O_4$).

Description Almost white tablets.

Identification (1) To a quantity of the powder, equivalent to about 10 mg of carbidopa, add 10 ml of methanol, shake, and filter, separately prepare 2 of the filtrate. To one solution add 1 ml each of the fresh 0.2% ferrous sulfate solution and 1% potassium sodium tartrate solution, and 20-40 mg of ammonium acetate. A bluish-purple colour is produced. Add one drop of concentrated ammonia solution, shake, then the purple colour is getting more intense. To another solution, add 0.5 ml of *p*-dimethylamino-

benzaldehyde solution (To 0.4 g of *p*-dimethylamino-benzaldehyde, add 0.1 mol/L sulfuric acid solution to 10 ml, an orange yellow colour is produced.

(2) The light absorption of the solution under Assay exhibits maximum at 281 nm (Appendix IV A).

Dissolution Carry out the dissolution test (Appendix X C, method 1), using 750 ml of 0.1 mol/L hydrochloric acid solution as the dissolution medium, adjust the rotational speed of the basket to 50 rpm. Withdraw a quantity of the solution at 30 minutes and filter. Carry out the method described under Assay, using above filtrate, beginning at the words "Measure the absorbance...". Calculate the dissolution of $C_{10}H_{14}N_2O_4$ from each tablet. Not less than 70% of the labelled amount is dissolved.

Other requirements Comply with the general requirements for tablets (Appendix I A).

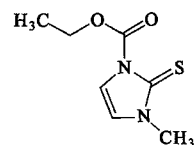
Assay Weigh accurately and powder 20 tablets. Transfer a quantity, accurately weighed, equivalent to about 50 mg of carbidopa, to a 100 ml volumetric flask, dissolve carbidopa with 0.1 mol/L hydrochloric acid solution and dilute to volume, shake and filter, measure accurately 5 ml of the successive filtrate to a 50 ml volumetric flask, dilute to volume with 0.1 mol/L hydrochloric acid solution, shake. Measure the absorbance of the resulting solution at 281 nm (Appendix IV A). Calculate the content of Carbidopa, taking 123 as the value of A (1%, 1 cm).

Category As described under Carbidopa.

Strength 25 mg (calculated as $C_{10}H_{14}N_2O_4$)

Storage Preserve in tightly closed container, protected from light.

Carbimazole



$C_7H_{10}N_2O_2S$ 186.23

[22232-54-8]

Carbimazole is ethyl 3-methyl-2-thio-2,3-dihydro-1H-imidazole-1-carboxylate. It contains not less than 98.5% of $C_7H_{10}N_2O_2S$, calculated on the dried basis.

Description A white or almost white crystalline powder; odour, characteristic; tasteless at first, followed by a bitter taste.

Freely soluble in chloroform; sparingly soluble in ethanol; slightly soluble in water or ether.

Melting point 122-125°C (Appendix VI C).

Identification (1) Dissolve 10 mg in 5 ml of water by warming, cool to room temperature and add 1 ml of dilute potassium iodobismuthate TS; a scarlet colour is produced.

(2) The light absorption of the solution obtained in Assay exhibits maxima at 227 nm and 292 nm (Appendix IV A).

(3) The infrared absorption spectrum (Appendix IV C) is concordant with the reference spectrum of carbimazole (Appendix XVI).

Thiamazole Carry out the method for thin-layer chromatography (Appendix V B), using silica gel G as the coating substance and a mixture of chloroform-acetone (4 : 1) as

the mobile phase. Apply separately to the plate 10 μ l each of two solutions in chloroform containing (1) 10 mg per ml of the substance being examined and (2) 50 μ g per ml of thiamazole CRS. After developing and removal of the plate, dry it in air and spray with dilute potassium iodobismuthate TS. Any spot in the chromatogram other than the principal spot obtained with solution (1) is not more intense than the principal spot obtained with solution (2) (0.5%).

Loss on drying When dried to constant weight at 80°C, loses not more than 0.5% of its weight (Appendix VIII L).

Residue on ignition Not more than 0.1% (Appendix VIII N).

Assay Transfer about 50 mg, accurately weighed, to a 500 ml volumetric flask, add water to dissolve it and then dilute to volume, mix well. Measure accurately 10 ml to a 100 ml volumetric flask, add 10 ml of hydrochloric acid solution (9→100), add water to volume and mix well. Measure the absorbance of the resulting solution at 292 nm (Appendix IV A) and calculate the content of $C_7H_{10}N_2O_2S$, taking 557 as the value of A (1%, 1 cm).

Category Antithyroid agent.

Storage Preserve in tightly closed containers.

Preparation Carbimazole Tablets

Carbimazole Tablets

Carbimazole Tablets contain not less than 90.0% and not more than 110.0% of the labelled amount of carbimazole ($C_7H_{10}N_2O_2S$).

Description White tablets.

Identification (1) Comply with test (1) for Identification described under Carbimazole, using a quantity of powdered tablets equivalent to about 10 mg of carbimazole. (2) The light absorption of the solution obtained in the Assay exhibits maxima at 227 nm and 292 nm (Appendix IV A).

Thiamazole Powder 20 tablets, with a quantity of chloroform, triturate to dissolve carbimazole, filter. Wash the filter with chloroform, combine the filtrate and washing into a 10 ml volumetric flask, dilute to volume with chloroform, mix well and use it as solution (1). Dissolve an accurately weighed quantity of thiamazole CRS in chloroform to produce a solution of 100 μ g per ml and use it as solution (2). Comply with the test for Thiamazole described under Carbimazole (1.0%).

Dissolution Carry out the dissolution test (Appendix X C, method 1), using 600 ml of hydrochloric acid solution (9→1000) as the dissolution medium, adjust the rotational speed of the basket to 50 rpm. Withdraw 5 ml of the solution at 45 minutes and filter. Measure the absorbance of the successive filtrate at 292 nm (Appendix IV A), and calculate the dissolution of $C_7H_{10}N_2O_2S$ from each tablet, taking 557 as the value of A (1%, 1 cm), not less than 75% of the labelled amount is dissolved.

Content uniformity Triturate 1 tablet in a mortar with a quantity of water. Transfer with 80 ml of water in portions to a 100 ml volumetric flask. Shake in a water bath at about 35°C for 5 minutes to dissolve the carbimazole. Cool to room temperature. Add water to volume, mix well and filter. Transfer 20 ml of the successive filtrate, accurately measured, to a 100 ml volumetric flask. Proceed as described in the Assay, beginning at the words "add 10 ml of hydrochloric acid solution...". Comply with the requirements (Appendix X E).

Other requirements Comply with the general requirements for tablets (Appendix I A).

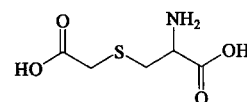
Assay Weigh accurately and powder 20 tablets. Weigh accurately a quantity of the powder equivalent to about 25 mg of carbimazole in a 250 ml volumetric flask and add about 100 ml of water. Shake thoroughly in a water bath at about 35°C for 5 minutes, cool to room temperature. Add water to volume, mix well and filter. Transfer 10 ml of the successive filtrate, accurately measured, to a 100 ml volumetric flask, add 10 ml of hydrochloric acid solution (9→100), dilute with water to volume and mix well. Measure the absorbance at 292 nm (Appendix IV A) and calculate the content of $C_7H_{10}N_2O_2S$, taking 557 as the value of A (1%, 1 cm).

Category As described under Carbimazole.

Strength 5 mg

Storage Preserve in tightly closed containers, protected from light.

Carbocysteine



$C_5H_9NO_4S$ 179.19

[2387-59-9]

Carbocysteine is S-(carboxymethyl)-cysteine. It contains not less than 98.0% and not more than 101.5% of $C_5H_9NO_4S$, calculated on the dried basis.

Description A white crystalline powder; odourless. Sparingly soluble in hot water; very slightly soluble in water; insoluble in ethanol or acetone; freely soluble in acid or alkaline solutions.

Specific optical rotation Dissolve about 5 g, accurately weighed, in 10 ml each of water and 5 mol/L sodium hydroxide solution, the solution is clear. Adjust pH value of the solution to 6.0 with 2 mol/L hydrochloric acid solution, transfer to a 50 ml volumetric flask, dilute with water to volume, mix well; -32.5° to -36.0° (Appendix VI E).

Identification (1) Dissolve about 50 mg in 5 ml of water on heating, add a few drops of ninhydrin TS and heat, a violet colour is produced.

(2) To about 0.1 g add 2 ml of sodium hydroxide TS, heat to boil, the odour of ammonia is perceived, the vapour turns moistened red litmus paper to blue; a black precipitate is produced on adding lead acetate TS.

(3) The infrared absorption spectrum (Appendix IV C) is concordant with the reference spectrum of carbocysteine (Appendix XVI).

Acidity A 1% suspension; pH 2.8-3.0 (Appendix VI H).

Clarity of solution Dissolve 0.50 g in 10 ml of 2 mol/L hydrochloric acid solution, the transmittance of the solution at 430 nm (Appendix IV A) is not less than 95.0%.

Cysteine Dissolve 0.20 g in 1 ml of 5% ammonia solution, add 3 ml of water and mix well, place in an ice water bath for 10 minutes, add 0.5 ml of 1% sodium nitroprusside solution and mix well, using the resulting solution as the test solution. To 1 ml of the solution containing 50 μ g of cysteine CRS per ml add 0.1 g of carbocysteine and 3 ml of water, then repeat the operation in the same manner as

described under the test solution, using the resulting solution as the reference solution. Any colour produced of the test solution is not more intense than that of the reference solution (0.05%).

Chlorides Dissolve 0.20 g in 10 ml of dilute nitric acid, add water to produce 50 ml, carry out the limit test for chlorides (Appendix VIII A), using 10 ml of the solution. Any opalescence produced is not more pronounced than that of a reference solution using 6.0 ml of sodium chloride standard solution (0.15%).

Loss on drying When dried at 105°C for 3 hours, loses not more than 0.5% of its weight (Appendix VIII L).

Residue on ignition Not more than 0.2% (Appendix VIII N), using 1.0 g.

Iron Dissolve 1.0 g in 10 ml of dilute hydrochloric acid, transfer to a 50 ml Nessler cylinder, add water to 25 ml, then add 50 mg of ammonium persulfate and dilute with water to 35 ml. Carry out the limit test for iron (Appendix VIII G). Any colour produced is not more intense than that of a reference solution using 1.0 ml of iron standard solution (0.001%).

Heavy metals Carry out the limit test for heavy metals (Appendix VIII H, method 2), using the residue obtained in the test for Residue on ignition; not more than 0.002%.

Assay Dissolve about 0.15 g, accurately weighed, in 10 ml of water and 4 ml of hydrochloric acid in a 250 ml conical flask. Add 20 ml of water and 1 drop of 0.05% methyl orange solution, titrate slowly with potassium bromate (0.01667 mol/L) VS at 18-25°C until the red colour disappears. Each ml of potassium bromate (0.01667 mol/L) VS is equivalent to 8.960 mg of $C_5H_9NO_4S$.

Category Mucolytic.

Storage Preserve in tightly closed containers, stored in a dry and cool place.

Preparation (1) Carbocysteine Granules
(2) Carbocysteine Oral Solution
(3) Carbocysteine Tablets

Carbocysteine Granules

Carbocysteine Granules contain not less than 90.0% and not more than 110.0% of the labelled amount of carbocysteine ($C_5H_9NO_4S$).

Description Orange-red to orange-yellow suspension granules; odour, fragrance; taste, sweet and feebly acid.

Identification (1) Comply with the test (1) for identification described under carbocysteine, using 0.1 g.
(2) Dissolve a quantity of the powdered granules equivalent to about 50 mg of carbocysteine, in 10 ml of 5% ammonia solution, filter. Use the filtrate as the test solution. Comply with the test (2) for identification described under carbocysteine tablets.

Other requirements Comply with the general requirements for granules (Appendix I N).

Assay Weigh accurately a quantity of mixed contents obtained in the test for weight variation equivalent to about 0.15 g of carbocysteine, carry out the method described under Carbocysteine, calculate the content of $C_5H_9NO_4S$.

Category As described under carbocysteine.

Strength (1) 0.2 g (2) 0.5 g

Storage Preserve in tightly closed containers, stored in a dry and cool place.

Carbocysteine Oral Solution

Carbocysteine Oral Solution contains not less than 90.0% and not more than 110.0% of the labelled amount of carbocysteine ($C_5H_9NO_4S$).

Description A brownish yellow to pale brown viscous liquid; taste, sweet; odour, aromatic.

Identification (1) Complies with the test (1) for identification described under Carbocysteine.

(2) Dilute a quantity with water to produce a solution containing 5 mg of carbocysteine per ml as the test solution. Dissolve 50 mg of carbocysteine CRS with 5% ammonia solution, using it as the reference solution. Carry out the thin-layer chromatography (Appendix V B), using silica gel G as the coating substance and a mixture of butanol-glacial acetic acid-water (6 : 2 : 2) as the mobile phase. Apply separately to the same plate 5 μ l each of above two solutions. After developing and removal of the plate, dry it in air, spray with 1% ninhydrin solution in butanol and heat. The colour and position of the principal spot in the chromatogram obtained with the test solution correspond to the principal spot obtained with the reference solution.

pH value 5.0-7.5 (Appendix VI H).

Other requirements Complies with the general requirements for oral solutions (Appendix I O).

Assay *Reference preparation* Dissolve an accurately weighed quantity of carbocysteine CRS in phosphate BS (pH 6.6) to produce a solution of 200 μ g per ml.

Test preparation Measure accurately a quantity of the mixed contents obtained from 10 containers, dilute with phosphate BS (pH 6.6) to produce a solution of 200 μ g per ml.

Procedure Transfer 2.0 ml each of the two solutions, accurately measured, to 50 ml volumetric flask separately, add accurately 1 ml of 2% ninhydrin solution and 2 ml of phosphate BS (pH 6.6) and mix well. Heat on a boiling water bath for 15 minutes, cool quickly to room temperature, dilute with water to volume, and mix well. Measure the absorbance at 567 nm (Appendix VI A). calculate the content of $C_5H_9NO_4S$.

Category As described under Carbocysteine.

Strength (1) 10 mg : 0.2 g (2) 10 ml : 0.5 g

Storage Preserve in tightly closed containers, stored in a cool place, protected from light.

Carbocysteine Tablets

Carbocysteine Tablets contain not less than 93.0% and not more than 107.0% of the labelled amount of carbocysteine ($C_5H_9NO_4S$).

Description White tablets.

Identification (1) Comply with the test (1) for Identification described under Carbocysteine, using 0.1 g of the powdered tablets.

(2) Dissolve a quantity of powdered tablets equivalent to about 50 mg of carbocysteine in 10 ml of 0.5% ammonia solution to produce a solution as the test solution. Dissolve 50 mg of carbocysteine CRS with 5% ammonia solution, using it as the reference solution. Carry out the thin-layer chromatography (Appendix V B), using silica gel G as the coating substance and a mixture of butanol-glacial acetic acid-water (6 : 2 : 2) as the mobile phase. Apply separately to the same plate 10 μ l each of above two solutions. After developing and removal of the plate, dry it in air, spray with 1% ninhydrin solution in butanol and heat. The colour and position of the principal spot in the chromatogram obtained with the test solution correspond to the principal spot obtained with the reference solution.

Dissolution Comply with the requirements for dissolution test (Appendix X C, method 1), using 1000 ml of phosphate BS (pH 6.6) as the dissolution medium, adjust the rotational speed of the paddle to 100 rpm. Withdraw 10

successive filtrate as the test solution. Dissolve about 12.5 mg of the carbocysteine CRS, accurately weighed, in the dissolution medium in a 50 ml volumetric flask and dilute to volume, mix well, as the reference solution. Transfer 2 ml (for strength 0.25 g) or 5 ml (for strength 0.1 g) of the test solution and 2 ml of the reference solution to 50 ml volumetric flask, add 2 ml of 2% ninhydrin solution and 2 ml of dissolution medium, mix well, and warm for 15 minutes in a water bath, cool to room temperature, dilute with water to volume and mix well. Measure the absorbance of the resulting solution at 567 nm (Appendix IV A), calculate the dissolution of carbocysteine from each tablet.

Other requirements Comply with the general requirements for tablets (Appendix I A).

Assay Weigh accurately and powder 10 tablets. Transfer an accurately weighed quantity of the powder equivalent to about 0.15 g of carbocysteine, carry out the method described under Carbocysteine, beginning at the words "in 10 ml of water and 4 ml of hydrochloric acid in a 250 ml conical flask...". Calculate the content of $C_5H_9NO_4S$.

Category As described under Carbocysteine.

Strength (1) 0.1 g (2) 0.25 g

Storage Preserve in tightly closed containers, stored in a dry and cool place.

Carbon Dioxide

CO₂ 44.01 [124-38-9]

Carbon Dioxide contains not less than 99.0% (ml/ml) of CO₂.

Description A colourless gas; odourless. The aqueous solution exhibits weak acid reaction.

Soluble in about 1 volume of water at normal pressure and 20°C.

Identification (1) On passing into barium hydroxide TS, a white precipitate is produced which dissolves in acetic acid with effervescence.

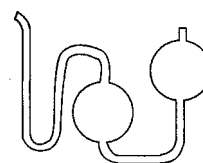
(2) Extinguishes a flame.

Acidity Add 0.2 ml of methyl orange IS to 100 ml of freshly boiled and cooled water and mix well. Transfer 50 ml each of the solution to Nessler cylinder (A) and (B). To cylinder (B) add 1.0 ml of hydrochloric acid (0.01 ml/L) VS and into cylinder (A) pass 1000 ml of the gas being examined at

a flow rate of 4000 ml/hr. The red colour in cylinder (A) is not more intense than that in cylinder (B).

Carbon monoxide, Phosphine, Hydrogen sulfide and Organic reducing substances To Nessler cylinder (A) and (B) add 25 ml of warm ammoniated silver nitrate TS and 3 ml of ammonia TS. Pass 1000 ml of the gas being examined into cylinder (A) at a flow rate of 4000 ml/hr. The resulting solution is clear and colourless compared with the solution in cylinder (B).

Assay Complete the Assay described under Oxygen, using the absorber shown in the figure and 125 ml of potassium hydroxide solution (1→2) as the absorbing liquid instead of copper wire and ammonia-ammonium chloride solution. Transfer acidified water (to methyl orange) into the reservoir, instead of saturated sodium chloride solution until the volume of the residual gas is constant. Measure the volume of the residual gas in the burette and calculate the content of CO₂.

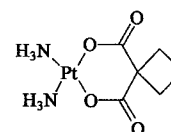


The metal cylinder containing Carbon Dioxide must be kept at room temperature for at least 6 hours before the determination.

Category Respiration center stimulant.

Storage Kept under compression in approved metal cylinder.

Carboplatin



$C_6H_{12}N_2O_4Pt$ 371.26

Carboplatin is *cis*-diammine [cyclobutane-1,1-dicarboxylato (2-)-O,O'] platinum. It contains not less than 98.0% and not more than 102.0% of the labelled amount of $C_6H_{12}N_2O_4Pt$, calculated on the dried basis.

Description A white powder or crystalline powder; odourless.

Sparingly soluble in water; insoluble in ethanol, acetone, chloroform or ether.

Identification (1) To about 5 mg add a little of thiourea and a quantity of water, the solution turns to yellow on heating. (2) Dissolve a quantity in water to produce a solution of about 1 mg per ml, add 3 drops of 2 mol/L sulfuric acid solution, heat to boiling, add 2 drops of mercuric potassium iodide TS, a yellow colour is produced, which turns to redish brown immediately, and then to pale blue, purple and a black precipitate is produced on standing for 5 minutes. (3) To 25 mg on a evaporating dish add 2 ml of chlorinated sulfoxide, stir thoroughly, evaporate on a water bath to dryness, add 2 ml of ethanol solution saturated with oxammonium hydrochloride, and 0.5% sodium hydroxide ethanol solution to make alkaline, heat, cool, add dilute sulfuric acid to make the solution acidic, to the supernatant

add several drops of ferric chloride TS, the solution turns to brownish red or purple.

(4) The infrared absorption spectrum (Appendix IV C) is concordant with the reference spectrum of carboplatin (Appendix XVI).

Clarity of solution Dissolve 80 mg in 10 ml of water, the solution is clear.

Acidity or alkalinity pH 5.5-7.5 (Appendix VI H), using the solution obtained in the test for Clarity of solution.

Related substances Dissolve a quantity of the substance being examined in water to produce solutions of 1 mg per ml (solution 1) and 10 µg per ml (solution 2). Carry out the method as described under the Assay. Inject 10 µl of solution (2) into the column, adjust the attenuation so that the principal peak height in the chromatogram is 20%-25% of the full scale of the chart. Inject separately 10 µl of above two solutions, and record the chromatogram for three times the retention time of the principal peak. The sum of the areas of all peaks other than the principal peak in the chromatogram obtained with solution (1) is not greater than twice the area of the principal peak in the chromatogram obtained with solution (2).

Acid soluble barium Dissolve 80 mg in 10 ml of water, add 2 ml of dilute hydrochloric acid, heat to boiling for 5 minutes, replenish the evaporated water, cool to room temperature, filter through a filter paper moistened with hydrochloric acid solution (1 → 40), wash the residue and the funnel with a quantity volume (about 2 ml) of water, combine the washings and the filtrate, add 0.5 ml of dilute sulfuric acid, allow to stand for 30 minutes, no precipitate is produced.

Loss on drying When dried to constant weight at 105°C, loses not more than 0.5% of its weight (Appendix VIII L).

Assay Carry out the method for high performance liquid chromatography (Appendix V D), using a column packed with octadecylsilane bonded silica gel and water as the mobile phase, flow rate is 2 ml per minute, detection wavelength is 229 nm and the number of the theoretical plates of the

peak of carboplatin. The resolution factor between the peaks of carboplatin and internal standard complies with the related requirements.

Internal standard solution Dilute about 25 mg of ferritin, accurately weighed, in water in a 25 ml volumetric flask and dilute to volume, mix well.

Procedure Dissolve about 25 mg, accurately weighed, in water in a 25 ml volumetric flask and dilute to volume, mix well. Measure accurately 5 ml each of the test solution and the internal standard solution to a 25 ml volumetric flask, dilute with water to volume, mix well, inject 10 µl of the resulting solution into the column, and record the chromatogram. Repeat the operation, using carboplatin CRS instead of the substance being examined, calculate the content of $C_6H_{12}N_2O_4Pt$ with respect to the peak area obtained in the chromatogram by the internal standard method.

Category Antineoplastic.

Storage Preserve in hermetically sealed containers, stored in a cool and dark place and protected from light.

Preparation Carboplatin for Injection

Carboplatin for Injection

Carboplatin for Injection is a sterile, lyophilized

preparation of carboplatin and an equal amount of dextran 40 or mannitol. It contains not less than 90.0% and not more than 110.0% of the labelled amount of $C_6H_{12}N_2O_4Pt$.

Description A white, friable mass or powder; odourless.

Identification Complies with tests (1), (2) and (3) for Identification described under carboplatin.

Clarity of solution A solution of 10 mg per ml in Water for Injection is clear.

Acidity or alkalinity pH 5.5-7.5 (Appendix VI H), using the solution obtained in test for Clarity of solution.

Related substances Complies with the test for Related substances described under carboplatin, using a solution of about 1 mg per ml in water.

Sterility Complies with the test for sterility (Appendix XI H), using a solution of 5 mg per ml in sterile water.

Pyrogens Complies with the test for pyrogens (Appendix XI D), using 1 ml of a solution of 5 mg per ml in Sodium Chloride Injection per kg of rabbit's weight.

Other requirements Complies with the general requirements for injections (Appendix I B).

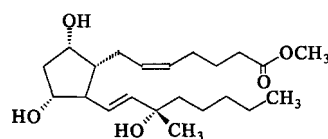
Assay Weigh accurately a quantity of the mixed contents in the test for weight variation, carry out the Assay described under Carboplatin.

Category As described under Carboplatin.

Strength (1) 50 mg (2) 100 mg

Storage Preserve in well closed containers, protected from light.

Carboprost Methylate



$C_{22}H_{38}O_5$ 382.54

[35700-21-1]

Carboprost Methylate is (Z)-7-[(1R,2R,3R,5S)-3,5-Dihydroxy-2-[(E)-(3S)-3-hydroxy-3-methyl-1-octenyl] cyclopentyl] -5-heptenoic acid methyl ester. It contains not less than 91.0% of $C_{22}H_{38}O_5$, calculated on the dried basis.

Description A white to pale yellow solid substance. Freely soluble in ether or ethanol; slightly soluble in water.

Identification (1) The retention time of the principal peak of Carboprost Methylate in the substance being examined in the chromatogram obtained in the Assay is identical with that of the principal peak of Carboprost Methylate CRS in the chromatogram of the reference solution.

(2) The infrared absorption spectrum (Appendix IV C) is concordant with the reference spectrum of Carboprost Methylate (Appendix XVI).

15-epimer Carry out the method for high performance liquid chromatography (Appendix V D), using the conditions described under Assay. Dilute the test solution under Assay with methanol to produce a pretest solution for about 8 mg per ml, inject 20 µl this solution into the column. Adjust

the attenuation so that the principal peak height in the chromatogram is about 10% of full scale of the chart. Then inject 20 μ l the test solution under Assay into the column, and record the chromatogram for twice the retention time of the principal peak. If there is the peak of 15-epimer in the chromatogram of the test solution, its area is not greater than 4.0% of that of the peak of carboprost methylate.

Loss on drying When dried in vacuum for 24 hours at room temperature, loses not more than 3.0% of its weight (Appendix VIII L).

Assay Carry out the method for high performance liquid chromatography (Appendix V D), using a column packed with octadecylsilane bonded silica gel and a mixture of methanol-water (70 : 30) as the mobile phase. Detection wavelength is 202 nm. Dissolve a quantity of 15-epimer CRS in the test solution to produce a solution of 0.2 mg each of 15-epimer and carboprost methylate per ml, and test with this solution. The number of theoretical plates of the column is not less than 2000, calculated with reference to the peak of carboprost methylate. The resolution factor between the peaks of 15-epimer and carboprost methylate is more than 1.2.

Test preparation and procedure Dissolve a quantity, accurately weighed, in methanol to produce a solution of 0.2 mg per ml. Inject 20 μ l of the resulting solution, accurately measured, into the column, record the peak area obtained in the chromatogram. Repeat the operation, using the carboprost methylate CRS instead of the substance being examined. Calculate the content of $C_{22}H_{38}O_5$ with respect to the peak area obtained in the chromatogram by the external standard method.

Category Prostaglandin.

Storage Preserve in tightly closed containers, stored at a temperature below -5°C and protected from light.

Preparation Carboprost Methylate Suppositories

Carboprost Methylate Suppositories

Carboprost Methylate Suppositories contain not less than 90.0% and not more than 110.0% of the labelled amount of carboprost methylate ($C_{22}H_{38}O_5$).

Description Creamy white to pale yellow suppositories.

Identification The retention time of the principal peak of the substance being examined in the chromatogram obtained in the Assay is identical with that of the principal peak of carboprost methylate CRS.

Other requirements Comply with the general requirements for suppositories (Appendix I D).

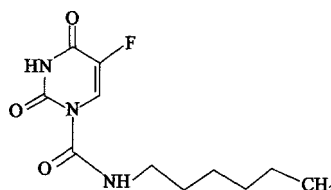
Assay Triturate 10 suppositories, accurately weighed, in an agate mortar and mix well. Weigh accurately a quantity, equivalent to about 2 mg of carboprost methylate, into a 10 ml volumetric flask, add methanol to volume, stopper tightly and sonicate in a water bath at 45°C for 3 minutes until carboprost methylate is solved, freeze in a refrigerator. Centrifuge after the suppository base has frozen and allow it to warm to room temperature. Use supernatant liquid as the test solution. Carry out the method described under the Assay of Carboprost Methylate. Calculate the content of $C_{22}H_{38}O_5$ with respect to the peak area obtained in the chromatogram by the external standard method.

Category As described under Carboprost Methylate.

Strength (1) 0.5 mg (2) 1 mg

Storage Preserve in well closed containers, stored at a temperature below -5°C and protected from light.

Carmofur



$C_{11}H_{16}FN_3O_3$ 257.26

[61422-45-5]

Carmofur is 5-fluoro-N-hexyl-3,4-dihydro-2,4-dioxopri-midine-1 (2H)-carboxamide. It contains not less than 98.5% and not more than 101.5% of $C_{11}H_{16}FN_3O_3$, calculated on the dried basis.

Description A white crystalline powder; odourless, tasteless. Very soluble in dimethylformamide; freely soluble in trichloromethane; slightly soluble in methanol, ethanol or benzene; practically insoluble in water.

Melting range $110-114^{\circ}\text{C}$, with decomposition (Appendix VI C).

Identification (1) Transfer about 1 ml of saturated solution of chromium trioxide in sulfuric acid to a test tube. Rotate the test tube, the solution is coated evenly on the wall; add about 2 mg of the substance being examined, heat gently, rotate the test tube, the solution can no longer be coated evenly on the wall, but attached to the wall with greasiness. (2) The light absorption of a solution of 10 μ g per ml in trichloromethane exhibits a maximum at 258 nm (Appendix IV A). (3) The infrared absorption spectrum (Appendix IV C) is concordant with the reference spectrum of carmofur (Appendix XVI).

Chlorides To 2.0 g add 100 ml of water, shake 15 minutes and filter. Measure 25 ml of the filtrate, carry out the limit test for chlorides (Appendix VIII A). Any opalescence produced is not more pronounced than that of a reference solution using 5.0 ml of sodium chloride standard solution (0.01%).

Sulfates Carry out the limit test for sulfates (Appendix VIII B), using 50 ml of the filtrate obtained in the test for Chlorides. Any opalescence produced is not more pronounced than that of a reference solution using 2.0 ml of potassium sulfate standard solution (0.02%).

Fluorine Weigh accurately about 30 mg and carry out the limit test for fluorides (Appendix VIII E). It contains not less than 6.6% and not more than 7.4% of fluorine.

Related substances Carry out the method for thin-layer chromatography (Appendix V B), using silica gel GF₂₅₄ as the coating substance and a mixture of toluene-acetone (5 : 3) as the mobile phase. Apply separately to the plate 15 μ l each of two solutions in a mixture of methanol-glacial acetic acid (99 : 1) containing (1) 20 mg per ml, (2) 0.1 mg per ml of the substance being examined, after developing and removal of the plate, dry it in air and examine under ultra-violet light 254 nm. Any spot in the chromatogram other than the principal spot obtained with the solution (1) is not more intense than the principal spot obtained with the solution (2).

Loss on drying When dried in vacuum over phosphorous

pentoxide to constant weight, loses not more than 0.3% of its weight (Appendix VIII L).

Heavy metals To 0.50 g add 20 ml of water, shake 15 minutes and filter. To the filtrate, add 2 ml of acetate BS (pH 3.5) and sufficient water to produce 25 ml. Carry out the limit test for heavy metals (Appendix VIII H, method 1), not more than 0.002%.

Assay Dissolve about 0.2 g, weigh accurately, in 10 ml of dimethylformamide, add 5 drops of 0.3% thymol blue in anhydrous methanol, titrate with tetrabutylammonium hydroxide (0.1 mol/L) VS until the colour changes to blue. Perform a blank determination and make any necessary correction. Each ml of tetrabutylammonium hydroxide VS is equivalent to 25.73 mg of $C_{11}H_{16}FN_3O_3$.

Category Antineoplastic.

Storage Preserve in tightly closed containers, protected from light.

Preparation Carmofur Tablets

Carmofur Tablets

Carmofur Tablets contain not less than 90.0% and not more than 110.0% of the labelled amount of carmofur ($C_{11}H_{16}FN_3O_3$).

Description White tablets.

Identification (1) Complies with the test (1) for Identification described under Carmofur. Using a quantity of the powdered tablets equivalent to about 10 mg of carmofur. (2) The light absorption of the solution obtained under the Assay exhibits maximum at 258 nm (Appendix IV A).

Dissolution Carry out the dissolution test (Appendix X C, method 1), using 24 ml of dilute hydrochloric acid and 210 ml of ethanol diluted with water to 1000 ml as the dissolution medium, adjust the rotational speed of the basket to 100 rpm. Withdraw the solution at 60 minutes and filter. Measure accurately 5 ml of the successive filtrate into a 25 ml volumetric flask, dilute to volume with the dissolution medium and mix well as the test solution. Dissolve an accurately weighed carmofur CRS in a quantity of ethanol, dilute with the dissolution medium to produce a solution of about 8 µg per ml as the reference solution. Measure the absorbances of the test solution and the reference solution at 260 nm. Calculate the dissolution of $C_{11}H_{16}FN_3O_3$ from each tablet. Not less than 70% of the labelled amount is dissolved.

Other requirements Comply with the general requirements for tablets (Appendix I A).

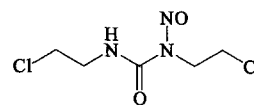
Assay Weigh accurately and powder 20 tablets. Weigh accurately a quantity of the powder, equivalent to about 30 mg of carmofur, into a 100 ml volumetric flask, dissolve carmofur with a quantity of trichloromethane and dilute with the same solvent to volume, shake thoroughly and filter. Measure accurately 2 ml of the successive filtrate into a 50 ml volumetric flask, dilute to volume with trichloromethane, mix well. Measure the absorbance of the solution at 258 nm (Appendix IV A), calculate the content of $C_{11}H_{16}FN_3O_3$, taking 454 as the value of A (1%, 1 cm).

Category As described under Carmofur.

Strength 50 mg

Storage Preserve in tightly closed containers, and protected from light.

Carmustine



$C_5H_9Cl_2N_3O_2$ 214.05

[154-93-8]

Carmustine is 1,3-bis (α -chloroethyl) -1-nitrosourea. It contains not less than 96.0% and not more than 101.0% of $C_5H_9Cl_2N_3O_2$, calculated on the dried basis.

Description Colourless to pale yellow or pale yellowish green crystals or a crystalline powder; odourless. Soluble in methanol or ethanol; insoluble in water.

Melting point 30-32°C, with decomposition (Appendix VI C).

Identification (1) To about 50 mg add 5 ml of 0.5 mol/L sodium hydroxide solution, heat on a water bath for 5 minutes, shake thoroughly to dissolve carmustine, add 1 drop of phenolphthalein IS and nitric acid solution (1→2) dropwise until the colour disappears, then add 1 ml of 0.1 mol/L silver nitrate solution, a white precipitate is produced.

(2) To a quantity add water to produce a solution of 10 µg per ml. To 2 ml of the solution add 1 ml of sulfanilamide solution prepared by dissolving 50 mg of sulfanilamide in 10 ml of 2 mol/L hydrochloric acid solution, warm on a water bath at 50°C for 45 minutes, cool in an ice bath, add 0.2 ml of 1% N-1 (methyl naphthyl) ethylenediamine hydrochloride solution, a red colour is produced after 10 minutes. (3) The light absorption of the solution obtained in the Assay exhibits a maximum at 230 nm (Appendix IV A).

Loss on drying When dried in vacuum over phosphorous pentoxide to constant weight, loses not more than 0.5% of its weight (Appendix VIII L).

Assay Dissolve a quantity, accurately weighed, in dehydrated ethanol to produce a solution of 20 µg per ml, measure the absorbance of the solution at 230 nm (Appendix IV A). Calculate the content of $C_5H_9Cl_2N_3O_2$, taking 270 as the value of A (1%, 1 cm) (the operation should be completed within 30 minutes below 20°C).

Category Antineoplastic.

Storage Preserve in hermetically sealed containers, stored in a cool place and protected from light.

Preparation Carmustine Injection

Carmustine Injection

Carmustine Injection is a sterile solution of Carmustine in Macrogol. It contains not less than 90.0% and not more than 110.0% of the labelled amount of carmustine ($C_5H_9Cl_2N_3O_2$).

Description A clear, pale yellow liquid.

Identification Complies with the test for Identification described under Carmustine.

Other requirements Complies with the general requirements for injections (Appendix I B).

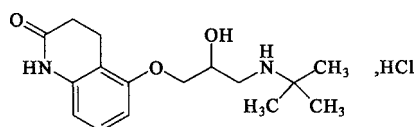
Assay Dissolve an accurately weighed quantity in absolute ethanol to produce a solution of 20 µg per ml. Carry out the Assay described under Carmustine.

Category As described under Carmustine.

Strength 2 g : 125 mg

Storage Preserve in well closed containers, protected from light and stored in a cold place.

Carteolol Hydrochloride



$C_{16}H_{24}N_2O_3 \cdot HCl$ 328.84 [51781-21-6]

Carteolol Hydrochloride is 5- [3- (*tert*-Butylamino)-2-hydroxypropoxy]-3,4-dihydrocarbostyryl monohydrochloride. It contains not less than 99.0% of $C_{16}H_{24}N_2O_3 \cdot HCl$, calculated on the dried basis.

Description A white crystalline powder.

Soluble in water; sparingly soluble in methanol; very slightly soluble in ethanol or glacial acetic acid; practically insoluble in ether.

Identification (1) Dissolve about 0.1 g in 5 ml of water, add 5 drops of ammonium reineckate TS; pale red precipitation is produced.

(2) The light absorption of the solution of 8 µg per ml in water exhibits maxima at 215 nm and 252 nm (Appendix IV A).

(3) The infrared absorption spectrum (Appendix IV C) is concordant with the reference spectrum of carteolol hydrochloride (Appendix XVI).

(4) Yields the reactions characteristic of chlorides (Appendix III).

Acidity Dissolve 1.0 g in 100 ml of water, pH 5.0-6.0 (Appendix VI H).

Clarity and colour of solution A solution of 1.0 g in 30 ml of water is clear and colourless.

Related substances Carry out the method for thin-layer chromatography (Appendix V B), using silica gel GF₂₅₄ as the coating substance and a mixture of chloroform-methanol-concentrated ammonia solution (50 : 20 : 1) as the mobile phase. Dissolve 0.20 g in 10 ml of methanol, which is used as the test solution. Transfer 2 ml of the solution, accurately measured, to a 100 ml volumetric flask, dilute with methanol to volume and mix well; transfer 1 ml of the solution, accurately measured, to a 10 ml volumetric flask, dilute with methanol to volume and mix well, which is used as the reference solution. Apply separately to the plate 10 µl of each of two solutions. After developing and removal of the plate, dry it in air and examine under ultraviolet light (254 nm). Any spot in the chromatogram other than the principal spot obtained with the test solution is not more intense than the principal spot obtained with the reference solution.

Loss on drying When dried at 105°C for 3 hours, loses not more than 0.5% of its weight (Appendix VIII L), using about 1.0 g.

Residue on ignition Not more than 0.1% (Appendix VIII N), using about 1.0 g.

Heavy metals Carry out the limit test for heavy metals (Appendix VIII H, method 2), using the residue obtained in the test for Residue on ignition; not more than 0.001%.

Arsenic To 1.0 g in a crucible pot, add 10 ml of a solution of magnesium nitrate in ethanol (1→50) and ignite gently to ash; wet with a little of nitric acid if any carbide existing and incinerate with strong heat. Cool and dissolve the ash in 3 ml of hydrochloric acid on a water bath; transfer with a little of water to the conical flask, add a drop of methyl orange IS and neutralize with ammonia TS or dilute hydrochloric acid, which is used as the test solution. Carry out the limit test for arsenic (Appendix VIII J, method 2) using 2 ml of arsenic standard solution; not more than 0.0002%.

Assay Dissolve about 0.5 g, accurately weighed, in 30 ml of glacial acetic acid by heating on a water bath, cool and add 70 ml of acetic anhydride. Carry out the method for potentiometric titration (Appendix VII A), titrate with perchloric acid VS (0.1 mol/L). Perform blank determination and make any necessary correction. Each ml of perchloric acid VS (0.1 mol/L) is equivalent to 32.88 mg of $C_{16}H_{24}N_2O_3 \cdot HCl$.

Category Beta-adrenoceptor antagonist.

Storage Preserve in tightly closed containers.

Preparation Carteolol Hydrochloride Eye Drops

Carteolol Hydrochloride Eye Drops

Carteolol Hydrochloride Eye Drops contain not less than 95.0% and not more than 105.0% of carteolol hydrochloride ($C_{16}H_{24}N_2O_3 \cdot HCl$), with a quantity of benzalkonium chloride as an antimicrobial preservative.

Description A clear, colourless liquid.

Identification (1) The light absorption of the solution of 8 µg per ml exhibits maxima at 215 nm and 252 nm (Appendix IV A).

(2) Dilute a quantity to produce a solution containing about 5 mg of Carteolol Hydrochloride per ml as a test solution. Prepare a reference solution of about 5 mg of carteolol hydrochloride CRS per ml. Carry out the method for thin-layer chromatography (Appendix V B), using silica gel GF₂₅₄ as the coating substance and a mixture of chloroform-methanol-concentrated ammonia solution (50 : 20 : 1) as the mobile phase but allowing the solvent front to ascend about 12 cm above the line of application. Apply separately to the plate 2 µl of each of above two solutions. After developing and removal of the plate, dry it in air, and examine under ultraviolet light (254 nm). The fluorescent spot in the chromatogram obtained with the test solution corresponds in position and colour to the spot obtained with the reference solution.

pH value pH 6.2-7.2 (Appendix VI H).

Osmolality 0.9-1.1 (Appendix IX G).

Other requirements Comply with the general requirements for eye preparations (Appendix I G).

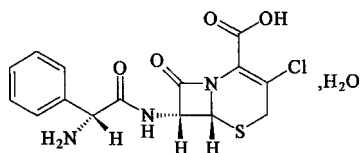
Assay Dilute a quantity, accurately measured, with water to produce a solution containing about 16 µg of carteolol hydrochloride per ml. Measure the absorbance of the resulting solution at 252 nm (Appendix IV A). Repeat the operation using carteolol hydrochloride CRS instead of the eye drops. Calculate the content of $C_{16}H_{24}N_2O_3 \cdot HCl$.

Category As described under Carteolol Hydrochloride.

Strength (1) 5 ml : 50 mg (2) 5 ml : 100 mg

Storage Preserve in tightly closed containers.

Cefaclor



$C_{15}H_{14}ClN_3O_4S \cdot H_2O$ 385.82 [53994-73-3]

Cefaclor is (6*R*, 7*R*)-7-[(*R*)-2-Amino-2-phenylacetamido]-3-chloro-8-oxo-5-thia-1-aza-bicyclo[4.2.0]oct-2-ene-2-carboxylic acid monohydrate. It contains not less than 95.0% of $C_{15}H_{14}ClN_3O_4S$, calculated on the anhydrous basis.

Description A white to slightly yellow powder or crystalline powder; odour, slight; taste, bitter. Slightly soluble in water; practically insoluble in methanol, ethanol, chloroform or methylene chloride.

Specific optical rotation +105° to +120°, in a solution of 4 mg per ml in water (Appendix VI E).

Specific absorbance Measure the absorbance of a solution of 20 µg per ml in water at 264 nm (Appendix IV A), the value of *A* (1%, 1 cm) is 230-255.

Identification (1) Dissolve a quantity in water to produce a solution of about 2 mg per ml, filter, using the successive filtrate as solution (1). Dissolve a quantity of cefaclor CRS in water to produce solution (2) of about 2 mg per ml. Dilute a quantity of solution (1) and (2) with water to produce solution (3) of 2 mg per ml respectively. Carry out the method for thin-layer chromatography (Appendix V B), using a freshly prepared mixture of 0.1 mol/L citric acid solution-dipotassium hydrogen phosphate solution (0.1 mol/L) -6.6% solution of ninhydrin in acetone (60 : 40 : 1.5) as the mobile phase. Coat the clean plate with homogeneous slurry of 2.5 g of silica gel H in 8 ml of a 0.1% solution of carboxymethylcellulose sodium, dry it in air and activate at 105°C for 1 hour, allow it to cool in a desiccator. Apply separately to the plate 2 µl each of the three solutions. After developing and removal of the plate, dry it in air and examine. The colour and position of the principal spot in the chromatogram obtained with solution (1) correspond to that obtained with solution (2), and only a principal spot in the chromatogram obtained with solution (3).

(2) The retention time of principal peak of cefaclor in the substance being examined in the chromatogram obtained in the Assay is identical with that of the principal peak of cefaclor CRS solution in the chromatogram.

(3) The infrared absorption spectrum (Appendix IV C) is concordant with the reference spectrum of cefaclor (Appendix XVI).

(1) or (2) may be used alternatively.

Acidity Dissolve a quantity in water to produce a solution of 25 mg per ml, pH 3.0-4.5 (Appendix VI H).

Related substances Carry out the method for high performance liquid chromatography (Appendix V D), using a column packed with octadecylsilane bonded silica gel and a 0.78% solution of sodium dihydrogen phosphate (dissolve

7.8 g of sodium dihydrogen phosphate in water and dilute to 1000 ml, adjust pH value to 4.0 with phosphoric acid) as mobile phase A, a mixture of a 0.78% solution of sodium dihydrogen phosphate (pH 4.0) -acetonitrile (55 : 45) as mobile phase B. The flow rate is 1.0 ml/min and detection wavelength is 220 nm. Dissolve a quantity of cefaclor CRS and cefaclor δ-3-isomer CRS in 0.27% solution of sodium dihydrogen phosphate (pH 2.5) to produce a solution of 25 µg separately per ml, inject 20 µl into the column, record the chromatogram. The retention time of peak of cefaclor is about 23-29 minutes. The resolution factor between the peaks of cefaclor and cefaclor δ-3-isomer is not less than 2.0. The tail factor of the column is less than 1.2.

Time (minute)	mobile phase A(%)	mobile phase B(%)
0	95	5
30	75	25
45	0	100
50	0	100
51	95	5
61	95	5

Procedure Dissolve 50 mg, accurately weighed, in a 0.27% solution of sodium dihydrogen phosphate (pH 2.5) in a 10 ml volumetric flask and dilute to volume, shake well, as solution (1). Measure accurately 1 ml into a 100 ml volumetric flask, dilute with the above solvent to volume, mix well as the solution (2). Inject 20 µl of solution (2) into the column, adjust the attenuation so that the principal peak height in the chromatogram is 25% of the full scale of the chart. Inject separately 20 µl into the column, record the chromatogram. Each peak area and the sum of the areas of all peaks other than the principal peak are not greater than 1/2 (0.5%) and 2 (2.0%) of area of the principal peak in the chromatogram obtained with solution (2) respectively. Disregard any peak with an area less than 0.1 times area of the principal peak in the chromatogram obtained with solution (2).

Water 3.0%-6.5% (Appendix VIII M, method 1, A).

Heavy metals Carry out the limit test for heavy metals (Appendix VIII H, method 2), using 1.0 g; not more than 0.003%.

Assay Carry out the method for high performance liquid chromatography (Appendix V D), using a column packed with octadecylsilane bonded silica gel and a mixture of potassium dihydrogen phosphate solution (dissolve 6.8 g of potassium dihydrogen phosphate in water and dilute to 1000 ml, mix well, adjust pH value to 3.4 with phosphoric acid)-acetonitrile (92 : 8) as the mobile phase. The flow rate is 1 ml/min and the detection wavelength is 254 nm. Dissolve an accurately weighed quantity of cefaclor δ-3-isomer CRS and cefaclor CRS in mobile phase to produce a mixed solution of 0.2 mg per ml. Inject 20 µl into the column. The resolution factor between peaks of cefaclor and cefaclor δ-3-isomer complies with the related requirements. The number of the theoretical plates of the column is not less than 1500, calculated with reference to the peak of cefaclor.

Procedure Dissolve 20 mg, accurately weighed, into a 100 ml volumetric flask in mobile phase and dilute to volume to produce a solution of 0.2 mg per ml. Inject 20 µl into the column. Repeat the operation, using cefaclor CRS instead of the substance being examined. Calculate the content of $C_{15}H_{14}ClN_3O_4S$ with respect to the peak area obtained in the chromatogram by the external standard method.

Category β -lactam antibiotic, cephalosporin.

Storage Preserve in tightly closed containers, protected from light.

Preparation (1) Cefaclor Capsules
(2) Cefaclor Granules
(3) Cefaclor for Suspension
(4) Cefaclor Tablets

Cefaclor Capsules

Cefaclor Capsules contain not less than 90.0% and not more than 110.0% of the labelled amount of cefaclor ($C_{15}H_{14}ClN_3O_4S$).

Description Capsules containing almost white to slightly yellow powder.

Identification Dissolve a quantity of the contents of the capsules in water to produce a solution of about 2 mg of cefaclor per ml and filter. The successive filtrate complies with tests (1) and (2) for Identification described under Cefaclor.

Water Not more than 8.0% (Appendix VIII M, method 1 A), using a quantity of the contents of the capsules.

Dissolution Carry out the dissolution test (Appendix X C method 1), using 900 ml of water as the dissolution medium, adjust the rotational speed of the paddle to 100 rpm. Withdraw the solution at 30 minutes, filter. Dilute an accurately measured quantity of the successive filtrate with water to produce a solution of 25 μ g per ml. Dissolve an accurately weighed quantity of the mixed contents in the test for weight variation of contents in water to produce a reference solution of 25 μ g of cefaclor ($C_{15}H_{14}ClN_3O_4S$) per ml according to the labelled amount. Measure the absorbance of the resulting solutions at 264 nm (Appendix IV A). Calculate the dissolution of $C_{15}H_{14}ClN_3O_4S$ from each capsule. Not less than 80% of the labelled amount is dissolved.

Related substances Carry out the method as described under Cefaclor, using an accurately weighed quantity of the mixed contents obtained in the test for weight variation of contents equivalent to about 500 mg of cefaclor. Dissolve the cefaclor in 0.27% solution of sodium dihydrogen phosphate (pH 2.5) and dilute to volume in a 100 ml volumetric flask, mix well and filter, use the successive filtrate as the test solution. Dilute 1 ml of the filtrate with a 0.27% solution of sodium dihydrogen phosphate (pH 2.5) to volume in a 100 ml volumetric flask to volume, mix well as the reference solution. Each peak area of all peaks other than the principal peak in the chromatogram obtained with the test solution is not greater than that of the principal peak in the chromatogram obtained with the reference solution respectively (1.0%).

Other requirements Comply with the general requirements for capsules (Appendix I E).

Assay Dissolve an accurately weighed quantity of the mixed contents in the test for weight variation of contents equivalent to about 100 mg of cefaclor in mobile phase to produce a solution of 0.2 mg of cefaclor per ml, mix well and filter. Inject 20 μ l of the successive filtrate into the column, carry out the Assay under Cefaclor.

Category As described under Cefaclor.

Strength 0.25 g (calculated as $C_{15}H_{14}ClN_3O_4S$)

Storage Preserve in tightly closed containers, stored in a

cool, dry and dark place and protected from light.

Cefaclor Granules

Cefaclor Granules contain not less than 90.0% and not more than 110.0% of the labelled amount of cefaclor ($C_{15}H_{14}ClN_3O_4S$).

Description Suspension granules; odour, fragrant; taste, sweet.

Identification Dissolve a quantity in water to produce a solution of about 2 mg of cefaclor per ml, filter, the successive filtrate complies with the tests (1) or (2) for Identification described under Cefaclor.

Acidity A suspension of 25 mg of cefaclor per ml in water, pH 3.0-5.0 (Appendix VI H).

Water Not more than 3.0% (Appendix VIII M, method 1 A).

Other requirements Comply with the general requirements for granules (Appendix I N).

Assay Dissolve an accurately weighted quantity of the mixed contents obtained in the test for weight variation equivalent to about 100 mg of cefaclor in mobile phase and dilute to produce a solution of 0.2 mg of cefaclor per ml (sonicate when necessary), filter, inject 20 μ l of successive filtrate into the column, carry out the Assay described under Cefaclor.

Category As described under Cefaclor.

Strength Calculated as $C_{15}H_{14}ClN_3O_4S$
(1) 0.1 g (2) 0.125 g (3) 0.25 g

Storage Preserve in tightly closed containers, stored in a cool, dry and dark place and protected from light.

Cefaclor for Suspension

Cefaclor for Suspension contains not less than 90.0% and not more than 110.0% of the labelled amount of cefaclor ($C_{15}H_{14}ClN_3O_4S$).

Description Fine particle or powder; odour, fragrant; taste, sweet.

Identification Dissolve a quantity in water to produce a solution of about 2 mg of cefaclor per ml, filter, the successive filtrate complies with the tests (1) or (2) for Identification described under Cefaclor.

Acidity A suspension solution of 25 mg per ml in water, pH 3.0-5.0 (Appendix VI H).

Related substances Carry out the method as described under Cefaclor. Using an accurately weighed quantity of the mixed contents obtained from the test for weight variation of contents equivalent to about 500 mg of cefaclor. Dissolve the cefaclor in 0.27% solution of sodium dihydrogen phosphate (pH 2.5) and dilute to volume in a 100 ml volumetric flask, mix well and filter use the successive filtrate as the test solution. Dilute 1 ml of the filtrate with a 0.27% solution of sodium dihydrogen phosphate (pH 2.5) to volume in a 100 ml volumetric flask to volume mix well as the reference solution. Each peak area of all peaks other than the principal peak in the chromatogram obtained with the test solution is not greater twice than that of the principal peak in the

chromatogram obtained with the reference solution respectively (2%).

Water Not more than 2.0% (Appendix VIII M, method 1, A).

Other requirements Complies with the general requirements for suspensions (Appendix I O).

Assay Dissolve an accurately weighed quantity of the mixed contents obtained in the test for weight variation equivalent to about 100 mg of cefaclor in mobile phase and dilute to produce a solution of 0.2 mg of cefaclor per ml (ultrasonic treatment when necessary), filter, inject 20 μ l of successive filtrate into the column, carry out the Assay described under Cefaclor.

Category As described under Cefaclor.

Strength Calculated as $C_{15}H_{14}ClN_3O_4S$
(1) 0.125 g (2) 1.5 g

Storage Preserve in tightly closed containers, stored in a cool, dry and dark place and protected from light.

Cefaclor Tablets

Cefaclor Tablets contain not less than 90.0% and not more than 110.0% of the labelled amount of cefaclor ($C_{15}H_{14}ClN_3O_4S$).

Description Film coated tablets with white to slightly yellow core.

Identification To a quantity of powdered tablets add water to produce a solution of about 2 mg of cefaclor per ml and filter. The successive filtrate complies with tests (1) or (2) for Identification described under Cefaclor.

Water Not more than 8.0% (Appendix VIII M, method 1 A) using a quantity of powdered tablets.

Dissolution Carry out the dissolution test (Appendix X C method 1), using 900 ml of water as the dissolution medium, adjust the rotational speed of the paddle to 100 rpm. Withdraw a quantity of the solution at 30 minutes, filter. Dilute an accurately measured quantity of the successive filtrate with water to produce a solution of 25 μ g per ml. Powder finely 10 tablets. Dissolve an accurately weighed quantity of the powdered tablets in water to produce a reference solution of 25 μ g of cefaclor ($C_{15}H_{14}ClN_3O_4S$) per ml according to the labelled amount. Measure the absorbance of the resulting solutions at 264 nm (Appendix IV A). Calculate the dissolution of $C_{15}H_{14}ClN_3O_4S$ from each tablet. Not less than 80% of the labelled amount is dissolved.

Related substances Carry out the Related substances under cefaclor using an accurately weighed quantity equivalent to about 500 mg of cefaclor of the mixed contents obtained from the test for Assay. Dissolve the cefaclor in 0.27% solution of sodium dihydrogen phosphate (pH 2.5) and dilute to volume in a 100 ml volumetric flask, mix well and filter use the successive filtrate as the test solution. Dilute 1 ml of the filtrate with a 0.27% solution of sodium dihydrogen phosphate (pH 2.5) to volume in a 100 ml volumetric flask to volume mix well as the reference solution. Each peak area of all peaks other than the principal peak in the chromatogram obtained with the test solution is not greater than that of the principal peak in the chromatogram obtained with the reference solution respectively (1.0%).

Other requirements Comply with the general requirements for tablets (Appendix I A).

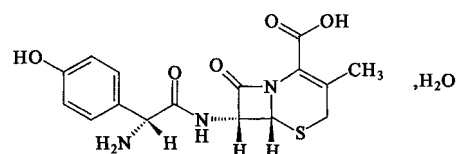
Assay Weigh accurately and powder finely 10 tablets. Dissolve an accurately weighed quantity equivalent to about 100 mg of cefaclor in mobile phase to produce a solution of 0.2 mg of cefaclor per ml, mix well and filter. Inject 20 μ l of the successive filtrate into the column, carry out the Assay described under Cefaclor.

Category As described under Cefaclor.

Strength 0.25 g (Calculated as $C_{15}H_{14}ClN_3O_4S$)

Storage Preserve in tightly closed containers, stored in a cool, dry and dark place, and protected from light.

Cefadroxil



$C_{16}H_{17}N_3O_5S \cdot H_2O$ 381.41 [66592-87-8]

Cefadroxil is (6R, 7R)-3-methyl-7-[(R)-2-amino-2-(4-hydroxyphenyl)acetamido]-8-oxo-5-thia-1-azabicyclo[4.2.0]oct-2-ene-2-carboxylic acid monohydrate. It contains not less than 95.0% of $C_{16}H_{17}N_3O_5S$, calculated on the anhydrous basis.

Description A white or almost white crystalline powder; odour characteristic. Slightly soluble in water; practically insoluble in ethanol, chloroform or ether.

Specific optical rotation $+165^\circ$ to $+178^\circ$, in a solution of 6 mg per ml in water (Appendix VI E).

Identification (1) The retention time of the principal peak of the substance being examined in the chromatogram obtained in the Assay is identical with that of cefadroxil CRS.

(2) The infrared absorption spectrum (Appendix IV C) is concordant with the reference spectrum of cefadroxil (Appendix XVI).

Crystallinity Complies with the test for crystallinity (Appendix IX D).

Acidity Dissolve a quantity in water to produce a solution of 5 mg per ml, pH 4.0-6.0 (Appendix VI H).

Related substances Dissolve an accurately weighed quantity in mobile phase to produce a solution of 0.7 mg per ml as the test solution. Measured accurately 1 ml to an 100 ml volumetric flask, add mobile phase to volume and mix well, as the reference solution. Dissolve a quantity of 7-aminodesacetoxy cephalosporanic acid CRS and α -p-hydroxyphenylglycine CRS in mobile phase to produce a mixed impurity solution of 7 μ g per ml respectively. Carry out the method as described under Assay. Inject 10 μ l of the reference solution into the column. Adjust the attenuation so that the principal peak height in the chromatogram is 20%-25% of the full scale of the chart. Inject 10 μ l of the test solution, the reference solution and the mixture impurity solution into the column and record the chromatograms for three times retention time of the principal peak in the test solution. Calculate the content of 7-aminodesacetoxy cephalosporanic acid and α -p-hydroxyphenylglycine with respect to the peak area in the chromatogram obtained with test solution by the external standard method, both are not more than 1.0%. Other single peak area other

than the principle peak is not more than the peak area of cefadroxil in the reference solution (1.0%). The total peaks area other than the principle peak are not more than three times the peak area of cefadroxil in the reference solution (3.0%). (disregard any peak with an area less than 0.05 times area of the principal peak in the chromatogram obtained with the reference solution).

Water 4.2%-6.0% (Appendix VIII M, method 1 A).

Assay Carry out the method for high performance liquid chromatography (Appendix V D), using a column packed with octadecylsilane bonded silica gel and a mixture of 0.05 mol/L potassium dihydrogen phosphate solution (adjust to pH 5.5 with 10 mol/L sodium hydroxide solution)-acetonitrile (96 : 4) as mobile phase. Detection wavelength is 230 nm. Dissolve a quantity of cefadroxil CRS and 7-aminodesacetoxy cephalosporanic acid CRS in mobile phase to produce a mixed solution of 0.5 mg of cefadroxil and 10 µg of 7-aminodesacetoxy cephalosporanic acid per ml. Inject 10 µl of the mixture solution into the column and record the chromatogram. The ratio of retention time between the peak of cefadroxil and that of the 7-aminodesacetoxy cephalosporanic acid is not less than 2.0.

Procedure Dissolve an accurately weighed quantity in the mobile phase to produce a solution of 0.3 mg per ml, inject 10 µl into the column. Repeat the operation, using cefadroxil CRS instead of the substance being examined, calculate the content of $C_{16}H_{17}N_3O_5S$ with respect to the peak area obtained in the chromatogram by the external standard method.

Category β-lactam antibiotic, cephalosporins.

Storage Preserve in tightly closed containers, stored in a cool place and protected from light.

Preparation (1) Cefadroxil Capsules
(2) Cefadroxil Granules
(3) Cefadroxil Tablets

Cefadroxil Capsules

Cefadroxil Capsules contain not less than 90.0% and not more than 110.0% of the labelled amount of cefadroxil ($C_{16}H_{17}N_3O_5S$).

Description Capsules containing white or almost white powder or granule.

Identification The contents of the capsules comply with the test (1) for Identification described under Cefadroxil.

Related substances Dissolve a quantity of the contents in mobile phase to produce a solution of 0.7 mg per ml, filter and use the successive filtrate as the test solution. Carry out the Related substances described under Cefadroxil.

Water Not more than 8.0% (Appendix VIII M, method 1 A).

Dissolution Carry out the dissolution test (Appendix X C, method 1), using 900 ml of water as the dissolution medium, adjust the rotational speed of the basket to 100 rpm. Withdraw the solution at 30 minutes and filter. Dilute a quantity of the successive filtrate with water to produce a solution of 25 µg per ml. Dissolve an accurately weighed quantity, equivalent to about the average weight in each capsule, of the mixed contents in the test for weight variation of contents in water to produce a solution of 25 µg per ml calculated by the labelled amount. Measure the absorbance of the resulting solutions separately at 263 nm

(Appendix IV A). Calculate the dissolution of $C_{16}H_{17}N_3O_5S$ from each capsule. Not less than 80% is dissolved.

Other requirements Comply with the general requirements for capsules (Appendix I E).

Assay To an accurately weighed quantity, equivalent to about 30 mg of cefadroxil, of the mixed content obtained from weight variation of contents add mobile phase and dilute to volume in a 100 ml volumetric flask, shake thoroughly and filter. Carry out the Assay described under cefadroxil, using an accurately measured 10 µl of successive filtrate.

Category As described under Cefadroxil.

Strength Calculated as $C_{16}H_{17}N_3O_5S$
(1) 0.125 g (2) 0.25 g (3) 0.5 g

Storage Preserve in tightly closed containers, protected from light and stored in a cool and dark place.

Cefadroxil Granules

Cefadroxil Granules contain not less than 90.0% and not more than 110.0% of the labelled amount of cefadroxil ($C_{16}H_{17}N_3O_5S$).

Description Soluble granules; taste, sweet.

Identification The retention time of principal peak of the substance being examined in the chromatogram obtained in the Assay is identical with the principal peak of cefadroxil CRS in the chromatogram of the reference solution.

Acidity A solution of 50 mg per ml in water, pH 4.5-6.0 (Appendix VI H).

Related substances Dissolve a quantity of the powder as described under Assay in mobile phase to produce a solution of 0.7 mg per ml Cefadroxil, filter and use the successive filtrate as test solution. Carry out the Related substance described under cefadroxil. Calculate the content of 7-aminodesacetoxy cephalosporanic acid and α-p-hydroxy-phenylglycine with respect to the peak area obtained in the chromatogram of test solution by the external standard method, the both are not more than 1.0%. Other single peak area other than the principle peak is not more than the peak area of cefadroxil in the reference solution (1.0%). (disregard any peak with an area less than 0.05 times area of the principal peak in the chromatogram obtained with reference solution).

Loss on drying When dried to constant weight at 105°C, loses not more than 2.0% of its weight (Appendix VIII L).

Other requirements Comply with the general requirements for granules (Appendix I N).

Assay Carry out the Assay described under Cefadroxil, using an accurately weighed quantity, equivalent to about 30mg of Cefadroxil, of the mixed contents obtained in the test for weight variation of contents. Dissolve the Cefadroxil in the mobile phase and dilute to volume in an 100 ml volumetric flask, mix well, and filter. Inject 10 µl of the successive filtrate into the column.

Category As described under Cefadroxil.

Strength 0.125 g (calculated as $C_{16}H_{17}N_3O_5S$)

Storage Preserve in tightly closed container and store in a cool place.

Cefadroxil Tablets

Cefadroxil tablets contain not less than 90.0% and not more than 110.0% of the labelled amount of Cefadroxil ($C_{16}H_{17}N_3O_5S$).

Description White or almost white tablets.

Identification The retention time of principal peak of the substance being examined in the chromatogram obtained in the Assay is identical with that of cefadroxil CRS.

Related substances Dissolve a quantity of the powder in mobile phase to produce a solution of 0.7 mg per ml, filter and use the successive filtrate as the test solution. Carry out the Related substances described under Cefadroxil.

Dissolution Comply with the requirements for dissolution test (Appendix X C, method 2), using 900 ml of water as the dissolution medium, adjust the rotational speed of the paddle to 50 rpm. Withdraw a quantity of the solution at 30 minutes and filter. Dilute a quantity of the successive filtrate, accurately measured, with water to produce a solution of 25 μ g per ml. Powder 10 tablets and weigh accurately a quantity of the powder equivalent to average weight, and dissolve with water to produce a solution of 25 μ g per ml calculated by the labelled amount. Measure the absorbances of the resulting solutions at 263 nm (Appendix IV A). Calculate the dissolution of $C_{16}H_{17}N_3O_5S$ from each tablet. Not less than 75% is dissolved.

Other requirements Comply with the general requirements for tablets (Appendix I A).

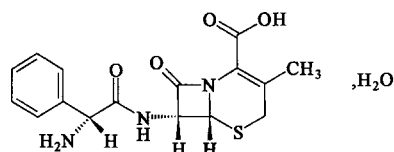
Assay Powder 10 tablets, accurately weighed, and dissolve a quantity of the powder accurately weighed, equivalent to about 30 mg of cefadroxil, in the mobile phase and dilute to volume in a 100 ml volumetric flask, mix well, and filter. Carry out the Assay described under Cefadroxil. Inject 10 μ l of the successive filtrate into the column.

Category As described under Cefadroxil.

Strength calculated as $C_{16}H_{17}N_3O_5S$ (1) 0.125 g
(2) 0.25 g

Storage Preserve in tightly closed container and store in a cool place.

Cefalexin



$C_{16}H_{17}N_3O_4S \cdot H_2O$ 365.41 [23325-78-2]

Cefalexin is the monohydrate of (6*R*, 7*R*)-[(aminophenylacetyl) amino]-3-methyl-8-oxo-5-thia-1-azabicyclo[4.2.0]oct-2-ene-2-carboxylic acid. It contains not less than 95.0% of $C_{16}H_{17}N_3O_4S$, calculated on the anhydrous basis.

Description A white to slightly yellow crystalline powder; odour, slight.

Slightly soluble in water; insoluble in ethanol, chloroform or ether.

Specific optical rotation +149° to +158°, in a solution of 5 mg per ml in water (Appendix VI E).

Specific absorbance Measure the absorbance of a solution of 20 μ g per ml in water at 262 nm (Appendix IV A), the value of *A* (1%, 1 cm) is 220-245.

Identification (1) The retention time of the principal peak of the substance being examined in the chromatogram obtained in the Assay is identical with that of cefalexin CRS. (2) The infrared absorption spectrum (Appendix IV C) is concordant with the reference spectrum of cefalexin (Appendix XVI).

Acidity Dissolve 50 mg in 10 ml of water, pH 3.5-5.5 (Appendix VI H).

Related substances Carry out the method for high performance liquid chromatography (Appendix V D), using a column packed with octadecylsilane bonded silica gel and a mixture of water-0.01 mol/L sodium acetate solution (adjusting pH to 5.0 with glacial acetic acid)-methanol (21 : 55 : 24) as the mobile phase. Detection wavelength is 220 nm. Dissolve a quantity of the substance being examined, accurately weighed, in the mobile phase to produce solutions of 0.4 mg per ml (solution 1) and 4 μ g per ml (solution 2). Dissolve 10 mg each of 7-aminodesacetoxycephalosporanic acid CRS and α -phenylglycine CRS, accurately weighed, in a 100 ml volumetric flask, add 4 ml of 7.3% hydrochloric acid solution, sonicate to dissolve, dilute to volume with the mobile phase and mix well. Dilute 2.0 ml to volume with the mobile phase in a 50 ml volumetric flask, mix well (solution 3). Inject 20 μ l of solution (3) into the column, the resolution factor between the peaks of 7-aminodesacetoxycephalosporanic acid and α -phenylglycine complies with the related requirements. Inject 20 μ l of solution (2) into the column, adjust the attenuation so that the principal peak height in the chromatogram is 20%-25% of the full scale of the chart. Inject separately 20 μ l each of solution (1) (2) and (3), and record the chromatogram for twice the retention time of the principal peak. The contents of 7-aminodesacetoxycephalosporanic acid and α -phenylglycine calculated with respect to the peak areas obtained with solution (1) by the external standard method are separately not more than 1.0%, and any other peak area and the sum areas of other peaks other than principal peak are not greater than 1.5 times and 2.5 times the principal peak area in the chromatogram obtained with solution (2) respectively. Disregard any peak with an area less than 0.05 times of area of the principal peak in the chromatogram obtained with solution (2).

Water 4.0%-8.0% (Appendix VIII M, method 1 A).

Residue on ignition Not more than 0.2% (Appendix VIII N).

Assay Carry out the method for high performance liquid chromatography (Appendix V D), using a column packed with octadecylsilane bonded silica gel and a mixture of water-methanol-3.86% sodium acetate solution-4% acetic acid solution (742 : 240 : 15 : 3) as the mobile phase. The value of *g* (the number of theoretical plates of the column) is not less than 1500, calculated with reference to the peak of cefalexin.

Procedure Dissolve about 50 mg, accurately weighed, in the mobile phase in a 50 ml volumetric flask and dilute to volume, mix well. Transfer 10 ml of the solution into a 50 ml volumetric flask, dilute with the mobile phase to volume and mix well, inject 10 μ l into the column. Repeat the operation, using cefalexin CRS instead of the substance being examined, calculate the content of $C_{16}H_{17}N_3O_4S$.

Category β -Lactam antibiotic, Cephalosporin.

Storage Preserve in tightly closed containers, stored in a dark and cool place and protected from light.

Preparation (1) Cefalexin Capsules
(2) Cefalexin Granules
(3) Cefalexin for Suspension
(4) Cefalexin Tablets

Cefalexin Capsules

Cefalexin Capsules contain not less than 90.0% and not more than 110.0% of the labelled amount of cefalexin ($C_{16}H_{17}N_3O_4S$).

Identification The retention time of the principal peak of the substance being examined in the chromatogram obtained in the Assay is identical with that of cefalexin CRS.

Related substances Dissolve a quantity of the contents of capsules in the mobile phase to produce a solution of 0.4 mg per ml, filter and use the successive filtrate as the test solution. Carry out the method described under Cefalexin. The contents of 7-aminodesacetoxycephalosporanic acid and α -phenylglycine calculated with respect to the peak areas by the external standard method are separately not more than 1.0%, and any other peak area and the sum areas of other peaks other than principal peak are not greater than twice and 3 times of the principal peak area in the chromatogram obtained with solution (2) respectively. (Disregard any peak with an area less than 0.05 times of area of the principal peak in the chromatogram obtained with solution (2).)

Water Not more than 9.0% (Appendix VIII M, method 1 A).

Dissolution Carry out the dissolution test (Appendix X C, method 1), using 900 ml of water as the dissolution medium, adjust the rotational speed of the basket to 100 rpm. Withdraw the solution at 45 minutes and filter. Dilute a quantity of the successive filtrate with water to produce a solution of 25 μ g per ml. Dissolve an accurately weighed quantity of cefalexin CRS in water and dilute with the same solvent to produce a solution of 25 μ g per ml. Measure the absorbances of the resulting solutions respectively at 262 nm (Appendix IV A). Calculate the dissolution of $C_{16}H_{17}N_3O_4S$ from each capsule. Not less than 80% is dissolved.

Other requirements Comply with the general requirements for capsules (Appendix I E).

Assay To an accurately weighed quantity, equivalent to about 0.1 g of cefalexin, of the mixed content obtained in weight variation of contents, add a quantity of the mobile phase and shake thoroughly to dissolve cefalexin in a 100 ml volumetric flask. Dilute with the mobile phase to volume, mix well and filter. Transfer an accurately measured 10 ml of successive filtrate to a 50 ml volumetric flask, dilute with the mobile phase to volume, mix well. Carry out the Assay described under cefalexin, using 10 μ l of the resulting solution.

Category As described under Cefalexin.

Strength Calculated as $C_{16}H_{17}N_3O_4S$
(1) 0.125 g (2) 0.25 g

Storage Preserve in tightly closed containers, protected from light and stored in a dark and cool place.

Cefalexin Granules

Cefalexin Granules contain not less than 90.0% and not more than 110.0% of the labelled amount of cefalexin ($C_{16}H_{17}N_3O_4S$).

Description Soluble granules.

Identification The retention time of the principal peak of the substance being examined in the chromatogram obtained in the Assay is identical with that of cefalexin CRS.

Acidity A suspension of 25 mg per ml in water, pH 4.0-6.0 (Appendix VI H).

Water Not more than 2.0% (Appendix VIII M, method 1 A).

Other requirements Comply with the general requirements for granules (Appendix I N).

Assay To an accurately weighed quantity, equivalent to about 0.1 g of cefalexin, of the mixed content obtained in weight variation of contents add a quantity of mobile phase and shake thoroughly to dissolve cefalexin in a 100 ml volumetric flask. Dilute with the mobile phase to volume, mix well and filter. Transfer an accurately measured 10 ml of successive filtrate to a 50 ml volumetric flask, dilute with mobile phase to volume, mix well. Carry out the Assay described under Cefalexin, using 10 μ l of the resulting solution.

Category As described under Cefalexin.

Strength Calculated as $C_{16}H_{17}N_3O_4S$
(1) 50 mg (2) 125 mg

Storage Preserve in tightly closed containers, protected from light, store in a dark and cool place.

Cefalexin for Suspension

Cefalexin for suspension contains not less than 90.0% and not more than 110.0% of the labelled amount of cefalexin ($C_{16}H_{17}N_3O_4S$).

Description powder, odour fragrant, taste, sweet.

Identification The retention time of the principal peak of the substance being examined in the chromatogram obtained in the Assay is identical with that of cefalexin CRS.

Acidity A suspension of 25 mg per ml in water, pH 4.0-6.0 (Appendix VI H).

Ratio of sedimental volume Carry out the test for ratio of sedimental volume (Appendix I O), add water according to the ratio of administration and shake for 1 minute, allow to stand for 45 minutes (for multidose). The result should comply with the requirements.

Water Not more than 2.0% (Appendix VIII M, method 1 A).

Other requirements Complies with the general requirements for suspension (Appendix I O).

Assay Carry out the Assay described under Cefalexin, using an accurately weighed quantity, equivalent to about 50 mg of Cefalexin, of the mixed contents obtained from the test for weight variation of contents. Dissolve the cefalexin in the mobile phase and dilute to volume in a 50 ml volumetric flask, mix well, and filter. Dilute 10 ml of the successive

filtrate with the mobile phase to the volume in a 50 ml volumetric flask. Inject 10 μ l of the successive filtrate into the column.

Category As described under Cefalexin.

Strength Calculated as $C_{16}H_{17}N_3O_4S$ (1) 0.5 g (2) 1.5 g

Storage Preserve in tightly closed containers, protected from light and store in a dark and cool place.

Cefalexin Tablets

Cefalexin Tablets contain not less than 90.0% and not more than 110.0% of the labelled amount of cefalexin ($C_{16}H_{17}N_3O_4S$).

Description White tablets or Sugar or film coated tablets with white or creamy yellow cores.

Identification The retention time of the principal peak of the substance being examined in the chromatogram obtained in the Assay is identical with that of cefalexin CRS.

Related substances Dissolve a quantity of the powdered tablets in the mobile phase to produce a solution of 0.4 mg per ml. Filter and use the successive filtrate as the test solution. Carry out the method described under Cefalexin. The contents of 7-aminodesacetoxycephalosporanic acid and α -phenylglycine calculated with respect to the peak areas obtained with solution (1) by the external standard method are separately not more than 1.0%, and any other peak area and the sum areas of other peaks other than principal peak are not greater than twice and 3 times of the principal peak area in the chromatogram obtained with solution (2) respectively. Disregard any peak with an area less than 0.05 times of area of the principal peak in the chromatogram obtained with solution (2).

Dissolution Carry out the dissolution test (Appendix X C, method 1), using 900 ml of water as the dissolution medium, adjust the rotational speed of the basket to 100 rpm. Withdraw the solution at 45 minutes and filter. Dilute a quantity of the successive filtrate with water to produce a solution of 25 μ g per ml. Weigh and powder 10 tablets. Dissolve a quantity, equivalent to about the average weight in each tablet, of the powder in water to produce a solution of 1 mg per ml calculated by the labelled amount. Filter, dilute an accurately measured quantity of the successive filtrate in water to produce a solution of 25 μ g per ml. Measure the absorbance of the resulting solutions separately at 262 nm (Appendix IV A), calculate the dissolution of $C_{16}H_{17}N_3O_4S$ from each tablet. Not less than 80% is dissolved.

Other requirements Comply with the general requirements for tablets (Appendix I A).

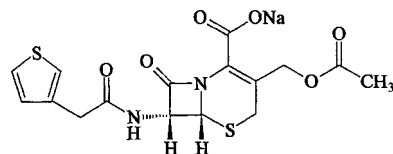
Assay Weigh and powder 10 tablets. To an accurately weighed quantity, equivalent to about 0.1 g of cefalexin, add a quantity of mobile phase and shake thoroughly to dissolve cefalexin in a 100 ml volumetric flask. Dilute with the mobile phase to volume, mix well and filter. Transfer an accurately measured 10 ml of successive filtrate to a 50 ml volumetric flask, dilute with the mobile phase to volume, mix well. Carry out the Assay described under cefalexin, using 10 μ l of the resulting solution.

Category As described under Cefalexin.

Strength Calculated as $C_{16}H_{17}N_3O_4S$
(1) 0.125 g (2) 0.25 g (3) 0.5 g

Storage Preserve in tightly closed containers, protected from light and stored in a dark and cool place.

Cefalotin Sodium



$C_{16}H_{15}N_2NaO_6S_2$ 418.43

[58-71-9]

Cefalotin Sodium is sodium (6R, 7R)-3-(hydroxymethyl)-8-oxo-7-[2-(2-thienyl) acetamido]-5-thia-1-azabicyclo [4.2.0] oct-2-ene-2-carboxylate acetate (ester). It contains not less than 90.0% of $C_{16}H_{15}N_2O_6S_2$, calculated on the anhydrous basis.

Description A white or almost white crystalline powder; almost odourless.

Freely soluble in water; slightly soluble in ethanol; insoluble in chloroform or ether.

Specific optical rotation +124° to +134° at 25°C, in a solution of 10 mg per ml in water (Appendix VI E).

Identification (1) The retention time of the principal peak of the substance solution being examined in the chromatogram obtained in Assay is identical with that of cefalotin CRS.

(2) The infrared absorption spectrum (Appendix IV C) is concordant with the reference spectrum of cefalotin sodium (Appendix XVI).

(3) Yields the flame reaction of sodium salts (Appendix III).

Acidity Dissolve a quantity in water to produce a solution of 0.1 g per ml, pH 4.5-7.0 (Appendix VI H).

Clarity and colour of solution To 5 portions each of 0.6 g add 5 ml of water respectively the solutions are clear and colourless; any opalescence produced is not more pronounced than that of reference suspension 1 (Appendix IX B); any colour produced is not more intense than that of reference solution Y₅ or YG₅ (Appendix IX A, method 1).

Light absorption The absorbance of a solution of 20 μ g per ml in water at 237 nm (Appendix IV A) is 0.65-0.72.

Related substances Dissolve a quantity in mobile phase to produce solution (1) containing 1.0 mg per ml; measure accurately 1 ml to a 100 ml volumetric flask, dilute with mobile phase to volume, mix well as solution (2). Carry out the method as described under Assay. Inject 10 μ l of solution (2) into the column. Adjust the attenuation so that the principal peak height in the chromatogram is about 20% of full scale of the chart. Inject immediately 10 μ l of the two solutions respectively into the column and record the chromatograms for four times the retention time of the principal peak. Each peak area other than principal peak in the chromatogram obtained with solution (1) is not greater than the area of the principal peak in the chromatogram obtained with solution (2); the sum of the areas of all peaks other than principal peak in the chromatogram obtained with solution (1) is not greater than 3 times area of the principal peak in the chromatogram obtained with solution (2) respectively. Disregard any peak with an area less than 0.05 times of area of the principal peak in the chromatogram obtained with solution (2).

Water Not more than 1.2% (Appendix VIII M, method 1 A).

Pyrogens Complies with the test for pyrogens (Appendix XI D), using 1 ml of solution of 50 mg per ml in sterile Water for Injection per kg of rabbit's weight.

Sterility Complies with the test for sterility (Appendix XI H, membrane filtration method). Dissolve a quantity in a suitable solution, and then transfer it into not less than 500 ml of 0.9% sterile sodium chloride solution.

Assay Carry out the method for high performance liquid chromatography (Appendix V D), using a column packed with octadecylsilane bonded silica gel and a mixture of acetate buffer (Dissolve 21.5 g of sodium acetate in water and add water to produce 1000 ml, adjust to pH 5.9 ± 0.1 with glacial acetic acid)-acetonitrile-ethanol (790 : 150 : 70) as mobile phase. The temperature of column is 40°C. The detection wavelength is 254 nm. Heat 5 ml of cefalotin CRS solution in a water bath at 90°C for 10 minutes to produce desacetylcephalothin and cool to room temperature, inject immediately 10 μ l into the column. Adjust the attenuation so that the peak height of desacetylcephalothin in the chromatogram is about 50% of full scale of the chart. The resolution factor between peaks of cefalotin and desacetylcephalothin is not less than 9.0, the tailing factor of the peak of cefalotin is not more than 1.8.

Procedure Dissolve a quantity, accurately weighed, in mobile phase to produce a solution of 1 mg of cefalotin per ml. Inject 10 μ l into the column and record the chromatogram. Repeat the operation, using cefalotin CRS instead of the substance being examined, calculate the content of $C_{16}H_{16}N_2O_6S_2$ with respect to the peak area obtained in the chromatogram by the external standard method.

Category β -lactam antibiotic, Cephalosporin.

Storage Preserve in hermetically sealed containers, stored in a cool, dry and dark place.

Preparation Cefalotin Sodium for Injection

Cefalotin Sodium for Injection

Cefalotin Sodium for Injection is a sterile powder of Cefalotin Sodium. It contains not less than 90.0% of cefalotin ($C_{16}H_{16}N_2O_6S_2$), calculated on the anhydrous basis. It contains not less than 95.0% and not more than 105.0% of the labelled amount of cefalotin ($C_{16}H_{16}N_2O_6S_2$), calculated with reference to the average weight of contents.

Description A white or almost white crystalline powder.

Identification Complies with the tests for Identification described under Cefalotin Sodium.

Clarity and colour of solution To 5 containers add water to produce solutions of 0.1 g per ml, the solutions are clear and colourless; any opalescence produced is not more pronounced than that of reference suspension 1 (Appendix IX B); any colour produced is not more intense than that of reference solution Y₈ or YG₈ (Appendix IX A, method 1).

Related substances Using an accurately weighed quantity of the mixed contents obtained from the test for weight variation of contents, mixed well, carry out the test for Related substances described under cefalotin. Each peak area other than principle area in the chromatogram is not greater than the area of the principal peak in the chromatogram obtained with the reference solution; the sum of the area of all peaks other than principal area in the chromatogram is not greater than 3 times of area of the principal peak in the

chromatogram obtained with the reference solution respectively, disregard any peak with an area less than 0.05 times area of the principal peak in the chromatogram obtained with the reference solution.

Water Not more than 1.5% (Appendix VIII M, method 1 A).

Acidity, Pyrogens and Sterility Complies with the requirements described under Cefalotin Sodium.

Other requirements Complies with the general requirements for injections (Appendix I B), except that the weight variation of contents is not more than $\pm 7.0\%$.

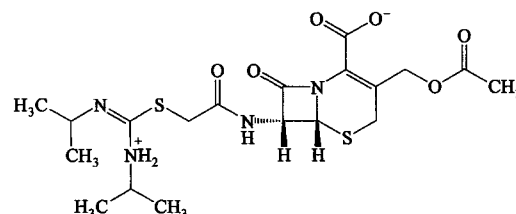
Assay Carry out the Assay described under Cefalotin Sodium, using an accurately weighed quantity of the mixed contents obtained in the test for weight variation of contents.

Category As described under Cefalotin Sodium.

Strength Calculated as $C_{16}H_{16}N_2O_6S_2$
(1) 0.5 g (2) 1 g

Storage Preserve in tightly closed containers, stored in a cool, dry and dark place.

Cefathiamidine



$C_{19}H_{28}N_4O_6S_2$ 472.5 g

Cefathiamidine is (6*R*, 7*R*) -3 [(Acetyl) methyl] -7- α -(*N*, *N*'-diisopropylamidinothio)-acetamido]-8-oxo-5-thia-1-azabicyclo [4.2.0] oct-2-ene-2-carboxylic acid, inner salt. It contains not less than 97.0% of $C_{19}H_{28}N_4O_6S_2$, calculated on the anhydrous basis.

Description A white or almost white crystalline powder; almost odourless; hygroscopic. Very soluble in water; slightly soluble in ethanol; insoluble in acetone, chloroform or ether.

Specific optical rotation $+135^\circ$ to $+145^\circ$, in a solution of 10 mg per ml in water (Appendix VI E).

Identification (1) The retention time of the principal peak of the substance being examined in the chromatogram obtained in Assay is identical with that of cefathiamidine CRS.

(2) Carry out the method for thin-layer chromatography (Appendix V B) using a freshly prepared mixture of methanol-isopropanol-phosphate BS (pH 5.8) (7 : 2 : 1) filtered as mobile phase. Coat the clean plate with homogeneous slurry of 2.5 g of silica gel G mixed in a 1% phosphate BS (pH 5.8) containing carboxymethylcellulose sodium. Dry in air and activate at 105°C for 1 hour, and allow it to cool in a desiccator. Apply separately to the plate 1 μ l each of three solutions (1) containing 20 mg per ml of the substance being examined in water (2) containing 20 mg per ml of cefathiamidine CRS in water (3) obtained by mixing equal quantity of solution (1) and solution (2). After developing and removal of the plate, dry it in air and heat it at 100°C for 30 minutes. Expose it to iodine vapor and examine. The colour and position of the principal spot in the chromatogram obtained with solution (1) correspond to that obtained with solution (2), and only a principal spot in

the chromatogram obtained with solution (3).

(3) The infrared absorption spectrum (Appendix IV C) is concordant with the reference spectrum of cefathiamidine (Appendix XVI).

Test (1) or (2) may be used alternatively.

Crystallinity Complies with the test for crystallinity (Appendix IX D).

Acidity Dissolve a quantity in water to produce a solution of 0.1 g per ml. pH 4.0-6.0 (Appendix VI H).

Clarity and colour of solution Dissolve each of 5 portions in water to produce solution containing 0.1 g per ml respectively. The solutions are clear and colourless; any opalescence produced is not more pronounced than that of reference suspension 1 (Appendix IX A); any colour produced is not more intense than that of reference solution Y₆ or YG₆ (Appendix IX A, method 1).

Water Not more than 1.5% (Appendix VIII M, method 1 A).

Related substances Carry out the method as described under Assay. Dissolve a quantity in water to produce solution (1) containing 0.5 mg per ml and solution (2) containing 5 µg per ml respectively. Inject 10 µl of solution (2) into the column. Adjust the attenuation so that the principal peak height in chromatogram is about 20% of full scale of the chart. Inject separately 10 µl into the column and record the chromatograms for four times retention time of the principal peak. The sum of the area of all peaks other than principal peak in the chromatogram obtained with solution (1) is not greater than 2.5 times area of the principal peak in the chromatogram obtained with solution (2) (not more than 2.5%). Each peak area in the chromatogram obtained with solution (1) other than principal peak is not greater than that of the principal peak in the chromatogram obtained with solution (2) (not more than 1.0%). Disregard any peak with the area less than 0.05 times of area of the principal peak in the chromatogram obtained with solution (2).

Residual solvent Carry out the method for residual solvents (Appendix VIII P). The gas chromatograph is equipped with a flame-ionization detector, a capillary column packed with 6% cyanopropylphenyl and 94% dimethyl silicone (or stationary phase with similar polarity), maintaining the temperature of the column at 30°C. The injection port and the detector are maintained at 140°C and 250°C respectively, inject 1.0 µl. The resolution factor between the principal peaks complies with the related requirements.

Reference standard solution To a quantity of dichloromethane, acetone and ethanol, add water to produce a solution containing 0.03 mg of dichloromethane per ml, 0.25 mg of acetone per ml, and 0.25 mg of ethanol per ml.

Procedure: Dissolve 0.1 g of substance being examined, accurately weighed, in 2 ml of water. Inject 10 µl into the column, record the chromatogram. Repeat the operation, using 1.0 µl of reference standard solution. Calculate the contents with respect to the peak area obtained in the chromatogram by external standard method. The content of dichloromethane is not more than 0.06%, the content of ethanol and acetone is not more than 0.5%.

Bacterial endotoxin Carry out the test for bacterial endotoxin (Appendix XI E); less than 0.075 EU per mg of cefathiamidine.

Sterility Complies with the test for sterility (Appendix XI H, membrane filtration method), dissolving each portion in sterile water and dilute with not less than 500 ml of 0.9% sterile sodium chloride solution.

Assay Carry out the method for high performance liquid

chromatography (Appendix V D), using a column packed with octadecylsilane bonded silica gel and a mixture of phosphate BS (Dissolve 2.76 g of anhydrous disodium hydrogen phosphate and 1.29 g of citric acid in 1000 ml of water)-acetonitrile (80 : 20) as the mobile phase. Detector wavelength is 254 nm and the number of the theoretical plates of the column is not less than 3000, calculated with reference to the peak of cefathiamidine.

Procedure Dissolve an accurately weighed quantity in water to produce a solution of 0.1 mg per ml. Inject 10 µl into the column and record the chromatogram. Repeat the operation, using cefathiamidine CRS instead of the substance being examined. Calculate the content of C₁₉H₂₈N₄O₆S₂ with respect to the peak area obtained in the chromatogram by the external standard method.

Category β-lactam antibiotic, cephalosporin.

Storage Preserve in tightly closed containers, stored in a cool, dry and dark place and protected from light.

Preparation Cefathiamidine Sodium for Injection

Cefathiamidine for Injection

Cefathiamidine for Injection is a sterile powder of Ceftezole Sodium. It contains not less than 97.0% of C₁₉H₂₈N₄O₆S₂, calculated on the anhydrous basis. It contains not less than 90.0% and not more than 110.0% of the labelled amount of cefathiamidine (C₁₉H₂₈N₄O₆S₂), calculated with reference to the average weight of contents.

Description A white to slightly yellow crystalline powder; almost odourless; hygroscopic.

Identification Complies with the tests for Identification described under Cefathiamidine.

Clarity and colour of solution To each of 5 containers add water to produce solutions of 0.1 g per ml. The solutions are clear and colourless; any opalescence produced is not more pronounced than that of reference suspension 1 (Appendix IX B); any colour produced is not more intense than that of reference solution Y₇ or YG₇ (Appendix IX A, method 1).

Water Not more than 2.0% (Appendix VIII M, method 1 A).

Related substance Carry out the method described under Cefathiamidine, using an accurately weighed quantity of the mixed contents obtained from the test for weight variation of contents. The sum of the areas of all peaks other than principal peak in the chromatogram obtained with solution (1) is not greater than three times area of the principal peak in the chromatogram obtained with solution (2) (not more than 3.0%). Each peak area in the chromatogram obtained with solution (1) other than principal peak is not greater than that of the principal peak in the chromatogram obtained with solution (2) respectively (not more than 1.0%). Disregard any peak with the area less than 0.05 times area of the principal peak in the chromatogram obtained with solution (2).

Crystallinity, Acidity, Bacterial endotoxin and Sterility Complies with the requirements described under Cefathiamidine.

Other requirements Complies with the general requirements for injections (Appendix I B).

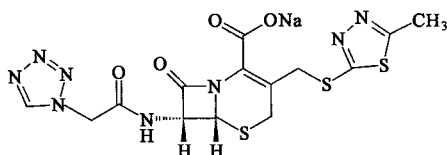
Assay Carry out the Assay described under cefathiamidine, using an accurately weighed quantity of the mixed contents obtained from the test for weight variation of contents.

Category As described under cefathiamidine.

Strength 0.5 g

Storage Preserve in tightly closed containers, stored in a cool and dry place and protected from light.

Cefazolin Sodium



$C_{14}H_{13}N_5NaO_4S_3$ 476.50

[27164-46-1]

Cefazolin Sodium is sodium (6*R*, 7*R*)-3-[[[(5-methyl-1,3,4-thiadiazol-2-yl) thio] methyl]-7-[(1*H*-tetrazol-1-yl) acetamido]-8-oxo-5-thia-1-azabicyclo [4.2.0] oct-2-ene-2-carboxylate. It contains not less than 86.0% of $C_{14}H_{13}N_5O_4S_3$, calculated on the anhydrous basis.

Description A white or almost white powder or crystalline powder; odourless; taste slightly bitter; hygroscopic. Freely soluble in water; slightly soluble in methanol; insoluble in ethanol, acetone or benzene.

Specific optical rotation -15° to -24° , in a solution of 50 mg per ml in water (Appendix VI E).

Specific absorbance Measure the absorbance of an aqueous solution of 16 μ g per ml at 272 nm (Appendix IV A), the value of *A* (1%, 1 cm) is 264-292.

Identification (1) The retention time of the principal peak of the substance being examined in the chromatogram is identical with that of the principal peak of the reference solution in the chromatogram obtained in the Assay.

(2) To a quantity of the substance being examined add water to produce a solution of 16 μ g per ml. The light absorption of the solution exhibits a maximum at 272 nm (Appendix IV A).

(3) Yields the flame reaction of sodium salts (Appendix III).

Acidity Dissolve a quantity in water to produce a solution of 0.1 g per ml, pH 4.5-6.5 (Appendix VI H).

Clarity and colour of solution To 5 portions each of 0.6 g add 5 ml of water respectively, the solutions are clear and colourless; any opalescence produced is not more pronounced than that of reference suspension 1 (Appendix IX B); any colour produced is not more intense than that of reference solution Y₃ or YG₃ (Appendix IX A, method 1).

Related substances Carry out the method for high performance liquid chromatography (Appendix V D), using a column packed with octadecylsilane bonded silica gel. Using phosphate buffer solution (weigh disodium hydrogen phosphate R ($Na_2HPO_4 \cdot 12H_2O$) 2.91 g and potassium dihydrogen phosphate 0.71 g and dissolve with water and dilute to 1000 ml) as mobile phase A and using acetonitrile as mobile phase B. The flow rate is 1.2 ml/min. The wavelength of detector is 254 nm. The column temperature is 45°C. The gradient elution is performed linearly as followed. Dissolve about 10 mg in 10 ml of 0.2% sodium

hydroxide solution. Allow to stand for 15-30 minutes. Accurately measure 1.0 ml of the solution and dilute to 10 ml with mobile phase A. Mix well and use as system suitability solution. Inject 10 μ l into the column. The resolution factor between the cefazolin peak and the adjacent peaks comply with requirements. Inject 10 μ l of reference solution into column. Adjust attenuation so that the cefazolin peak height in the chromatogram is about 20% of full scale of the chart. Dissolve a quantity of the substance being examined, accurately weighed, in mobile phase A to produce a solution of 2.5 mg per ml used as test solution. Accurately measure 1.0 ml of test solution and dilute to 100 ml with mobile phase A used as reference solution. Inject 10 μ l of test solution and reference solution respectively into column and record the chromatogram. Any peak area other than the principal peak is not greater than the cefazolin peak in the chromatogram obtained with the reference solution (1.0%). The sum of the areas of all peaks other than the principal peak is not greater than 3.5 times of the sum areas of the cefazolin peak in the chromatogram obtained with the reference solution (3.5%). (Disregard any peak with an area less than 0.05 times that of the sum area of the cefazolin peak in the chromatogram obtained with reference solution.)

Time(minute)	mobile phase A(%)	mobile phase B(%)
0	98	2
2	98	2
4	85	15
10	60	40
11.5	35	65
12	35	65
15	98	2
21	98	2

Cefazolin polymer Carry out the method for size exclusion chromatography (Appendix V H), using a column 1.3-1.6 cm in internal diameter, 30-40 cm in column length, packed with sephadex G-10 (40-120 μ m), using 0.1 mol/L phosphate BS (pH 7.0) [a mixed solution of 0.1 mol/L disodium hydrogen phosphate and 0.1 mol/L sodium dihydrogen phosphate (61 : 39)] as the eluent A and water as the eluent B with a flow rate 1.5 ml per minute. Detection wavelength is 254 nm. Inject 200 μ l of 0.1 mg/ml blue dextran 2000 solution, using eluent A and eluent B as mobile phase separately, the number of theoretical plates is not less than 700, calculated with reference to blue glucosan 2000, and the tailing factors are not more than 2.0. The ratio of the retention time of blue dextran 2000 peak in eluent A to eluent B should be between 0.93 and 1.07. The ratio of the retention time of the principle peak of reference solution and the polymer peak of test solution to blue dextran 2000 peak of the corresponding system should be between 0.93 and 1.07. Using eluent B as mobile phase, inject accurately 200 μ l of reference solution into column. The relative standard deviation (RSD) for replicate injections of reference solution is less than 5.0%.

Reference solution Dissolve about 20 mg of cefazolin CRS, accurately weighed, in water and dilute to produce a solution of 10 μ g per ml.

Procedure Dissolve about 0.2 g, accurately weighed, in water and dilute to volume in a 10 ml volumetric flask, mix well. Inject 200 μ l of the resulting solution into the column

immediately, using eluent A as mobile phase and record the chromatogram. Inject accurately 200 μ l of the reference solution, using eluent B as mobile phase and record the chromatogram. Calculate the content of cefazolin polymer with reference to cefazolin with respect to the peak area obtained in the chromatogram by the external standard method; not more than 0.03%.

Water Not more than 2.5% (Appendix VIII M, method 1 A).

Bacterial endotoxin Carry out the test for bacterial endotoxin (Appendix XI E); less than 0.1 EU per mg of cefazolin.

Sterility Complies with the test for sterility (Appendix XI H, membrane filtration method), dissolving each portion in 500 ml of 0.9% sterile sodium chloride solution.

Assay Carry out the method for high performance liquid chromatography (Appendix V D), using a column packed with octadecylsilane bonded silica gel and a mixture of disodium hydrogen phosphate citric acid solution (Dissolve 1.33 g of anhydrous disodium hydrogen phosphate and 1.12 g of citric acid in 1000 ml of water)-acetonitrile (88 : 12) as the mobile phase. The wavelength of the detector is 254 nm and the retention time for cefazolin is about 7.5 minutes.

Procedure Dissolve a quantity, accurately weighed, in the mobile phase to produce a solution of 0.1 mg per ml, shake thoroughly. Inject 10 μ l in the column and record the chromatogram. Repeat the operation, using cefazolin CRS instead of the substance being examined, calculate the content of $C_{14}H_{14}N_8O_4S_3$ with respect to the peak area obtained in the chromatogram by the external standard method.

Category β -lactam Antibiotic, cephalosporin.

Storage Preserve in hermetically sealed containers, stored in a cool, dark and dry place.

Preparation Cefazolin Sodium for Injection

Cefazolin Sodium for Injection

Cefazolin Sodium for Injection is a sterile powder of cefazolin Sodium. It contains not less than 86.0% of cefazolin ($C_{14}H_{14}N_8O_4S_3$), calculated on the anhydrous basis. Each container contains not less than 95.0% and not more than 105.0% of the labelled amount of cefazolin ($C_{14}H_{14}N_8O_4S_3$), calculated with reference to the average weight of contents.

Description A white or almost white powder or crystalline powder; odourless.

Identification Complies with the tests for Identification described under Cefazolin Sodium.

Clarity and colour of solution To each of 5 containers add water to produce a solution of 0.1 g per ml, the solutions are clear and colourless; any opalescence produced is not more pronounced than that of reference suspension 1 (Appendix IX B); any colour produced is not more intense than that of reference solution Y₅ or YG₅ (Appendix IX A, method 1).

Related substances Carry out the method as described under Cefazolin Sodium, using an accurately weighed quantity of the mixed contents obtained from the test for weight variation of contents. Comply with the requirements.

Cefazolin polymer Carry out the method as described under

Cefazolin Sodium, using an accurately weighed quantity of the mixed contents obtained from the test for weight variation of contents. Calculate the content of cefazolin polymer with reference to cefazolin; not more than 0.04%.

Water Not more than 3.0% (Appendix VIII M, method 1 A).

Acidity, Bacteria endotoxin and Sterility Complies with the requirement described under Cefazolin Sodium.

Other requirements Complies with the general requirements for injections (Appendix I B).

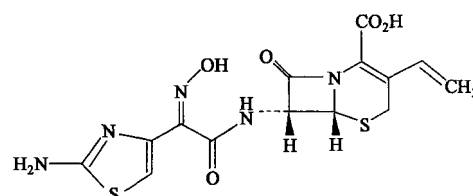
Assay Carry out the Assay described under Cefazolin Sodium, using an accurately weighed quantity of the mixed contents obtained from the test for weight variation of contents.

Category As described under Cefazolin Sodium.

Strength Calculated as $C_{14}H_{14}N_8O_4S_3$
(1) 0.5 g (2) 1.0 g

Storage Preserve in well closed containers, stored in a cool, dark and dry place.

Cefdinir



$C_{14}H_{13}N_5O_5S_2$ 395.42

Cefdinir is (6R, 7R)-7-[(Z)-2-(2-Aminothiazol-4-yl)-2-hydroxyiminoacetyl-amino]-8-oxo-3-vinyl-5-thia-1-azabicyclo[4.2.0]oct-2-ene-2-carboxylic acid. It contains not less than 94.0% of $C_{14}H_{13}N_5O_5S_2$, calculated on the anhydrous basis.

Description A slightly yellow to yellow crystalline powder; odour, slight. Slightly soluble in phosphate BS (pH 7.0); insoluble in water, ethanol, ether.

Specific optical rotation -58° to -66° , in a solution of 10 mg per ml in phosphate BS (pH 7.0) (Appendix VI E).

Specific absorbance Measure the absorbance of a solution of 10 μ g per ml in phosphate BS (pH 7.0) at 287 nm (Appendix VI A), the value of A (1%, 1 cm) is 570-610.

Identification (1) The retention time of the principal peak of the substance being examined is identical with that of the principal peak of the reference solution in the chromatogram obtained in the Assay.

(2) The infrared absorption spectrum (Appendix VI C) is concordant with the reference spectrum of cefdinir CRS.

Crystallinity Complies with the test for crystallinity (Appendix VI D).

Acidity A suspension of 10 mg per ml in water, pH 2.5-4.5 (Appendix VI H).

Related substances Dissolve a quantity in phosphate BS (pH 7.0), and dilute with mobile phase A to produce a solution of 1.5 mg per ml as the test solution. Transfer 1 ml, accurately measured, to a 100 ml volumetric flask, dilute to volume with mobile phase A, mix well, take it as reference solution. Carry out the method for high performance liquid

chromatography (Appendix V D), using a column packed with octadecylsilane bonded silica gel and a solution of 0.4 ml of 0.1 mol/L disodium edetate solution in 1000 ml of 0.25% tetramethylammonium hydroxide solution (adjust pH value to 5.5 with phosphoric acid) as mobile phase A, a solution of 0.4 ml of 0.1 mol/L disodium edetate solution in the mixture of 0.25% tetramethylammonium hydroxide solution (adjust pH value to 5.5 with phosphoric acid)-acetonitrile-methanol (500 : 300 : 200) as mobile phase B. Detection wavelength is 254 nm and column temperature is 40°C. Dissolve the cefdinir CRS in phosphate BS (pH 7.0), using the mobile phase A to produce a solution of 1.5 mg per ml, heat it in a water bath for 30 minutes and cool, inject 20 µl into the column, the retention time of the principal peak of cefdinir is about 22 minutes, the retention time of the principal peak of E-isomer is about 33 minutes. The number of the theoretical plate of the column is not less than 7000, calculated with reference to the peak of cefdinir. The resolution factor between peaks of cefdinir and adjacent peak is not less than 1.0. Inject 20 µl of reference solution into the column. Adjust the attenuation so that the principal peak height in chromatogram is 20% of full scale of the chart, inject separately 20 µl of the test solution and reference solution into the column and record the chromatograms of the principal peak. The sum of the area of all impurity peaks in the chromatogram obtained with test solution is not greater than 3 times area of the principal peak in the chromatogram obtained with reference solution respectively (not more than 3.0%). The area of E-isomer peak in the chromatogram obtained with the test solution is not greater than of 0.8 time area of the principal peak in the chromatogram obtained with the reference solution respectively (0.8%). Disregard any peak with an area less than 0.05 times area of the principal peak in the chromatogram obtained with reference solution.

Time (minutes)	mobile phase A (per cent V/V)	mobile phase B (per cent V/V)
0	95	5
2	95	5
22	75	25
32	50	50
37	50	50
38	95	5
48	95	5

Water Not more than 2.0% (Appendix VIII M method 1 A), using a mixture of formamide and methanol (2 : 1) instead of methanol.

Residue on ignition Not more than 0.2% (Appendix VIII N), using 1.0 g.

Heavy metal Carry out the limit test for heavy metals (Appendix VIII H, method 2), using the residue obtained in the test for residue on ignition; not more than 0.001%.

Assay Carry out the method for high performance liquid chromatography (Appendix V D), using a column packed with octadecylsilane bonded silica gel and a 0.1 mol/L solution of disodium dihydrogen ethylenediamine tetraacetate 0.4 ml in mixture of 0.25% tetramethylammonium hydroxide (adjust pH value to 5.5 with phosphoric acid)-acetonitrile-methanol (900 : 60 : 40) as the mobile phase. detection wavelength is 254 nm and the number of the theoretical plates of the column is not less than 2000, calculated with reference to the peak of cefdinir.

Procedure Dissolve about 20 mg, accurately weighed, in phosphate BS (pH 7.0) in a 100 ml volumetric flask and dilute to volume, mix well. Inject 20 µl of the resulting solution into the column. Repeat the operation, using cefdinir CRS instead of the substance being examined. Calculate the content of $C_{14}H_{13}N_5O_5S_2$ with respect to the peak area obtained in the chromatogram by the external standard method.

Category β -lactam antibiotic, cephalosporin.

Storage Preserve in tightly closed containers, stored in a cool place and protected from light.

Preparation Cefdinir Capsules

Cefdinir capsules

Cefdinir capsules contain not less than 90.0% and not more than 110.0% of the labelled amount of cefdinir ($C_{14}H_{13}N_5O_5S_2$).

Description A slightly yellow or yellow powder or granules.

Identification (1) The retention time of the principal peak of the substance being examined is identical with that of the principal peak of the reference solution in the chromatogram obtained in the Assay.

(2) To an accurately weighed quantity equivalent to about 10 mg of cefdinir of the mixed content. The light absorption of a solution of 10 µg per ml in phosphate BS (pH 7.0) exhibits maxima at 287 nm and 224 nm, and a minimum at 248 nm (Appendix IV A).

Loss on drying When dried in vacuum over phosphorous pentoxide to constant weight at 60°C, loses not more than 3.0% of its weight (Appendix VIII L).

Dissolution Carry out the dissolution test (Appendix X C, method 2), using a solution of hydrochloric acid (dilute hydrochloric acid, 24 → 1000) 900 ml as the dissolution medium, adjust the rotational speed of the paddle to 50 rpm. Withdraw the solution after exactly 30 minutes and filter. Dilute a quantity of the successive filtrate with the above hydrochloric acid solution in amber-coloured volumetric flask to produce a solution of 10 µg per ml. Dissolve a quantity of cefdinir CRS in phosphate BS (pH 7.0) in amber-coloured volumetric flask to produce a solution of 250 µg per ml, filter, dilute the successive filtrate, accurately measured, with the above dissolution medium to produce a solution of 10 µg per ml. Measure the absorbances of the resulting solutions at 280 nm (Appendix IV A). Calculate the dissolution of $C_{14}H_{13}N_5O_5S_2$ from each capsules. Not less than 75% of the labelled amount is dissolved.

Related substances Carry out the method as described under Cefdinir, using an accurately weighed quantity of the mixed contents obtained from the test for weighed variation of contents. Dissolve the Cefdinir in phosphate BS (pH 7.0), with the mobile phase A to produce a solution of 1.5 mg per ml, filter and use the successive filtrate as the test solution. the area of E-isomer peak in the chromatogram obtained with the test solution is not more than 0.8%, and the sum of areas other than cefdinir is not more than 3.5%. Disregard any peak with an area less than 0.05 times area of the principal peak in the chromatogram obtained with reference solution.

Other requirements Comply with the general requirements for capsules (Appendix I E).

Assay Carry out the assay described under cefdinir. Dissolve a quantity of the mixed contents in the test for weigh variation

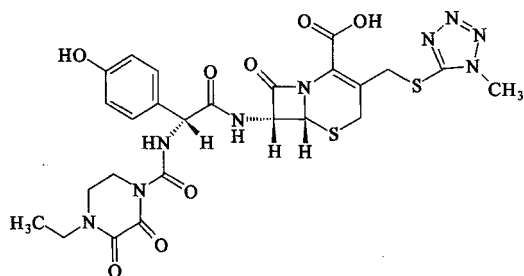
of contents equivalent to about 50 mg of cefdinir, accurately weighed, in 250 ml amber-coloured volumetric flask with phosphate BS (pH 7.0), dilute to volume with the mobile phase, mix well, filter and inject 20 μ l of the successive filtrate into the column.

Category As described under Cefdinir.

Strength 0.1 g

Storage Preserve in tightly closed containers, stored in a cool place and protected from light.

Cefoperazone



$C_{25}H_{27}N_9O_8S_2$ 645.68

[62893-19-0]

Cefoperazone is (6*R*, 7*R*)-3-[[[(1-methyl-1*H*-tetrazol-5-yl)thio]methyl]-7-[(*R*)-2-(4-ethyl-2,3-dioxo-1-piperazinecarboxamido)-2-*p*-hydroxyphenyl]acetamido]-8-oxo-5-thia-1-azabicyclo[4.2.0]oct-2-ene-2-carboxylic acid. It contains not less than 98.0% of $C_{25}H_{27}N_9O_8S_2$, calculated on the anhydrous basis.

Description A white or almost white crystalline powder; odourless; taste, slightly bitter; hygroscopic. Soluble in acetone or dimethyl sulfoxide; slightly soluble in methanol or ethanol; very slightly soluble in water or ethyl acetate.

Specific optical rotation -30° to -38° , in a solution of 30 mg per ml in a mixture of phosphate buffer solution [adjusted with potassium dihydrogen phosphate solution (1 mol/L) to the pH 6.0 with potassium hydroxide solution (10 mol/L)]-acetonitrile (90 : 10) (Appendix VI E).

Identification (1) Dissolve 10 mg in a mixture of 2 ml of water and 3 ml of hydroxylamine hydrochloride solution [mix well one part of 34.8% hydroxylamine hydrochloride solution, one part of sodium acetate-sodium hydroxide solution (dissolve 10.3 g of sodium acetate and 86.5 g of sodium hydroxide in sufficient water to produce 1000 ml) and 4 parts of ethanol], shake thoroughly. Allow to stand for 5 minutes, add 1 ml of acidic ferric ammonium sulfate TS, mix well; a reddish-brown colour is produced.

(2) The retention time of the principal peak of the substance being examined in the chromatogram is identical with that of the principal peak of the reference solution in the chromatogram obtained in the Assay.

Acidity Mix well a quantity with water to produce a suspension of 10 mg per ml, pH 2.0-4.0 (Appendix VI H).

Water Not more than 6.0% (Appendix VIII M, method 1 A).

Assay Carry out the method for high performance liquid chromatography (Appendix V D) using a column packed with octadecylsilane bonded silica gel and a mixture triethylamine acetic acid solution (to 14 ml of triethylamine add 5.7 ml of glacial acetic acid in a 100 ml volumetric flask, dilute with water to volume)-acetonitrile-water (1.2 : 180 :

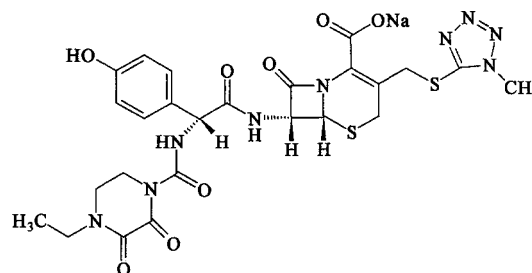
820) adjusted pH value to 3.0 ± 0.2 with glacial acetic acid as the mobile phase. Wavelength of the detector is 254 nm. Dissolve a quantity of cefoperazone CRS, cefoperazone impurity A CRS previously dissolved in acetonitrile and cefoperazone S-isomer in a small amount of phosphate buffer solution (mix 39.0 ml of 0.2 mol/L sodium dihydrogen phosphate solution with 61.0 ml of 0.2 mol/L disodium hydrogen phosphate solution, pH 7.0), and dilute with mobile phase to produce a mixed solution containing 0.2 mg each of the four substances per ml, inject 20 μ l of the mixed solution into the column. The elute order is cefoperazone impurity A, cefoperazone and cefoperazone S-isomer, the resolution factors between two adjacent peaks complies with the related requirements.

Procedure Dissolve about 50 mg, accurately weighed, in mobile phase and dilute with the mobile phase to 100 ml in a 100 ml volume flask and mix well. Inject 20 μ l of the resulting solution into the column and record the chromatogram. Dissolve a quantity of cefoperazone CRS in phosphate buffer described above, dilute with mobile phase to produce to a solution of 0.5 mg per ml and repeat the operation. Calculate the content of $C_{25}H_{27}N_9O_8S_2$ with respect to the peak area obtained in the chromatogram by the external standard method.

Category β -lactam antibiotic, cephalosporin.

Storage Preserve in tightly closed containers, stored in a cool place.

Cefoperazone Sodium



$C_{25}H_{26}N_9NaO_8S_2$ 667.66

[62893-20-3]

Cefoperazone Sodium is the sodium salt of (6*R*, 7*R*)-3-[[[(1-methyl-1*H*-tetrazol-5-yl)thio]methyl]-7-[(*R*)-2-(4-ethyl-2,3-dioxo-1-piperazine carboxamido)-2-*p*-hydroxyphenyl]acetamido]-8-oxo-5-thia-1-azabicyclo[4.2.0]oct-2-ene-2-carboxylate. It contains not less than 88.0% of $C_{25}H_{27}N_9O_8S_2$, calculated on the anhydrous basis.

Description A white to slightly yellow powder or crystalline powder; odourless; hygroscopic. Soluble in water; slightly soluble in methanol; very slightly soluble in ethanol; insoluble in acetone or ethyl acetate.

Specific optical rotation -15° to -25° in a solution of 10 mg per ml in water (Appendix VI E).

Identification (1) The retention time of the principal peak of the substance being examined in the chromatogram is identical with that of the principal peak of the reference solution in the chromatogram obtained in the Assay.

(2) The infrared absorption spectrum of the substance being examined (Appendix IV C) is concordant with the reference spectrum of cefoperazone sodium (Appendix XVI).

(3) Yields the flame reaction of sodium salts (Appendix

III).

Acidity To a quantity add water to produce a solution of 0.25 g per ml, pH 4.5-6.5 (Appendix VI H).

Clarity and colour of solution Dissolve separately each of the 5 portions with water to produce solutions of 0.1 g per ml, the solutions are clear and colourless; any opalescence produced is not more pronounced than that of reference suspension 1 (Appendix IX B); any colour produced is not more intense than that of reference solution Y₄ (Appendix IX A, method 1).

Cefoperazone polymer Carry out the method for size exclusion chromatography (Appendix V H), using a column 1.3-1.6 cm in internal diameter, 30-40 cm in column length packed with sephadex G-10 (40-120 μ m), 0.01 mol/L phosphate BS (pH 7.0) [a mixed solution of 0.01 mol/L disodium hydrogen phosphate and 0.01 mol/L sodium dihydrogen phosphate (61 : 39)] as the eluent A and water as the eluent B with a flow rate 1 ml per minute. Detection wavelength is 254 nm. Inject 200 μ l of 1 mg/ml blue dextran 2000 solution, using eluent A and eluent B as mobile phase separately, the number of theoretical plates is not less than 700, calculated with reference to blue dextran 2000, and the tailing factor is less than 2.0. The ratio of the retention time of blue dextran 2000 peak in eluent A to eluent B should be between 0.93 and 1.07. The proportions of the retention time of the principle peak of reference solution and the polymer peak of test solution to blue dextran 2000 peak of the related system should be between 0.93 and 1.07. Using eluent B as the mobile phase, inject accurately 200 μ l of reference solution into column. The relative standard deviation (RSD) for replicate injections of reference solution is less than 5.0%.

Reference solution Dissolve about 25 mg of cefoperazone CRS, accurately weighed, in water and dilute to produce a solution of 100 μ g per ml.

Procedure Dissolve about 0.2 g, accurately weighed, in water and dilute to volume in a 10 ml volumetric flask, mix well. Inject 200 μ l of the resulting solution into the column immediately, using eluent A as the mobile phase, and record the chromatogram. Inject 200 μ l of the reference solution, using eluent B as the mobile phase, and record the chromatogram. Calculate the content of cefoperazone polymer with reference to cefoperazone with respect to the peak area obtained in the chromatogram by the external standard method; not more than 0.4%.

Related substances Carry out the method as described under Assay. Inject 20 μ l of the reference solution into the column. Adjust the attenuation so that the cefoperazone peak height in the chromatogram is about 15% of full scale of the chart. Dissolve a quantity of the substance being examined, accurately weighed, in mobile phase to produce a test solution of 0.5 mg per ml. Transfer 1 ml of test solution, measured accurately, in a 100 ml volumetric flask, dilute with mobile phase to volume and mix well as reference solution. Dissolve a quantity of the cefoperazone impurity A, accurately weighed, in mobile phase to produce a impurity reference solution of 15 μ g per ml. Inject accurately 20 μ l of test solution, impurity reference solution and reference solution respectively into column and record the chromatogram for four times the retention time of the cefoperazone peak. Calculate the content of cefoperazone impurity A with respect to the peak area obtained in the chromatogram by the external standard method; not more than 3.0%. Each peak area other than the principal peak and impurity A is not greater than twice the principal peak in the chromatogram obtained with the reference solution (2%). The sum of the areas of all peaks other than the

principal peak is not greater than five times of area of the principal peak in the chromatogram obtained with the reference solution (5.0%). Disregard any peak with an area less than 0.1 times area of the principal peak in the chromatogram obtained with reference solution.

Acetone Carry out the method for Head-Space gas chromatography (VIII P). Using a capillary column of HP-5 (or equivalent). Column temperature is 80°C. A Flame Ionization Detector (FID) is used. The temperature of detector is 250°C and injection port is 100°C. Head-space injection is used. The equilibrium temperature of head-space vials is 80°C holding 30 minutes. Inject volume is 1.0 ml. Dissolve 100 mg of the substance being examined, accurately weighed in the head-space vials and pipette 3 ml of water accurately in the vials and mix well. Seal the vials as test solution. weigh accurately 33 mg of acetone in 50 ml volumetric flask, add water to volume and mix well. Accurately pipette 3.0 ml in the head-space vials and seal the vials as standard solution. Inject the test solution and standard solution to the column separately and record the chromatogram. Calculate the content with respect to the peak area obtained in the chromatogram by external standard method. The content of acetone is not more than 2.0%.

Water Not more than 5.0% (Appendix III M, method 1A).

Bacterial endotoxin Carry out the test for bacterial endotoxin (Appendix XI E); less than 0.05 EU per mg of cefoperazone.

Sterility Complies with the test for sterility (Appendix XI H, membrane filtration method), dissolving each portion in 500 ml of 0.9% sterile Sodium Chloride Solution.

Assay Carry out the Assay described under Cefoperazone.

Category β -lactam antibiotic, cephalosporin.

Storage Preserve in tightly closed containers, stored in a cold place.

Preparation Cefoperazone Sodium for Injection

Cefoperazone Sodium and Sulbactam Sodium for Injection

Cefoperazone Sodium and Sulbactam Sodium for Injection is a sterile mixture of Cefoperazone Sodium and Sulbactam Sodium (1 : 1). It contains not less than 43.5% of cefoperazone ($C_{25}H_{27}N_9O_8S_2$) and 44.5% of sulbactam ($C_8H_{11}NO_5S$) per mg respectively, calculated on the anhydrous basis. It contains not less than 90.0% and not more than 115.0% of the labelled amount of cefoperazone ($C_{25}H_{27}N_9O_8S_2$) and sulbactam ($C_8H_{11}NO_5S$), calculated with the reference to the average weight of contents.

Description A White or almost white powder.

Identification (1) The retention time of two principal peaks of the substance being examined in the chromatogram obtained in the Assay are identical with that of principal peaks of cefoperazone CRS and sulbactam CRS in the chromatogram of the reference solution correspondingly.

(2) Carry out the method for thin-layer chromatography (Appendix V B), using silica gel G as the coating substance and a mixture of ethyl acetate-acetone-acetic acid-water (10 : 5 : 2 : 2) as the mobile phase. Apply separately to the plate

2.5 μ l each of test solution containing 10 mg of the substance being examined per ml, reference solution (1) containing 5 mg of sulbactam CRS per ml in water respectively, and reference solution (2) containing 5 mg of cefoperazone CRS per ml in acetone. After developing and removal of the plate, dry it in air and visualize with iodine vapor. The position of the principal spots in the chromatogram obtained with the test solution correspond to the principal spots obtained with the reference solutions.

(3) Yields the flame reaction of sodium salts (Appendix III).

Test (1) and (2) may be used alternatively.

Acidity Dissolve a quantity in water to produce a solution of 125 mg of cefoperazone per ml, pH 3.5-6.5 (Appendix VI H).

Clarity and colour of solution To each of 5 containers add water to produce a solution of 50 mg of cefoperazone per ml, the solution is clear and colourless; any opalescence produced is not more pronounced than that of reference suspension 1 (Appendix IX B); any colour produced is not more intense than that of reference solution Y₄ (Appendix IX A method 1).

Related substances Carry out the method as described under Assay. Inject 10 μ l of the reference solution into the column. Adjust the attenuation so that the cefoperazone peak height in the chromatogram is about 25% of full scale of the chart. Dissolve a quantity of the substance being examined, accurately weighed, in mobile phase to produce a solution of 4 mg per ml as test solution. Transfer 1 ml of test solution, accurately measured, in a 100 ml volumetric flask, dilute with mobile phase to volume and mix well as reference solution. Inject accurately 10 μ l of test solution and reference solution respectively into the column and record the chromatogram for three times the retention time of the cefoperazone peak. The sum of the areas of all peaks other than the principal peak is not greater than five times of the sum areas of the cefoperazone peak and sulbactam peak in the chromatogram obtained with the reference solution (5.0%). Disregard any peak with an area less than 0.05 times that of the sum area of the cefoperazone peak and sulbactam peak in the chromatogram obtained with reference solution.

Water Not more than 4.0% (Appendix VIII M method 1).

Bacterial endotoxin Carry out the test for bacterial endotoxin (Appendix XI E); less than 0.125 EU per mg.

Sterility Dissolve the content of each container in 500 ml of 0.9% sterile sodium chloride solution. The solution complies with the test for sterility (Appendix XI H, membrane filtration method).

Other requirements Complies with the general requirements for injections (Appendix I B).

Assay Carry out the method for high performance liquid chromatography (Appendix V D), using a column packed with octadecylsilane bonded silica gel and a mixture of 0.005 mol/L tetrabutylammonium hydroxide solution (to 6.6 ml of 40% tetrabutylammonium hydroxide solution add 1800 ml of water, adjust pH value to 4.0 with 1 mol/L phosphoric acid solution, add water to 2000 ml, mix well)-acetonitrile (750 : 250) as the mobile phase. Detection wavelength is 220 nm. Dissolve a quantity of cefoperazone CRS and sulbactam CRS in a small amount of phosphate BS [mix 39.0 ml of 0.2 mol/L disodium hydrogen phosphate solution with 61.0 ml of 0.2 mol/L sodium dihydrogen phosphate solution and adjust pH value to 7.0 with phosphoric acid] and dilute with mobile phase to produce a solution containing 1 mg each of two substances per ml. Heat for 30 minutes at 60°C in a

water bath to produce cefoperazone degradation product peak which the relative retention time is about 0.9. Inject 10 μ l into column and record the chromatogram. The number of the theoretical plates of the column is not less than 3000, calculated with reference to the peak of cefoperazone, the resolution factors between the peaks of cefoperazone degradation product and sulbactam, the resolution factors between cefoperazone and adjacent peak comply with the requirement.

Procedure Dissolve a quantity of the mixed contents obtained in the test for weight variation of contents (equivalent to 100 mg cefoperazone), accurately weighed, in mobile phase in a 200 ml volumetric flask, dilute to volume and mix well. Inject 10 μ l into the column and record the chromatogram. Dissolve about 25 mg of cefoperazone CRS and sulbactam CRS in phosphate buffer solution described above in a 50 ml volumetric flask, dilute with mobile phase to volume, and repeat the operation. Calculate the content of C₂₅H₂₇N₉O₈S₂ and C₈H₁₁NO₅S with respect to the peak area obtained in the chromatogram by the external standard method.

Category β -Lactam antibiotic.

Strength (1) 1 g (C₂₅H₂₇N₉O₈S₂ 0.5 g : C₈H₁₁NO₅S 0.5 g)
(2) 2 g (C₂₅H₂₇N₉O₈S₂ 1.0 g : C₈H₁₁NO₅S 1.0 g)
(3) 3 g (C₂₅H₂₇N₉O₈S₂ 1.5 g : C₈H₁₁NO₅S 1.5 g)

Storage Preserve in well closed containers, stored in a cold place.

Cefoperazone Sodium for Injection

Cefoperazone Sodium for Injection is a sterile powder or sterile lyophilized preparation of cefoperazone sodium. It contains not less than 88.0% of cefoperazone (C₂₅H₂₇N₉O₈S₂), calculated on the anhydrous basis. It contains not less than 95.0% and not more than 105.0% of the labelled amount of cefoperazone (C₂₅H₂₇N₉O₈S₂), calculated with reference to the average contents.

Description A white to slightly yellow crystalline powder or lyophilized powder or mass; odourless; hygroscopic. Freely soluble in water; sparingly soluble in methanol; very slightly soluble in ethanol; insoluble in acetone or ethyl acetate.

Specific optical rotation -15° to -25° , in a solution of 10 mg per ml in water (Appendix VI E).

Identification Complies with the tests for Identification described under Cefoperazone Sodium.

Clarity and colour of solution To each of 5 containers add water to produce a solution of 0.1 g per ml, the solutions are clear and colourless; any opalescence produced is not more pronounced than that of reference suspension 1 (Appendix IX B); any colour produced is not more intense than that of reference solution Y₆ (Appendix IX A, method 1).

Related substances Carry out the method as described under Cefoperazone Sodium. Calculate the content of cefoperazone impurity A with respect to the peak area obtained in the chromatogram by the external standard method; not more than 3.5%. Each peak area other than the principal peak and impurity A is not greater than 2.5 times of the principal peak in the chromatogram obtained with the reference solution (2.5%). The sum of the areas of all

peaks other than the principal peak is not greater than six times of area of the principal peak in the chromatogram obtained with the reference solution (6.0%). Disregard any peak with an area less than 0.1 times that of the sum area of the principal peak in the chromatogram obtained with reference solution.

Cefoperazone polymer Carry out the method described under Cefoperazone Sodium, using an accurately weighed quantity of the mixed contents obtained from the test for weight variation of contents. Calculate the content of cefoperazone polymer with reference to cefoperazone; not more than 0.8%.

Acidity, water, Bacterial endotoxin and Sterility As described under Cefoperazone Sodium.

Other requirements Complies with the general requirements for injections (Appendix I B).

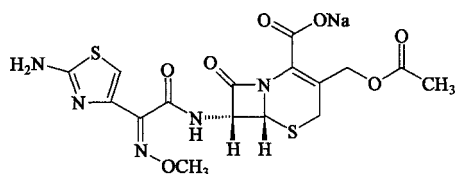
Assay Carry out the Assay described under Cefoperazone, using an accurately weighed quantity of the mixed contents obtained from the test for weight variation of contents.

Category As described under Cefoperazone Sodium.

Strength Calculated as $C_{25}H_{27}N_9O_8S_2$
(1) 0.5 g (2) 1.0 g (3) 2.0 g

Storage Preserve in well closed containers, stored in a cool place.

Cefotaxime Sodium



$C_{16}H_{16}N_5NaO_7S_2$ 477.45 [64485-93-4]

Cefotaxime Sodium is sodium (6*R*, 7*R*)-3-[(Acetyloxy) methyl]-7-[(2-amino-4-thiazolyl) (methoxyimino) acetyl amino]-8-oxo-5-thia-1-azabicyclo [4.2.0] oct-2-ene-2-carboxylic acid. It has a potency of not less than 86.0% of $C_{16}H_{16}N_5NaO_7S_2$, calculated on the anhydrous basis.

Description A white to pale yellowish-white crystal; odourless or slightly characteristic. Freely soluble in water; slightly soluble in ethanol; insoluble in chloroform.

Specific optical rotation $+56^\circ$ to $+64^\circ$, in a solution of 10 mg per ml in water (Appendix VI E).

Specific absorbance Measure the absorbance of a solution of 10 μ g per ml in hydrochloric acid solution (0.01 mol/L) at 262 nm (Appendix IV A), the value of *A* (1%, 1 cm) is 400-440, calculated on the anhydrous basis.

Identification (1) The retention time of the principal peak of the substance being examined in the chromatogram is identical with that of the principal peak of the reference solution in the chromatogram obtained in the Assay.

(2) The infrared absorption spectrum (Appendix IV C) is concordant with the reference spectrum of cefotaxime (Appendix XVI).

(3) Yields the flame reaction of sodium salts (Appendix III).

Acidity Dissolve a quantity in water to produce a solution of about 0.1 g per ml, pH 4.5-6.5 (Appendix VI H).

Clarity and colour of solution To 5 portions each add water to produce solutions of 0.1 g per ml respectively, the solutions are clear and colourless; any opalescence produced is not more pronounced than that of reference suspension 1 (Appendix IX B), any colour produced is not more intense than that of reference solution Y_8 or OY_8 (Appendix IX A).

Water Not more than 6.0% (Appendix VIII M, method 1 A).

Cefotaxime polymer Carry out the method for size exclusion chromatography (Appendix V H). Using a column with 1.3-1.6 cm in internal diameter and 30-40 cm in column length, packed with sephadex G-10 (40-120 μ m), a 0.1 mol/L phosphate buffer pH 7.0 [0.1 mol/L disodium hydrogen phosphate solution-0.1 mol/L sodium dihydrogen phosphate (61 : 39)] as eluent A and water as eluent B. The flow rate is 1.5 ml per minute and the detection wavelength is 254 nm. Inject 200 μ l of a solution containing 0.1 mg of blue dextran 2000 per ml into the column separately using eluent A and eluent B as the mobile phase. The number of the theoretical plates of the column is not less than 700, calculated with reference to blue dextran 2000, and the tailing factor is not more than 2.0. The ratio of retention time of blue dextran 2000 peak in eluent A to eluent B is between 0.93-1.07, the ratio of retention time of the polymer peak of the test solution and the principal peak of reference solution to the blue dextran 2000 peak in the corresponding system should be between 0.93-1.07. The relative standard deviation (RSD) of the areas of the principal peak in chromatogram obtained with accurately measured 200 μ l of the reference solution for 5 replicate injections is not more than 5.0%, using eluent B as the mobile phase.

Reference solution Dissolve an accurately weighed quantity of cefotaxime CRS in water to produce a solution of 100 μ g per ml.

Procedure Dissolve about 0.2 g, accurately weighed, with water in a 10 ml volumetric flask, dilute to volume with water, mix well as test solution. Inject immediately 200 μ l into the column and record the chromatogram, using eluent A as the mobile phase. Inject 200 μ l the reference solution into the column and record the chromatogram, using eluent B as the mobile phase. The content of cefotaxime polymer is not more than 0.5%, calculate as cefotaxime with respect to the peak area obtained in the chromatogram by the external standard method.

Bacterial endotoxin Carry out the test for bacterial endotoxin (Appendix XI E): less than 0.05 EU per 1 mg of cefotaxime.

Sterility Complies with the test for sterility (Appendix XI H, membrane filtration method). Dissolve the test in a suitable solution, and then transfer it into not less than 500 ml of 0.9% sterile sodium carbonate solution.

Assay Carry out the method for high performance liquid chromatography (Appendix V D), using a column packed with octadecylsiane bonded silica gel and a mixture of phosphate BS (Dissolve 60 mg of potassium dihydrogen phosphate and 1.2 g of disodium hydrogen phosphate in water and dilute to 1000 ml)-methanol (89 : 11) as the mobile phase. The wavelength of the detector is 254 nm and the number of the theoretical plates of the column is not less than 1200, calculated with reference to the peak of

cefotaxime sodium.

Procedure Dissolve about 40 mg, accurately weighed, in water in a 100 ml volumetric flask and dilute to volume, mix well. Transfer 5 ml of the solution in another 100 ml volume. Inject 2 μ l of the resulting solution into the column and record the chromatogram. Repeat the operation using cefotaxime CRS instead of the substance being examined, calculate the content of $C_{16}H_{16}N_5NaO_7S_2$.

Category β -lactam antibiotic, cephalosporin.

Storage Preserve in hermetically sealed containers, stored in a cool and dry place and protected from light.

Preparation Cefotaxime Sodium for Injection

Cefotaxime Sodium for Injection

Cefotaxime Sodium for Injection is a sterile powder of Cefotaxime Sodium. It contains not less than 86.0% of cefotaxime ($C_{16}H_{17}N_5O_7S_2$), calculated on the anhydrous basis. Each container contains not less than 93.0% and not more than 107.0% of the labelled amount of cefotaxime ($C_{16}H_{17}N_5O_7S_2$), calculated on basis of the average weight of contents.

Description A white to pale yellowish-white crystalline powder.

Identification Complies with the tests (1) and (3) for Identification described under Cefotaxime Sodium.

Clarity and colour of solution To each of 5 containers add water to produce solutions of 0.1 g per ml by the labelled amount, the solutions are clear and colourless; any opalescence produced is not more pronounced than that of reference suspension 1 (Appendix IX B), any colour produced is not more intense than that of reference solution Y_5 or OY_5 (Appendix IX A).

Water Not more than 6.0% (Appendix VIII M, method 1 A).

Cefotaxime polymer Carry out the method described under Cefotaxime Sodium, using an accurately weighed quantity of the mixed contents obtained from the test for weight variation of contents. Calculate the content of cefotaxime polymer with reference to cefotaxime; not more than 1.0%.

Acidity, Bacterial endotoxin and sterility Complies with the corresponding requirement described under Cefotaxime Sodium.

Other requirements Complies with the general requirements for injections (Appendix I B).

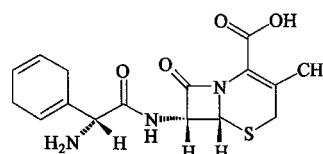
Assay Carry out the Assay described under Cefotaxime Sodium, using an accurately weighed quantity of the mixed contents obtained from the test for weight variation of contents.

Category As described under Cefotaxime Sodium.

Strength Calculated as $C_{16}H_{17}N_5O_7S_2$
(1) 0.5 g (2) 1.0 g (3) 2.0 g

Storage Preserve in well closed containers, stored in a cool and dry place and protected from light.

Cefradine



$C_{16}H_{19}N_3O_4S$ 349.40

[38821-53-3]

Cefradine is (6*R*, 7*R*)-7-[(*R*)-2-amino-2-(1,4-cyclohexadien-1-yl)-acetamido]-3-methyl-8-oxo-5-thia-1-azabicyclo[4.2.0]oct-2-ene-2-carboxylic acid. It contains not less than 90.0% of $C_{16}H_{19}N_3O_4S$, calculated on the anhydrous basis.

Description A white or almost white crystalline powder; odour, characteristic.

Sparingly soluble in water; practically insoluble in ethanol, chloroform or ether.

Specific optical rotation $+80^\circ$ to $+90^\circ$, in a solution of 10 mg per ml in acetate buffer solution (dissolve 1.36 g of sodium acetate in 50 ml of water, adjust to pH 4.6 with glacial acetic acid and add water to produce 100 ml), (Appendix VI E).

Identification (1) Carry out the method of thin-layer chromatography (Appendix V B), using silica gel G as the coating substance and a mix of 0.1 mol/L citric acid solution-0.2 mol/L disodium hydrogen phosphate solution-acetone (60 : 40 : 1.5) as the mobile phase. Activate the plate at 105°C for 1 hour and elute with a freshly prepared 5% (ml/ml) solution of *n*-tetradecane in *n*-hexane, dry in air. Apply separately to the plate 5 μ l each of the two solutions in water containing ① 6 mg of the substance being examined per ml and ② 6 mg of Cefradine CRS per ml. After developing and removal of the plate, heat it at 105°C for 5 minutes, spray with 0.1% solution of ninhydrin in the mobile phase, and heat at 105°C for 15 minutes. The colour and position of the principal spot in the chromatogram obtained with solution ① correspond to that of the principal spot in the chromatogram obtained with solution ②.

(2) The retention time of principal peaks of the substance being examined in the chromatogram is identical with that of the principal peak of the reference solution in the chromatogram obtained in the Assay.

(3) Dissolve a quantity in methanol evaporate to dryness at room temperature and prepare spectrum of the residue. The infrared absorption spectrum (Appendix IV C) is concordant with the reference spectrum of cefradine (Appendix XVI). (1) or (2) may be used alternatively.

Crystallinity Complies with the test for crystallinity (Appendix IX D).

Acidity To a quantity add water to produce a solution of 10 mg per ml, pH 3.5-6.0 (Appendix VI H).

Clarity and colour of solution To each of five portions (0.55 g of the substance being examined in each portion) add 0.15 g of sodium carbonate and 5 ml of water respectively. The solutions are clear and colourless; any opalescence produced is not more pronounced than that of reference suspension 1 (Appendix IX B); any colour produced is not more intense than that of reference solution Y_5 or YG_5 (Appendix IX A, method 1) (for parenteral administration).

Cefalexin Carry out the method described under Assay to produce a test solution. Dissolve about 20 mg of cefalexin

CRS, accurately weighed, in the mobile phase by ultrasonical treatment in a 50 ml volumetric flask, mix well and dilute to volume. Measure accurately 5 ml of the solution to a 50 ml volumetric flask, add mobile phase to volume, mix well, as reference solution. Carry out the method as described under Assay. Inject 10 μ l of the reference solution into the column. Adjust the attention so that the principal peak height in the chromatogram is about 20%-25% of full scale of the chart. Inject separately 10 μ l of the test solution and reference solution into the column and record the chromatogram. The content of cefalexin is not more than 5.0%, calculated on the anhydrous basis.

Cefradine polymer Carry out the method for column chromatography (Appendix V H), using a column with 1.3-1.6 cm in internal diameter and 30-40 cm height packed with sephadex G-10 (40-120 μ m), a 0.2 mol/L phosphate buffer solution (pH 8.0) [0.2 mol/L disodium hydrogen phosphate solution-0.2 mol/L sodium dihydrogen phosphate solution (95 : 5)] as eluent A and water as eluent B. The flow rate is 1.0 ml per minute and the detection wavelength is 254 nm. Inject 200 μ l of the solution of 0.1 mg/ml blue dextran 2000 per ml into the column using eluent A and eluent B separately. The number of the theoretical plates of the column is not less than 700 and the tailing factor is not more than 2.0, calculated with reference to the peak of blue dextran 2000. The ratio of retention time of blue dextran 2000 peak in eluent A to eluent B is 0.93-1.07, the ratio of retention time of the polymer peak of the test solution and the blue dextran 2000 peak in mobile phase A is 0.93-1.07, and the ratio of retention time of the principal peak of the reference solution and the blue dextran 2000 peak in mobile phase B is 0.93-1.07. The relative standard deviation (RSD) of the areas of the principal peak in the chromatogram obtained with 200 μ l of the reference solution for five replicate injections is not more than 5.0%, using eluent B as the mobile phase. (using a 0.2 mol/L sodium hydroxide solution and 0.5 mol/L sodium chloride solution to rinse the gel column, then rinse to neutrality with water if necessary).

Reference preparation Dissolve an accurately weighed quantity of Cefradine CRS in water to produce a solution of 10 μ g per ml.

procedure Dissolve about 0.2 g, accurately weighed, dilute with mobile phase A to 10 ml. Inject immediately 200 μ l into column and record the chromatogram, using eluent A as the mobile phase. Repeat the operation, using the reference solution instead of the solution of substance being examined and eluent B instead of the eluent A. The content of cefradine polymer is not more than 0.05%, calculated as cefradine ($C_{16}H_{19}N_3O_4S$) with respect to the peak area obtained in the chromatogram by the external standard method.

Related substances Carry out the method as described under Assay. Dissolve an accurately weighed quantity of the substance being examined in mobile phase to produce a solution of 1 mg per ml as test solution, dilute an accurately measured quantity with mobile phase to produce a reference solution of 5 μ g per ml. Dissolve an accurately weighed quantity in reference solution to produce an impurity reference solution containing 10 μ g per ml of each of cefalexin CRS, dihydrophenylglycine CRS and 7-aminodesacetoxy-cephalosporanic acid CRS. Inject 20 μ l of the impurity reference solution into the column, using 220 nm as the detected wavelength, the order of elution is 7-aminodesacetoxy-cephalosporanic acid, dihydrophenylglycine, cefalexin and cefradine. The resolution factor between each peak complies with the related requirements. Inject 20 μ l of the

reference solution into the column, using 254 nm as the detected wavelength, adjust the attenuation so that the principal peak height in the chromatogram is about 20%-25% of full scale of the chart. Inject separately 20 μ l of the test solution, the impurity reference solution and the reference solution into the column and record the chromatograms for 2.5 times of the retention time of the principal peak, using separately 220 nm and 254 nm as the detected wavelength. The each content of the dihydrophenylglycine (detected at 220 nm) and 7-aminodesacetoxy-cephalosporanic acid (detected at 254 nm) is not more than 1.0%, calculated with respectively area obtained in the chromatogram with the test solution by the external standard method. The area of each peak of other impurities (detected at 254 nm) is not more than 4 times of the area of principal peak in the chromatogram obtained with the reference solution (2.0%). The sum of the area of all other impurity peaks (detected at 254 nm) is not more than 5 times of the area of principal peak in the chromatogram obtained with the reference solution (2.5%).

Water Not more than 6.0% (Appendix VIII M, method 1 A).

Residue on ignition Not more than 0.2%, using 1.0 g (Appendix VIII N).

Heavy metals Carry out the limit test for heavy metals (Appendix VIII H, method 2), using the residue obtained in the test for residue on ignition; not more than 0.002%.

Bacterial endotoxin Dissolve a quantity in a solution of sodium carbonate (dissolve 2.56 g of sodium carbonate previously heated at 170°C for not less than 4 hours in Water for Injection to produce 100 ml). Carry out the test for bacterial endotoxin (Appendix XI E); less than 0.20 EU per mg of cefradine (for injection).

Sterility Complies with the test for sterility (Appendix XI H, membrane filtration method), dissolving each portion in 2.6% of sterile sodium carbonate and dilute with not less than 500 ml of 0.9% sterile sodium chloride solution.

Assay Carry out the method for high performance liquid chromatography (Appendix V D), using a column packed with an octadecylsilane bonded silica gel and a mixture of water-methanol-3.86% solution of sodium acetate-4% solution of acetic acid (1564 : 400 : 30 : 6) as the mobile phase, the flow rate is 0.7-0.9 ml per minute and the detection wavelength is 254 nm. The number of theoretical plates of the column is not less than 2500, calculated with reference to the peak of cefradine. Inject 10 μ l of the resulting solution prepared by mixing 10 volumes of cefradine CRS solution and 1 volume of cefalexin CRS stock solution (0.4 mg/ml) into the column, and record the chromatogram. The resolution factor between peaks of cefradine and cefalexin complies with the related requirements.

Procedure Dissolve about 70 mg of the substance being examined, accurately weighed, in mobile phase by ultrasonical treatment and dilute to 100 ml, mix well. Inject 10 μ l into the column and record the chromatogram. Repeat the operation, using cefradine CRS preparation instead of the substance being examined. Calculate the content of cefradine ($C_{16}H_{19}N_3OS$) by the external standard method.

Category β -lactam antibiotic, cephalosprin.

Storage Preserve in tightly closed containers filled with nitrogen, stored in a place below 10°C protected from light.

Preparations (1) Cefradine Capsules
(2) Cefradine for Injection

- (3) Cefradine for Suspension
- (4) Cefradine Granules
- (5) Cefradine Tablets

Cefradine Capsules

Cefradine Capsules contain not less than 90.0% and not more than 110.0% of the labelled amount of cefradine ($C_{16}H_{19}N_3O_4S$).

Description The contents are white to pale yellow powder or granules.

Identification The contents of cefradine capsules comply with the test (1) or test (2) for Identification described under Cefradine.

Cefalexin Carry out the test method described under Cefradine, using an accurately weighed quantity to prepare the test solution as described under Assay, the content of cefalexin is not more than 6.0% of the total amount of cefradine and cefalexin.

Related substances Carry out the test method described under Cefradine, the detection wavelength is 254 nm. Using a mixed contents obtained from the test for weight variation of contents, dissolve an accurately weighed quantity in mobile phase to produce a test solution of 1 mg per ml. The content of the 7-aminodesacetoxy-cephalosporanic acid is not more than 1.0%, calculated with respectively area obtained in the chromatogram with the test solution by the external standard method. The area of each peak of other impurities is not more than 5 times the area of principal peak in the chromatogram obtained with the reference solution (2.5%). The sum of the area of all other impurity peaks is not more than 6 times the area of principal peak in the chromatogram obtained with the reference solution (3.0%).

Water Not more than 7.0% (Appendix VIII M, method 1 A).

Dissolution Carry out the dissolution test (Appendix X C, Method 1), using 900 ml of 0.1 mol/L hydrochloric acid solution as the dissolution medium, adjust the rotational speed of the basket to 100 rpm. Withdraw the solution after exactly 45 minutes and filter. Dilute a quantity of the successive filtrate with 0.1 mol/L hydrochloric acid solution to produce a solution of 25 µg per ml. Dissolve an accurately weighed quantity, equivalent to about the average weight in each capsule, of the mixed contents in the test for weight variation of contents in 0.1 mol/L hydrochloride acid solution to produce a solution of 25 µg per ml according to the labelled amount. Measure the absorbances of resulting solutions at 255 nm (Appendix IV A). Calculate the dissolution of $C_{16}H_{19}N_3O_4S$ from each capsule. Not less than 80% of the labelled amount is dissolved.

Other requirements Comply with the general requirements for capsules (Appendix I E).

Assay Carry out the Assay described under Cefradine, using the mixed contents obtained from the test for weight variation of contents. To an accurately weighed quantity equivalent to about 70 mg of cefradine in a 100 ml volumetric flask, add 70 ml of the mobile phase, dissolve in an ultrasonic bath for 15 minutes and shake thoroughly for 10 minutes, dilute to volume with mobile phase, mix well and filter with 0.45 µm pore size membrane. Measure accurately 10 µl of the successive filtrate and inject into the column.

Category As described under Cefradine.

Strength Calculated as $C_{16}H_{19}N_3O_4S$
(1) 0.125 g (2) 0.25 g (3) 0.5 g

Storage Preserve in tightly closed containers, stored in a cool and dark place.

Cefradine for Injection

Cefradine for Injection is a sterile mixture of Cefradine and suitable amount of solubilizer. It contains not less than 95.0% and not more than 115.0% of the labelled amount of cefradine ($C_{16}H_{19}N_3O_4S$).

Description A white or almost white powder.

Identification The retention time of the principal peak in the chromatogram obtained with the test solution in the Assay is identical with that of the principal peak in the chromatogram obtained with the reference solution.

Alkalinity Dissolve a quantity in water to produce a solution containing 0.1 g of cefradine per ml, pH 8.0-9.6 (Appendix VI H).

Clarity and colour of solution Add water to each of 5 containers to produce solutions containing 0.1 g of cefradine per ml. The solutions are clear and colourless; any opalescence produced is not more pronounced than that of reference suspension 1 (Appendix IX B); any colour produced is not more intense than that of reference solution Y_8 or YG_8 (Appendix IX A, method 1).

Cefalexin Carry out the test method described under Cefradine, the content of cefalexin is not more than 6.0% of the total amount of cefradine and cefalexin.

Related substances Carry out the test method described under Cefradine, the detection wavelength is 254 nm. Using a mixed contents obtained from the test for weight variation of contents, dissolve an accurately weighed quantity in mobile phase to produce a test solution of 1 mg per ml. The content of the 7-aminodesacetoxy-cephalosporanic acid is not more than 1.0%, calculated with respectively area obtained in the chromatogram with the test solution by the external standard method. The area of each peak of other impurities is not more than 5 times of the area of principal peak in the chromatogram obtained with the reference solution (2.5%). The sum of the area of all other impurity peaks is not more than 6 times of the area of principal peak in the chromatogram obtained with the reference solution (3.0%).

Loss on drying When dried in vacuum over phosphorous pentoxide at 60°C for 3 hours, loses not more than 5.0% (Appendix VIII L) (containing of sodium carbonate).

Water Not more than 5.0% (Appendix VIII M, method 1 A) (containing of arginine).

Bacterial endotoxin Carry out the test for bacterial endotoxin (Appendix XI E); not more than 0.20 EU per mg of cefradine.

Sterility Complies with test for Sterility (Appendix XI H, membrane filtration method), dissolving each portion in not less than 500 ml of 0.9% sterile sodium chloride solution.

Other requirements Complies with the general requirements for injections (Appendix I B).

Assay Carry out the method described under Cefradine,

using the mixed contents obtained from the test for weight variation of contents. To an accurately weighed quantity equivalent to about 70 mg of cefradine in a 100 ml volumetric flask, add 70 ml of the mobile phase to dissolve the cefradine, and dilute to volume with the mobile phase, mix well, and filter. Measure accurately 10 μ l of the successive filtrate and inject into the column.

Category As described under Cefradine.

Strength Calculated as $C_{16}H_{19}N_3O_4S$
(1) 0.5 g (2) 1.0 g

Storage Preserve in well closed containers, stored in a dark and cool place.

Cefradine for Suspension

Cefradine for Suspension contains not less than 90.0% and not more than 120.0% of the labelled amount of cefradine ($C_{16}H_{19}N_3O_4S$).

Description powders; with flavors; odour, fragrant; taste, sweet.

Identification Complies with the test (1) or test (2) for Identification described under Cefradine.

Acidity A suspension of 25 mg per ml in water, pH 3.5-6.0 (Appendix VI H).

Ratio of sedimental volume Added water according to the ratio of administration, shake for 1 minute, allow to stand for 45 minutes (Appendix I O), ratio of sedimental volume should be not less than 0.90 (for maltidoses).

Water Not more than 1.5% (Appendix VIII M, method 1 A).

Cefalexin Carry out the test method described under Cefradine, the content of cefalexin is not more than 6.0% of the total amount of cefradine and cefalexin.

Other requirements Complies with the general requirements for oral suspensions (Appendix I O).

Assay Carry out the method described under Cefradine, using the mixed contents obtained from the test for filling or weight variation of contents. Dissolve an accurately weighed quantity equivalent to about 70 mg of cefradine in a 100 ml volumetric flask, with 70 ml of the mobile phase by ultrasonic treatment for 15 minutes, and dilute to volume with the mobile phase, mix well, and filter. Measure accurately 10 μ l of the successive filtrate and inject into the column.

Category As described under Cefradine.

Strength Calculated as $C_{16}H_{19}N_3O_4S$
(1) 0.125 g (2) 0.25 g (3) 1.5 g (4) 3.0 g

Storage Preserve in tightly closed containers, stored in a cool and dark place.

Cefradine Granules

Cefradine Granules contain not less than 90.0% and not more than 110.0% of the labelled amount of cefradine ($C_{16}H_{19}N_3O_4S$).

Description Suspension granules; odour fragrant; taste, sweet.

Identification Complies with test (1) or test (2) for Identification described under Cefradine.

Acidity A suspension of 25 mg per ml in water, pH 3.5-6.0 (Appendix VI H).

Water Not more than 1.5% (Appendix VIII M, method 1 A).

Cefalexin Carry out the test method described under cefradine, the content of cefalexin is not more than 6.0% of the total amount of cefradine and cefalexin.

Other requirements Comply with the general requirements for granules (Appendix I N).

Assay Carry out the method described under Cefradine, using the mixed contents obtained from the test for filling or weight variation of contents. Dissolve an accurately weighed quantity equivalent to about 70 mg of cefradine in a 100 ml volumetric flask, with 70 ml of the mobile phase by ultrasonic treatment for 15 minutes, and shake for 10 minutes, and dilute to volume with the mobile phase, mix well, and filter. Measure accurately 10 μ l of the successive filtrate and inject into the column.

Category As described under Cefradine.

Strength Calculated as $C_{16}H_{19}N_3O_4S$
(1) 0.125 g (2) 0.25 g

Storage Preserve in tightly closed container, store in a cool and dark place.

Cefradine Tablets

Cefradine Tablets contain not less than 90.0% and not more than 110.0% of the labelled amount of cefradine ($C_{16}H_{19}N_3O_4S$).

Description Film coated tablets with almost white or slight yellow cores.

Identification Complies with test (1) or test (2) for Identification described under Cefradine.

Cefalexin Carry out the test method described under Cefradine, the content of cefalexin is not more than 6.0% of the total amount of cefradine and cefalexin.

Related substances Carry out the test method described under Cefradine, the detection wavelength is 254 nm. Powder 10 tablets, accurately weighed, and dissolve an accurately weighed quantity of the powder in mobile phase to produce a test solution of 1 mg per ml. The content of the 7-aminodesacetoxy-cephalosporanic acid is not more than 1.0%, calculated with respectively area obtained in the chromatogram with the test solution by the external standard method. The area of each peak of other impurities is not more than 5 times the area of principal peak in the chromatogram obtained with the reference solution (2.5%). The sum of the area of all other impurity peaks is not more than 6 times the area of principal peak in the chromatogram obtained with the reference solution (3.0%).

Water Not more than 6.0% (Appendix VIII M, method 1 A).

Dissolution Carry out dissolution test (Appendix X C, method 2), using 900 ml of 0.12 mol/L hydrochloric acid solution as the dissolution medium, adjust the rotational speed of the paddle to 75 rpm. Withdraw a quantity of the solution after exactly 60 minutes and filter. Dilute a quantity of the successive filtrate, accurately measured, with 0.12 mol/L hydrochloric acid solution to produce a solution of

25 µg per ml. Powder 10 tablets and weigh accurately a quantity of the powder equivalent to average weight, and dissolve with 0.12 mol/L hydrochloric acid solution to produce a solution of 25 µg of cefradine per ml according to the labelled amount. Measure the absorbance of the resulting solutions at 255 nm (Appendix IV A). Calculate the dissolution of $C_{16}H_{19}N_3O_4S$ from each table. Not less than 85% is dissolved.

Other requirements Comply with the general requirements for tablets (Appendix I A).

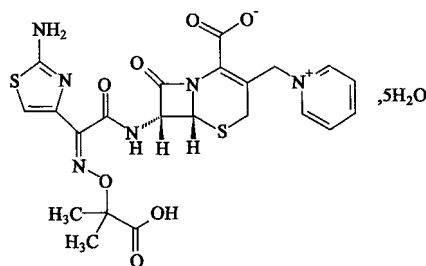
Assay Powder 10 tablets, accurately weighed, and dissolve a quantity of the powder accurately weighed, equivalent to about 70 mg of cefradine, with 70 ml of the mobile phase by ultrasonic treatment for 15 minutes, and shake for 10 minutes, and dilute to volume with the mobile phase, mix well, and filter. Carry out the Assay described under Cefradine. Injecting 10 µl of the successive filtrate into the column.

Category As described under Cefradine.

Strength Calculated as $C_{16}H_{19}N_3O_4S$
(1) 0.25 g (2) 0.5 g

Storage Preserve in tightly closed container, store in a cool and dark place.

Ceftazidime



$C_{22}H_{22}N_6O_7S_2 \cdot 5H_2O$ 636.65

[78439-06-2]

Ceftazidime is 1- { [(6R, 7R)-7-[2-(2-Amino-4-thiazolyl) glyoxylamido]-2-carboxy-8-oxo-5-thia-1-azabicyclo [4.2.0] oct-2-ene-3-yl] methyl } pyridinium hydroxide, inner salt, 7² (Z)-[O-(1-carboxy-1-methylethyl) oxime] pentahydrate. It contains not less than 95.0% of $C_{22}H_{22}N_6O_7S_2$, calculated on the dried basis.

Description A white or almost white crystalline powder; odourless or slightly and characteristic odour. Sparingly soluble in phosphate BS (pH 6.0), slightly soluble in water or methanol, insoluble in acetone or chloroform.

Specific absorbance Measure the absorbance of a solution of 10 µg per ml in phosphate BS (pH 6.0) at 257 nm (Appendix IV A), the value of A (1%, 1 cm) is 400-430.

Identification (1) The retention time of the principal peak of the substance being examined in the chromatogram obtained in the Assay is identical with that of the principal peak of ceftazidime CRS in the chromatogram of the reference solution correspondingly.

(2) The infrared absorption spectrum (Appendix IV C) is concordant with the reference spectrum of ceftazidime (Appendix XVI)

Acidity An aqueous solution of 5 mg per ml, pH 3.0-4.0

(Appendix VI H).

Clarity and colour of solution Dissolve 0.6 g each of 5 portions in 5 ml of sodium carbonate solution (1→100), the solutions are clear and colourless; any opalescence produced is not more pronounced than that of reference suspension 1 (Appendix IX B); any colour produced is not more intense than that of reference solution Y₆ (Appendix IX A, method 1).

Pyridine Carry out the method for high performance liquid chromatography (Appendix V D), using a column packed with octadecylsilane bonded silica gel and a mixture of acetonitrile-0.25 mol/L solution of ammonium dihydrogen phosphate (dissolve 57.515 g of ammonium dihydrogen phosphate in water and dilute to 2000 ml, mix well)-water (300 : 100 : 600) with a pH value adjusted to 7.0 by ammonia solution as the mobile phase. The flow rate is 1.0 ml/min and detection wavelength is 254 nm. The number of the theoretical plates of the column is not less than 3000, calculated with reference to the peak of pyridine. The relative standard deviation (RSD) of the areas of the principal peak in the chromatogram obtained with the reference solution for several replicate injections is not more than 3.0%.

Reference solution Dissolve about 1 g of pyridine CRS, accurately weighed, in water in a 100 ml volumetric flask, dilute with water to volume and mix well. Transfer accurately 10 ml to another 100 ml volumetric flask, dilute with water to volume, mix well, store at a temperature of below 15°C. Transfer accurately 2 ml to a 200 ml volumetric flask before using, dilute with phosphate buffer solution (dissolve 5.68 g of disodium hydrogen phosphate and 3.63 g of potassium dihydrogen phosphate in water and diluted to 1000 ml, mix well.) to volume, mix well.

Procedure Dissolve about 660 mg, accurately weighed, in the above phosphate buffer solution (pH 7.0) in a 100 ml volumetric flask and dilute to volume (store at below 15°C and used in 1 hr). Inject 20 µl into the column. Repeat the operation, using pyridine CRS instead of the substance being examined, the peak area obtained in the chromatogram by the external standard method. Not more than 0.12% of pyridine is found.

Ceftazidime polymer Carry out the method for size exclusion chromatography (Appendix V H). Using a column with 1.3-1.6 cm in internal diameter and 30-40 cm height packed with sephadex G-10 (40-120 µm), a 0.1 mol/L phosphate buffer containing 3.5% ammonia sulfate pH 7.0 [0.1 mol/L disodium hydrogen phosphate solution-0.1 mol/L sodium dihydrogen phosphate (61 : 39)] as eluent A and water as eluent B. The flow rate is 0.8 ml per minute and the detection wavelength is 254 nm. Inject 200 µl of a solution containing 0.1 mg of blue dextran 2000 per ml into the column separately using eluent A and eluent B. The number of the theoretical plates of the column is not less than 600 and the tailing factor is not more than 2.0, calculated with reference to the peak of blue dextran 2000, using eluent A and B as mobile phase. The ratio of retention time of blue dextran 2000 peak in the two mobile phases is between 0.93-1.07, the ratio of retention time of the polymer peak of the test solution and the blue dextran 2000 peak in mobile phase A is between 0.93-1.07, the ratio of retention time of the principal peak of the reference solution and the blue dextran 2000 peak in mobile phase B is between 0.93-1.07. The relative standard deviation (RSD) of the areas of the principal peak in chromatogram obtained with accurately measured 200 µl of the reference solution for 5 replicate injections is not more than 5.0%, using eluent B as the mobile phase.

Reference solution Dissolve about 20 mg of ceftazidime CRS, accurately weighed, in water to produce a solution of 100 µg per ml.

Procedure Dissolve about 0.2 g of the substance being examined, accurately weighed, in a 10 ml volumetric flask, add 20 mg of sodium carbonate, dilute to volume with water, mix well as test solution. Inject immediately 200 µl into the column and record the chromatogram, using eluent A as the mobile phase. Inject 200 µl the reference solution into the column and record the chromatogram, using eluent B as the mobile phase. The content of ceftazidime polymer is not more than 0.3%; calculate as ceftazidime with respect to the peak area obtained in the chromatogram by the external standard method.

Loss on drying When dried in vacuum to constant weight at 60°C, loses not less than 13.0%, and not more than 15.0% of its weight (Appendix VIII L).

Residue on ignition Not more than 0.2% (Appendix VIII N), using 1.0 g.

Heavy metals Carry out the limit test for heavy metals (Appendix VIII H, method 2) using the residue obtained in the test for Residue on ignition; not more than 0.002%.

Bacterial endotoxin Carry out the test for bacterial endotoxin (Appendix XI E); less than 0.1 EU per mg ceftazidime (Dilute the substance being examined with 1% sodium carbonate solution without pyrogens to produce a solution of 80 mg per ml, then dilute that solution to the needed concentration with water for bacterial endotoxin test).

Sterility Complies with the test for sterility (Appendix XI H, membrane filtration method). Dissolve the substance being examined in a quantity of sterile sodium carbonate solution (1→100), and then transfer it into not less than 500 ml of 0.9% sterile sodium chloride solution.

Assay Carry out the method for high performance liquid chromatography (Appendix V D), using a column packed with octadecylsilane bonded silica gel and a mixture of acetonitrile-phosphate buffer solution (dissolve 42.59 g of disodium hydrogen phosphate and 27.22 g of potassium dihydrogen phosphate in water and dilute to 1000 ml, mix well, and adjust pH to 7.0.)-water (40 : 200 : 1760) as the mobile phase. The flow rate is 1.5 ml per minute and detection wavelength is 254 nm. The resolution factor between peaks of ceftazidime and the impurities complies with the related requirements.

Procedure Dissolve an accurately weighed quantity equivalent to 250 mg of ceftazidime in water in a 250 ml volumetric flask, dilute to volume and mix well. Measure accurately 15 ml to a 100 ml volumetric flask before using, dilute with water to volume. Inject 20 µl into column and record the chromatogram; Dissolve an accurately weighed quantity in water to produce a solution of 1 mg of ceftazidime per ml as stock solution. Measure accurately 15 ml to a 100 ml volumetric flask before using, dilute with water to volume, mix well, and then repeat the operation. Calculate the content of $C_{22}H_{22}N_6O_7S_2$ with respect to the peak area obtained in the chromatogram by the external standard solution.

Category β-lactam antibiotic, Cephalosporin.

Storage Preserve in tightly closed containers, stored in a cool and dark place.

Preparation Ceftazidime for Injection

Ceftazidime for Injection

Ceftazidime for Injection is a sterile mixture of Ceftazidime and suitable amount of solubilizer of sodium carbonate. Each container contains not less than 90.0% and not more than 110.0% of the labelled amount of ceftazidime ($C_{22}H_{22}N_6O_7S_2$).

Description A white or almost white crystalline powder.

Identification (1) Complies with test (1) for Identification described under Ceftazidime.

(2) To a quantity add dilute acid, effervescence is produced with a gas of carbon dioxide evolving, when which is passed into calcium hydroxide TS, a white precipitate is produced immediately.

(3) Yields the flame reactions of sodium salts (Appendix III).

Acidity or alkalinity An aqueous solution of 0.1 g per ml, pH 5.0-7.5 (Appendix VI H).

Clarity and colour of solution To each of 5 containers add water to produce solutions of 0.1 g per ml according to the labelled amount respectively, the solutions are clear and colourless; any opalescence produced is not more pronounced than that of reference suspension 1 (Appendix IX B); any colour produced is not more intense than that of reference solution Y_6 (Appendix IX A, method 1).

Pyridine Dissolve an accurately weighed quantity of the mixed contents obtained in the test for weight variation of contents in water to produce a solution of 6 mg of ceftazidime per ml. Carry out the test for Pyridine described under Ceftazidime. Not more than 0.4% of pyridine is found.

Ceftazidime polymer Dissolve an accurately weighed quantity in water to produce a solution of 20 mg of ceftazidime per ml. Carry out the test for ceftazidime polymer described under Ceftazidime. Not more than 1.0% of ceftazidime polymer is found, calculated as ceftazidime ($C_{22}H_{22}N_6O_7S_2$).

Loss on drying When dried in vacuum to constant weight at 60°C, loses not more than 13.5% (Appendix VIII L).

Content uniformity Comply with the requirements for content uniformity (Appendix X E), calculated with reference to the content of each container determined from the Assay.

Bacterial endotoxin Carry out the test for bacterial endotoxin (Appendix XI E); less than 0.1 EU per 1 mg of ceftazidime.

Sterility Complies with the test for sterility (Appendix XI H, membrane filtration method). Dissolve the substance being examined in a suitable solution, and then transfer it into not less than 500 ml of 0.9% sterile sodium chloride solution.

Other requirements Complies with the general requirements for injections (Appendix I B).

Assay Dissolve the contents of 10 containers separately in water to produce a solution of 1 mg ceftazidime per ml. Measure accurately 15 ml to a 100 ml volumetric flask before using, dilute with water to volume, mix well, and then carry out the Assay described under Ceftazidime, calculated the average content of 10 containers.

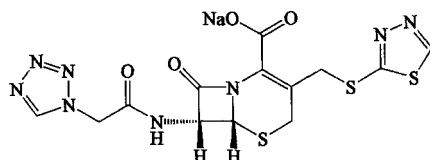
Category As described under Ceftazidime.

Strength Calculated as $C_{22}H_{22}N_6O_7S_2$

(1) 0.5 g (2) 1.0 g

Storage Preserve in well closed containers, stored in a cool and dark place.

Ceftezole Sodium



$C_{13}H_{11}N_8O_4NaS_3$ 462.47

Ceftezole Sodium is sodium (6R,7R)-3-[(1,3,4-thiadiazol-2-yl)thiomethyl]-8-oxo-7-[(2(1H)-tetrazol-1-yl)-acetamido]-5-thia-1-azabicyclo[4.2.0]oct-2-ene-2-carboxylate. It contains not less than 90.0% of $C_{13}H_{12}N_8O_4S_3$, calculated on the anhydrous basis.

Description A white to slightly yellow powder or crystalline powder; odourless; hygroscopic. Freely soluble in water; slightly soluble in methanol; insoluble in ethanol or ether.

Specific optical rotation -5° to -9° , in a solution of 100 mg per ml in water (Appendix VI E).

Specific absorbance Measure the absorbance of an aqueous solution of 16 μ g per ml at 272 nm (Appendix IV A), the value of A (1%, 1 cm) is 270-300.

Identification (1) The light absorption of an aqueous solution of 16 μ g per ml exhibits a maximum at 272 nm (Appendix IV A).

(2) The retention time of the principal peak of the substance to be examined in the chromatogram is identical with that of the principal peak of the reference solution in the chromatogram obtained in the Assay.

(3) Yields the flame reaction of sodium salts (Appendix III).

Acidity Dissolve a quantity in water to produce a solution of 0.1 g per ml, pH 4.5-6.5 (Appendix VI H).

Clarity and colour of solution Dissolve 0.6 g each of 5 portions in 5 ml of water respectively. The solutions are clear and colourless; any opalescence produced is not more pronounced than that of reference suspension 1 (Appendix IX A); any colour produced is not more intense than that of reference solution Y_6 or YG_6 (Appendix IX A, method 1).

Water Not more than 5.0% (Appendix VIII M, method 1 A).

Related substances Carry out the method as described under Assay. Dissolve a quantity in water to produce solution (1) containing 1 mg per ml and solution (2) containing 10 μ g per ml respectively. Inject 20 μ l of solution (2) into the column. Adjust the attenuation so that the principal peak height in chromatogram is about 20%-25% of full scale of the chart. Inject separately 20 μ l of the above two solutions into the column and record the chromatograms for two and a half times retention time of the principal peak. The sum of the area of all impurity peaks in the chromatogram obtained with solution (1) is not greater than twice area of the principal peak in the chromatogram obtained with solution (2) (not more than 2.0%). The area of any impurity peak in the chromatogram obtained with solution (1) is not greater than that of the principal peak in the chromatogram obtained with solution (2) (not more than 1.0%).

Pyrogens Complies with the test for pyrogens (Appendix XI D), using 1 ml of a solution of 60 mg per ml in sterile Water for Injection per kg of rabbit's weight.

Sterility Comply with the test for sterility (Appendix XI H, membrane filtration method), dissolving each portion in sterile water and dilute with not less than 500 ml of 0.9% sterile sodium chloride solution.

Assay Carry out the method for high performance liquid chromatography (Appendix V D), using a column packed with octadecylsilane bonded silica gel and a mixture of citric acid solution (Dissolve 3 g of citric acid in 900 ml of water)-acetonitrile (90 : 10) as the mobile phase. Detection wavelength is 254 nm and the number of the theoretical plates of the column is not less than 2000, calculated with reference to the peak of ceftezole.

Procedure Dissolve an accurately weighed quantity in water to produce a solution of 0.2 mg per ml and shake thoroughly. Inject 20 μ l into the column and record the chromatogram. Repeat the operation, using ceftezole CRS instead of the substance being examined. Calculate the content of $C_{13}H_{12}N_8O_4S_3$ with respect to the peak area obtained in the chromatogram by the external standard method.

Category β -lactam antibiotic, cephalosprin.

Storage Preserve in hermetically sealed containers, stored in a cool and dry place and protected from light.

Preparation Ceftezole Sodium for Injection.

Ceftezole Sodium for Injection

Ceftezole Sodium for Injection is a sterile powder of Ceftezole Sodium. It contains not less than 90.0% of ceftezole ($C_{13}H_{12}N_8O_4S_3$), calculated on the anhydrous basis. Each container contains not less than 90.0% and not more than 110.0% of the labelled amount of ceftezole ($C_{13}H_{12}N_8O_4S_3$).

Description A white to slightly yellow powder or crystalline powder; odourless; hygroscopic.

Identification Complies with the tests for Identification described under Ceftezole Sodium.

Clarity and colour of solution To each of 5 containers, add water to produce a solution of 0.1 g per ml. The solutions are clear and colourless; any opalescence produced is not more pronounced than that of reference suspension 1 (Appendix IX A); any colour produced is not more intense than that of reference solution Y_7 or YG_7 (Appendix IX A, method 1).

Water Not more than 5.5% (Appendix VIII M, method 1 A).

Acidity, Related substances, Pyrogens and sterility Complies with the requirement described under Ceftezole Sodium.

Other requirements Complies with the general requirements for injections (Appendix I B)

Assay Carry out the Assay described under Ceftezole Sodium, using an accurately weighed quantity of the mixed contents obtained from the test for weight variation of contents.

Category As described under Ceftezole Sodium.

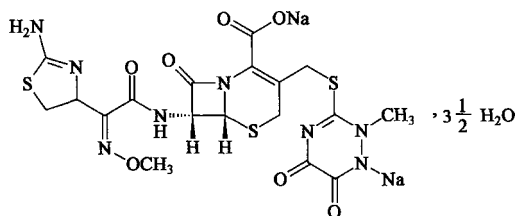
Strength Calculated as $C_{13}H_{12}N_8O_4S_3$

(1) 0.25 g (2) 0.5 g (3) 0.75 g (4) 1.0 g

(5) 1.5 g (6) 2.0 g (7) 4.0 g

Storage Preserve in well closed containers, stored in a cool and dry place and protected from light.

Ceftriaxone sodium



$C_{18}H_{16}N_8Na_2O_7S_3 \cdot 3\frac{1}{2}H_2O$ 661.59 [104376-79-6]

Ceftriaxone Sodium is (6*R*, 7*R*) -7- [2- (2-amino-4-thiazolyl) glyoxylamido] -8-oxo-3-[(1, 2,5,6-tetrahydro-2-methyl-5,6-dioxo-as-triazin-3-yl) -thio] methyl} -5-thia-1-azabicyclo [4.2.0] oct-2-ene-2-carboxylic acid, 7²- (Z) - (O-methyloxime) disodium salt sesquaterhydrate. It contains not less than 84.0% of ceftriaxone ($C_{18}H_{16}N_8O_7S_3$), calculated on the anhydrous basis.

Description A white or almost white crystalline powder; odourless.

Freely soluble in water; slightly soluble in methanol; practically insoluble in ether or chloroform.

Specific optical rotation -153° to -170° , in a solution of 10 mg per ml in water (Appendix VI E).

Specific absorbance Measure the absorbance of a solution of 10 μ g per ml in water at 241 nm (Appendix IV A), the value of *A* (1%, 1 cm) is 495-545.

Identification (1) The retention time of principal peak of the ceftriaxone in the substance being examined in the chromatogram obtained in the Assay is identical with that of the principal peak of ceftriaxone CRS in the chromatogram of the reference solution correspondingly.

(2) The infrared absorption spectrum (Appendix VI C) is concordant with the reference spectrum of ceftriaxone (Appendix XVI).

(3) Yields the flame reaction of sodium salts (Appendix III).

Crystallinity Complies with the test for crystallinity (Appendix IX D).

Acidity or alkalinity An aqueous solution of 0.1 g per ml, pH 6.0-8.0 (Appendix VI H).

Clarity and colour of solution Dissolve 0.6 g each of 5 portions in 5 ml of water respectively, the solutions are clear and colourless; any opalescence produced is not more pronounced than that of reference suspension 1 (Appendix IX B); any colour produced is not more intense than that of reference solution Y₇ or YG₇ (Appendix IX A, method 1).

Water 8.0%-11.0% (Appendix VIII M, method 1 A).

Related substances Carry out the method as described under Assay. Dissolve an accurately weighed quantity of ceftriaxone CRS in water to produce a reference solution of 2.2 μ g per ml. Inject 20 μ l into the column. Adjust the attenuation so that the principal peak height in the

chromatogram is about 20%-25% of full scale of the chart. The relative standard deviation (RSD) of the areas of the principal peak in the chromatogram obtained with the reference solution for several replicate injections is not more than 3.0%. Dissolve about 22 mg of the substance being examined, accurately weighed, in water in a 100 ml volumetric flask, and dilute to volume as a test solution. Inject 20 μ l of the test solution and the reference solution respectively into the column and record the chromatograms for 3 times the retention time of the principal peak. The sum of the area of all impurity peaks in the chromatogram obtained with the test solution is not greater than 2 times of the area of the principal peak in the chromatogram obtained with the reference solution (not more than 2.0%). The area of any impurity peak in the chromatogram obtained with the test solution is not greater than 0.5 times that of the principal peak in the chromatogram obtained with the reference solution (not more than 0.5%).

Ceftriaxone Polymer Carry out the method for size exclusion chromatography (Appendix V H), using a column 1.3-1.6 cm in internal diameter, 30-40 cm in column length, packed with sephadex G-10 (40-120 μ m), 0.1 mol/L phosphate buffer pH 7.0 [0.1 mol/L disodium hydrogen phosphate solution-0.1 mol/L sodium dihydrogen phosphate (61 : 39)] as the eluent A and water as the eluent B with a flow rate of 1 ml per minute. Detection wavelength is 254 nm. Inject 200 μ l of 1 mg/ml blue dextran 2000 solution, using eluent A and eluent B as mobile phase separately, the number of theoretical plates is not less than 700, the ratio of the retention time of blue dextran 2000 peak in eluent A to eluent B should be between 0.93-1.07. The ratio of the retention time of the principle peak of reference solution and the polymer peak of test solution to blue dextran 2000 peak of the corresponding system should be between 0.93-1.07. Using eluent B, inject accurately 200 μ l of reference solution into column. The relative standard deviation (RSD) for replicate injections of reference solution is less than 5.0%.

Reference solution Dissolve about 25 mg of ceftriaxone CRS, accurately weighed, in water and dilute with the same solvent to produce a solution of 100 μ g per ml.

Procedure Dissolve about 0.2 g, accurately weighed, in water and dilute to volume in a 10 ml volumetric flask, mix well. Inject 200 μ l of the resulting solution into the column immediately, using eluent A as the mobile phase, and record the chromatogram. Inject 200 μ l of the reference solution, using eluent B as the mobile phase and record the chromatogram. Calculate the content of ceftriaxone polymer with reference to ceftriaxone with respect to the peak area obtained in the chromatogram by the external standard method; not more than 0.5%.

Heavy metals Carry out the limit test for heavy metals (Appendix VIII H, method 2), using 1 g; not more than 0.002%.

Bacterial endotoxin Carry out the test for bacterial endotoxin (Appendix XI E); not more than 0.20 EU per mg.

Sterility Complies with the test for sterility (Appendix XI H, membrane filtration method), dissolve the substance being examined in a suitable solution, and then transfer it into not less than 500 ml of 0.9% sterile sodium chloride solution.

Assay Carry out the method for high performance liquid chromatography (Appendix V D), using a column packed with octadecylsilane bonded silica gel and a mixture of a 0.02 mol/L solution of *n*-octylamine-acetonitrile (73 : 27), adjust pH to 6.5 with phosphate as the mobile phase. The detection wavelength is 254 nm. Dissolve a quantity of the

substance being examined irradiated by UV light for 24 hours to produce a solution of 0.22 mg per ml, inject 20 μ l into the column and record the chromatogram. The resolution factor between peaks of ceftriaxone and ceftriaxone E-isomer is not less than 6.0.

Procedure Dissolve an accurately weighed quantity in water to produce a solution of 0.22 mg per ml. Inject 20 μ l into the column and record the chromatogram. Repeat the operation, using ceftriaxone CRS instead of the substance being examined, calculate the content of $C_{18}H_{18}N_8O_7S_3$ with respect to the peak area obtained in the chromatogram by the external standard method.

Category β -lactam antibiotic, cephalosprin.

Storage Preserve in hermetically sealed containers, stored in a cool and dry place and protected from light.

Preparation Ceftriaxone Sodium for Injection

Ceftriaxone Sodium for Injection

Ceftriaxone Sodium for Injection is a sterile powder of Ceftriaxone Sodium. It contains not less than 84.0% of ceftriaxone ($C_{18}H_{18}N_8O_7S_3$), calculated on the anhydrous basis. Each container contains not less than 90.0% and not more than 110.0% of the labelled amount of ceftriaxone ($C_{18}H_{18}N_8O_7S_3$), calculated with reference to the average weight of contents.

Description A white or almost white crystalline powder; odourless.

Identification Complies with tests (1) and (3) for Identification described under Ceftriaxone Sodium.

Clarity and colour of solution To each of 5 containers add water to produce solutions of 0.1 g per ml according to the labelled amount respectively, the solutions are clear and colourless; any opalescence produced is not more pronounced than that of reference suspension I (Appendix IX B); any colour produced is not more intense than that of reference solution YG₉ or OY₉ (Appendix IX A, method 1).

Related substances Carry out the test for Related substance described under Ceftriaxone Sodium, using an accurately weighed quantity of the mixed contents obtained in the test for weight variation of contents. The area of any impurity peak obtained with the test solution is not greater than that of the principal peak obtained with the reference solution (1.0%) and the sum of area of all impurity peaks is not greater than 4 times the area of principal peak obtained with the reference solution (4.0%).

Ceftriaxone polymer Carry out the test for Ceftriaxone polymer described under Ceftriaxone Sodium, using an accurately weighed quantity of the mixed contents obtained in the test for weight variation of contents. The ceftriaxone polymer is not more than 0.8%, calculated as ceftriaxone.

Acidity or alkalinity, Water, Bacterial endotoxin and Sterility Complies with the corresponding requirements described under Ceftriaxone Sodium.

Other requirements Complies with the general requirements for injections (Appendix I B).

Assay Carry out the Assay described under Ceftriaxone Sodium, using an accurately weighed quantity of the mixed contents obtained in the test for weight variation of contents.

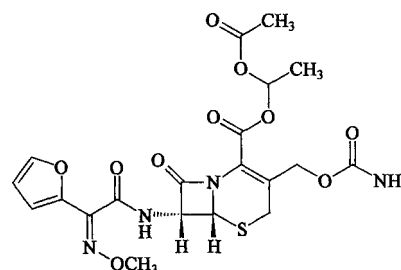
Category As described under Ceftriaxone Sodium.

Strength Calculated as $C_{18}H_{18}N_8O_7S_3$

(1) 0.25 g (2) 0.5 g (3) 1.0 g (4) 2.0 g

Storage Preserve in tightly closed containers, stored in a cool and dry place and protected from light.

Cefuroxime Axetil



$C_{20}H_{22}N_4O_{10}S$ 510.48

[64544-07-6]

Cefuroxime axetil is a mixture of (RS)-1-Hydroxyethyl (6R, 7R) -7- [2 (2-furyl) glyoxylamido] -3- (hydroxymethyl) -8-oxo-5-thia-1-azabicyclo [4.2.0] oct-2-ene-2-carboxylate, 7²-(Z) - (O-methyloxime), 1-acetate 3-carbamate. It contains not less than 75.0% of cefuroxime ($C_{16}H_{16}N_4O_8S$), calculated on the anhydrous basis.

Description A white or almost white powder; almost odourless; taste, bitter.

Freely soluble in acetone; soluble in chloroform; sparingly soluble in methanol or ethanol; slightly soluble in ether; insoluble in water.

Specific absorbance Measure the absorbance of a solution of 15 μ g per ml in methanol at 276 nm (Appendix IV A), the value of A (1%, 1 cm) is 390-420.

Identification (1) The retention times of the principal peaks of the diastereoisomers of cefuroxime axetil in the substance being examined in the chromatogram obtained in the Assay are identical with those of the principal peaks of diastereoisomers of cefuroxime axetil CRS in the chromatogram of the reference solution correspondingly.

(2) The infrared absorption spectrum (Appendix VI C) is concordant with the spectrum of cefuroxime axetil CRS (Appendix XVI).

Crystallinity No birefringence or extinction positions is produced (Appendix IX D).

Diastereoisomer Carry out the method and use the solution as described under Assay. The ratio of diastereoisomer A of cefuroxime axetil to the sum of the diastereoisomers A and B of cefuroxime axetil is between 0.48-0.55, calculated with reference to the peak area obtained in the chromatogram.

Related substances Dissolve an accurately weighed quantity in mobile phase to produce a test solution of about 0.25 mg per ml, transfer 1 ml to a 100 ml volumetric flask and dilute with mobile phase to volume to produce a reference solution. Carry out the method as described under Assay. Inject 20 μ l of the reference solution into the column. Adjust the attenuation so that any of the principal peaks' height in the chromatogram is about 20% of full scale of the chart. Inject separately 20 μ l of the test solution and the reference solution into the column immediately and record the chromatograms for 3.5 times the retention time of the

principal peak of diastereoisomer A. The sum of the area of the two E isomer in the chromatogram obtained with the test solution is not greater than the sum of the area of the two principal peaks in the chromatogram obtained with the reference solution, the area of the peak of Δ^3 isomer is not more than 1.5 times, the area of each peak of other impurities is not more than 0.5 times, the sum of the area of all impurity peaks is not more than 3 times. Disregard any peak with the area less than 0.05 times of the sum of the area of the two principal peaks in the chromatogram obtained with the reference solution.

Water Not more than 1.5% (Appendix VIII M, method 1 A).

Residue on ignition Not more than 0.2% (Appendix VIII N), using 1.0 g.

Heavy metals Carry out the limit test for heavy metals (Appendix VIII H, method 2), using the residue obtained in the test for Residue on ignition; not more than 0.002%.

Assay Carry out the method for high performance liquid chromatography (Appendix V D), using a column packed with octadecylsilane bonded silica gel and a mixture of methanol-0.2 mol/L ammonium dihydrogen phosphate solution (38 : 62) as the mobile phase. The detection wavelength is 278 nm. Dissolve an accurately weighed quantity of cefuroxime axetil CRS in mobile phase to produce a test solution of 0.2 mg per ml (sonicate when necessary), heat the solution in a water bath at 60°C at least for 1 hr to obtain some Δ^3 isomer of cefuroxime axetil. Expose a quantity of cefuroxime axetil to ultraviolet radiation for 24 hrs, and add the mobile phase to produce a solution of E isomer containing 0.2 mg per ml. Inject 20 μ l of the above two solutions into the column and record the chromatogram. The relative retention time of isomer A, B, Δ^3 and E is 1.0, 0.9, 1.2, 1.7 and 2.1 respectively. The resolution factors between peaks of diastereoisomer A and B, diastereoisomer A and Δ^3 comply with the requirements.

Procedure Weigh accurately a quantity equivalent to about 25 mg of cefuroxime to a 100 ml volumetric flask, add the mobile phase, shake to dissolve, dilute to volume and mix well. Inject 20 μ l into the column and record the chromatogram. Repeat the operation, using cefuroxime axetil CRS instead of the substance being examined, calculate the content of $C_{16}H_{16}N_4O_8S$ with respect to the areas of the two principal peaks of cefuroxime axetil obtained in the chromatogram by the external standard method.

Category β -lactam antibiotic, cephalosprin.

Storage Preserve in tightly closed containers, stored in a cool place and protected from light.

Preparation (1) Cefuroxime Axetil Capsules
(2) Cefuroxime Axetil Tablets

Cefuroxime Axetil Capsules

Cefuroxime Axetil Capsules contain not less than 90.0% and not more than 110.0% of the labelled amount of cefuroxime ($C_{16}H_{16}N_4O_8S$).

Description Capsules containing white or almost white powder or granules.

Identification The retention times of the two principal peaks in the chromatogram of the test solution obtained in the Assay are identical with those of the principal peaks of the diastereoisomer A and B in the chromatogram of the reference solution correspondingly.

Diastereoisomer Carry out the method and use the solution as described under Assay. The ratio of diastereoisomer A of cefuroxime axetil to the sum of the diastereoisomers A and B of cefuroxime axetil is between 0.48-0.55, calculated with reference to the peak area obtained in the chromatogram.

Related substances Carry out the method as described under Cefuroxime Axetil, using the test solution as described under Assay. Transfer 1 ml to 100 ml volumetric flask and dilute with the mobile phase to volume as the reference solution. The sum of the area of the two isomer in the chromatogram obtained with the test solution is not greater than 1.5 times the sum of the area of the two principal peaks in the chromatogram obtained with the reference solution (1.5%), the area of the peak of Δ^3 isomer is not more than 2 times (2.0%), the area of each peak of other impurities is not more than 1 times (1.0%), the sum of the area of all impurity peaks is not more than 4.5 times (4.5%). Disregard any peak with the area less than 0.05 times of the sum of the area of the two principal peaks in the chromatogram obtained with the reference solution.

Water Not more than 6.0% (Appendix VIII M, method 1 A).

Dissolution Carry out the dissolution test (Appendix X C method 2), using 900 ml of 0.07 mol/L of hydrochloride solution as the dissolution medium, adjust the rotational speed of the paddle to 55 rpm. Withdraw 5 ml of the solution after exactly 15 minutes and 45 minutes, filter and supply 5 ml of the dissolution medium accordingly in the vessel immediately. Dilute an accurately measured quantity of the successive filtrate with the dissolution medium to produce a test solution of about 15 μ g per ml. Dissolve an accurately weighed quantity of the mixed contents in the test for weight variation of contents in water to produce a reference solution of about 15 μ g per ml of cefuroxime axetil ($C_{20}H_{22}N_4O_{10}S$) according to the labelled amount. Measure the absorbance of the resulting solutions at 278 nm (Appendix IV A). Calculate the dissolution of $C_{20}H_{22}N_4O_{10}S$ from each capsules. Not less than 60% in 15 minutes and not less than 75% in 45 minutes of the labelled amount are dissolved.

Other requirements Comply with the general requirements for capsules (Appendix I E).

Assay Dissolve an accurately weighed quantity of the mixed and finely powdered contents in the test for weight variation of contents equivalent to about 125 mg of cefuroxime in 125 ml of methanol in a 100 ml volumetric flask, shake intensively, dilute with the mobile phase to volume, mix well and filter. Measure accurately 5 ml of the successive filtrate to a 25 ml volumetric flask, dilute with mobile phase to volume. Inject 20 μ l into the column immediately, carry out the method for the Assay described under Cefuroxime Axetil.

Category As described under Cefuroxime Axetil.

Strength Calculated as $C_{16}H_{16}N_4O_8S$
(1) 0.125 g (2) 0.25 g

Storage Preserve in tightly closed containers, stored in a cool place and protected from light.

Cefuroxime Axetil Tablets

Cefuroxime Axetil Tablets contain not less than 90.0% and not more than 110.0% of the labelled amount of cefuroxime ($C_{16}H_{16}N_4O_8S$).

Description Film coated tablets with almost white core.

Identification The retention times of the two principal peaks in the chromatogram obtained with the test solution in the Assay are identical with those of the principal peaks of the diastereomer A and B in the reference solution correspondingly.

Diastereoisomer Carry out the method and use the solution as described under Assay. The ratio of diastereoisomer A of cefuroxime axetil to the sum of the diastereoisomers A and B of cefuroxime axetil is between 0.48-0.55, calculated with reference to the peak area obtained in the chromatogram.

Related substances Carry out the method as described under Cefuroxime Axetil, using the test solution as described under Assay. Transfer 1 ml to 100 ml volumetric flask and dilute with the mobile phase to volume as the reference solution. The sum of the area of the two isomer in the chromatogram obtained with the test solution is not greater than 1.5 times of the sum of the area of the two principal peaks in the chromatogram obtained with the reference solution (1.5%), the area of the peak of Δ^3 isomer is not more than 2 times (2.0%), the area of each peak of other impurities is not more than 1 times (1.0%), the sum of the area of all impurity peaks is not more than 4.5 times (4.5%). Disregard any peak with the area less than 0.05 times of the sum of the area of the two principal peaks in the chromatogram obtained with the reference solution.

Water Not more than 6.0% (Appendix VIII M, method 1 A).

Dissolution Carry out the dissolution test (Appendix X C method 2), using 900 ml of 0.07 mol/L of hydrochloride solution as the dissolution medium, adjust the rotational speed of the paddle to 55 rpm. Withdraw 5 ml of the solution after exactly 15 minutes and 45 minutes, filter and supply 5 ml of the dissolution medium accordingly in the vessel immediately. Dilute an accurately measured quantity of the successive filtrate with the dissolution medium to produce a test solution of about 15 μ g per ml. Powder finely 10 tablets, dissolve an accurately weighed quantity of the powdered tablets in the hydrochloric acid solution to produce a reference solution of about 15 μ g per ml of cefuroxime axetil ($C_{20}H_{22}N_4O_{10}S$) according to the labelled amount. Measure the absorbance of the resulting solutions at 278 nm (Appendix IV A). Calculate the dissolution of $C_{20}H_{22}N_4O_{10}S$ from each tablet. Not less than 60% in 15 minutes and not less than 75% in 45 minutes of the labelled amount are dissolved.

Other requirements Comply with the general requirements for tablets (Appendix I A).

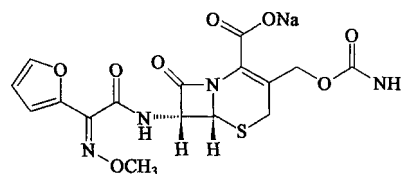
Assay Weigh accurately and powder finely 10 tablets. Dissolve an accurately weighed quantity of powdered tablets equivalent to about 125 mg of cefuroxime in 25 ml of methanol by shaking intensively. Dilute with the mobile phase to 100 ml, mix well and filter. Transfer 5 ml of the successive filtrate to a 25 ml volumetric flask and dilute with the mobile phase to volume. Inject 20 μ l into column immediately. Carry out the method for the Assay described under Cefuroxime Axetil.

Category As described under Cefuroxime Axetil.

Strength Calculated as $C_{16}H_{15}N_4O_8S$
(1) 0.125 g (2) 0.25 g

Storage Preserve in tightly closed containers, stored in a cool place and protected from light.

Cefuroxime Sodium



$C_{16}H_{15}N_4NaO_8S$ 446.37

[56238-63-2]

Cefuroxime Sodium is sodium (6R, 7R)-7-[2-(2-furyl) glyoxylamido]-3-(hydroxymethyl)-8-oxo-5-thia-1-azabicyclo[4.2.0]oct-2-ene-2-carboxylate. It contains not less than 86.0% of cefuroxime ($C_{16}H_{15}N_4O_8S$), calculated on the anhydrous basis.

Description A white to slightly yellow powder or crystalline powder; odourless; taste, bitter; hygroscopic. Freely soluble in water; sparingly soluble in methanol; insoluble in ethanol and chloroform.

Specific optical rotation $+55^\circ$ to $+65^\circ$, in a solution of 10 mg per ml in water (Appendix VI E).

Specific absorbance Measure the absorbance of a solution of 10 mg per ml in water at 274 nm (Appendix IV A), the value of A (1%, 1 cm) is 390-425.

Identification (1) The retention time of principal peak of cefuroxime in the substance being examined in the chromatogram obtained in the Assay are identical with that of the principal peak of cefuroxime CRS in the chromatogram of the reference solution correspondingly.

(2) The infrared absorption spectrum (Appendix VI C) is concordant with the reference spectrum of cefuroxime (Appendix XVI).

(3) Yields the reactions characteristic of sodium salts (Appendix III).

Acidity or alkalinity An aqueous solution of 0.1 g per ml, pH 6.0-8.5 (Appendix VI H).

Clarity of solution To 5 portions each of 0.6 g, add 5 ml of water respectively, the solutions are clear; any opalescence produced is not more pronounced than that of reference suspension 1 (Appendix IX B).

Colour of solution To 5 portions each of 0.6 g, add 5 ml of 0.05 mol/L disodium edetate solution respectively, the solutions are colourless; any colour produced is not more intense than that of reference solution Y_6 or YG_6 (Appendix IX A, method 1).

Related substances Dissolve a quantity in water to produce solution (1) containing 0.5 mg per ml and solution (2) containing 5 μ g per ml respectively. Carry out the method as described under Assay. Inject 20 μ l of solution (2) into the column. Adjust the attenuation so that the principal peak height in the chromatogram is 20%-25% of full scale of the chart. Inject immediately 20 μ l the two solutions respectively into the column and record the chromatograms for four times the retention time of the principal peak. The area of each impurity peaks in the chromatogram obtained with solution (1) is not greater than the area of the principal peak in the chromatogram obtained with solution (2); the sum of the area of all impurity peaks in the chromatogram obtained with solution (1) is not greater than 3 times area of the principal peak in the chromatogram obtained with solution

(2) respectively, disregard any peak with an area less than 0.05 times of area of the principal peak in the chromatogram obtained with solution (2).

Cefuroxime polymer Carry out the method for size exclusion chromatography (Appendix V H). Using a column with 1.3-1.6 cm in internal diameter and 30-40 cm height packed with sephadex G-10 (40-120 μm), a 0.025 mol/L phosphate buffer pH 7.0 [0.025 mol/L disodium hydrogen phosphate solution-0.025 mol/L sodium dihydrogen phosphate (61 : 39)] as eluent A and water as eluent B. The flow rate is 1.5 ml per minute and the detection wavelength is 254 nm. Inject 200 μl of a solution containing 0.1 mg of blue dextran 2000 per ml into the column separately using eluent A and eluent B. The number of the theoretical plates of the column is not less than 700 and the tailing factor is not more than 2.0, calculated with reference to the peak of blue dextran 2000, using eluent A and B as mobile phase. The ratio of retention time of blue dextran 2000 peak in the two mobile phases is between 0.93-1.07, the ratio of retention time of the polymer peak of the test solution and the blue dextran 2000 peak in mobile phase A is between 0.93-1.07, the ratio of retention time of the principal peak of the reference solution and the blue dextran 2000 peak in mobile phase B is between 0.93-1.07. The relative standard deviation (RSD) of the areas of the principal peak in chromatogram obtained with accurately measured 200 μl of the reference solution for 5 replicate injections is not more than 5.0%, using eluent B as the mobile phase.

Reference solution Dissolve an accurately weighed quantity of cefuroxime CRS in water to produce a solution of 40 μg per ml.

Procedure Dissolve about 0.2 g of the substance being examined accurately weighed, in a 10 ml volumetric flask, dilute to volume with water, mix well as test solution. Inject immediately 200 μl into the column and record the chromatogram, using eluent A as the mobile phase. Inject 200 μl the reference solution into the column and record the chromatogram, using eluent B as the mobile phase. The content of cefuroxime polymer is not more than 0.2%, calculate as cefuroxime with respect to the peak area obtained in the chromatogram by the external standard method.

Water Not more than 3.5% (Appendix VIII M, method 1 A).

Bacterial endotoxin Carry out the test for bacterial endotoxin (Appendix XI E): less than 0.10 EU per mg of cefuroxime.

Sterility Complies with the test for sterility (Appendix XI H, membrane filtration method). Dissolve the substance being examined in a suitable solution, and then transfer it into not less than 500 ml of 0.9% sterile sodium chloride solution.

Assay Carry out the method for high performance liquid chromatography (Appendix V D), using a column packed with octadecylsilane bonded silica gel and a phosphate buffer pH 3.4 (dilute 50 ml of 0.1 mol/L sodium acetate solution with 0.1 mol/L acetic acid solution to 1000 ml, and mix well) (1 : 10) as the mobile phase. The detection wavelength is 254 nm. Dissolve a quantity of cefuroxime CRS in water to produce a solution of 100 μg per ml, heat in a water bath at 60°C for 10 min to produce some descarbamoylcefuroxime. Inject 20 μl into the column and record the chromatogram. The resolution factor between peaks of cefuroxime and descarbamoylcefuroxime is not less than 2.0.

Procedure Dissolve an accurately weighed quantity in water to produce a solution of 0.5 mg per ml. Inject 20 μl into the

column. Repeat the operation, using cefuroxime CRS instead of the substance being examined, calculate the content of $\text{C}_{16}\text{H}_{16}\text{N}_4\text{O}_8\text{S}$ with respect to the peak area obtained in the chromatogram by the external standard method.

Category β -lactam antibiotic, cephalosprin.

Storage Preserve in tightly closed containers, stored in a cold place and protected from light.

Preparation Cefuroxime Sodium for Injection

Cefuroxime Sodium for Injection

Cefuroxime Sodium for Injection is a sterile powder of cefuroxime Sodium. It contains not less than 86.0% of cefuroxime ($\text{C}_{16}\text{H}_{16}\text{N}_4\text{O}_8\text{S}$), calculated on the anhydrous basis. Each container contains not less than 90.0% and not more than 110.0% of the labelled amount of cefuroxime ($\text{C}_{16}\text{H}_{16}\text{N}_4\text{O}_8\text{S}$), calculated with reference to the average weight of contents.

Description An white to slightly yellow powder or crystalline powder.

Identification Complies with test (1) and (3) for Identification described under Cefuroxime Sodium.

Acidity or alkalinity A solution of about a 0.1 g per ml in water, pH 6.0-8.5 (Appendix VI H).

Clarity of solution To each of 5 containers add water to produce solutions of 0.1 g per ml according to the labelled amount respectively, the solutions are clear; any opalescence produced is not more pronounced than that of reference suspension 1 (Appendix IX B).

Colour of solution To each of 5 containers add 0.05 mol/L disodium edetate solution to produce solutions of 0.1 g per ml according to the labelled amount respectively, the solutions are colourless; any colour produced is not more intense than that of reference solution Y_8 or YG_8 (Appendix IX A, method 1).

Cefuroxime polymer Weigh accurately a quantity of the substance being examined, carry out the test for cefuroxime polymer described under Cefuroxime. Not more than 0.3% of cefuroxime polymer is found, calculated as cefuroxime.

Related substance, Water, Bacterial endotoxin and Sterility Complies with the corresponding requirement described under Cefuroxime Sodium.

Other requirements Complies with the general requirements for injections (Appendix I B).

Assay Carry out the Assay described under Cefuroxime Sodium, using an accurately weighed quantity of the mixed contents obtained in the test for weight variation.

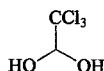
Category As described under Cefuroxime Sodium.

Strength Calculated as $\text{C}_{16}\text{H}_{16}\text{N}_4\text{O}_8\text{S}$

(1) 0.25 g (2) 0.5 g (3) 0.75 g (4) 1.0 g
(5) 1.25 g (6) 1.5 g (7) 1.75 g (8) 2.0 g
(9) 2.25 g (10) 2.5 g

Storage Preserve in well closed containers, stored in a cold place and protected from light.

Chloral Hydrate



$C_2H_3Cl_3O_2$ 165.40

Chloral Hydrate is 2,2,2-trichloro-1,1-ethanedi-ol. It contains not less than 99.0% of $C_2H_3Cl_3O_2$.

Description White or colourless transparent crystals; odour, pungent; taste, slightly bitter; volatilized slowly in air.

Very soluble in water; freely soluble in ethanol, chloroform or ether.

Identification Dissolve 0.2 g in 2 ml of water, add 2 ml of sodium hydroxide TS, a cloudy solution is produced, when heated, becomes two clear layers and gives off the odour of chloroform.

Acidity Dissolve 1.0 g in 10 ml of water, pH 4.0-6.0 (Appendix VI H).

Chloride Carry out the limit test for chlorides (Appendix VIII A), using 0.50 g. Any opalescence produced is not more pronounced than that of a reference using 5.0 ml of sodium chloride standard solution (0.01%).

Chloral alcoholate Dissolve 1.0 g in 4 ml of water, add 2 ml of sodium hydroxide TS, mix well and filter. To the filtrate add iodine TS dropwise until a deep brown colour is obtained; No yellow crystalline precipitate is formed within 1 hour.

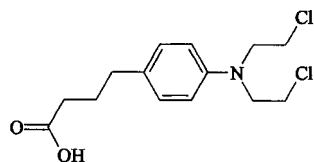
Residue on ignition Not more than 0.1% (Appendix VIII N).

Assay Dissolve about 4 g, accurately weighed, in 10 ml of water, add accurately 30 ml of sodium hydroxide (1 mol/L) VS, mix well. Allow to stand for 2 minutes, add a few drops of phenolphthalein IS, titrate with sulfuric acid (0.5 mol/L) VS until the red colour disappears. Add 6 drops of potassium chromate IS, titrate with silver nitrate (0.1 mol/L) VS. Calculate the volume of sodium hydroxide (1 mol/L) VS used in the reaction by deducting both the volume of sulfuric acid (0.5 mol/L) VS used in the first titration and 2/15 of the volume of silver nitrate (0.1 mol/L) VS used in the second titration from the volume of sodium hydroxide (1 mol/L) VS added. Each ml of sodium hydroxide (1 mol/L) VS is equivalent to 165.4 mg of $C_2H_3Cl_3O_2$.

Category Hypnotic and anticonvulsant.

Storage Preserve in tightly closed containers.

Chlorambucil



$C_{14}H_{19}Cl_2NO_2$ 304.22

[305-03-3]

Chlorambucil is 4- [bis (2-chloroethyl) amino]

benzenebutyric acid. It contains not less than 98.0% of $C_{14}H_{19}Cl_2NO_2$.

Description An almost white crystalline powder; odour, slight; darkens gradually on exposure to light. Very soluble in acetone; freely soluble in ethanol or chloroform; insoluble in water.

Melting range 64-68°C (Appendix VI C).

Identification (1) The light absorption of a 15 μ g per ml solution in dehydrated ethanol exhibits maxima at 257 nm and 302 nm; minima at 225 nm and 280 nm (Appendix IV A). (2) The infrared absorption spectrum (Appendix IV C) is concordant with the reference spectrum of chlorambucil (Appendix XVI).

(3) Dissolve 10 mg in 5 ml of acetone, add 5 ml of water, shake well, heat in a water bath. The solution yields the reactions characteristic of chlorides (Appendix III).

Related substances Carry out the method for thin-layer chromatography (Appendix V B), using silica gel HF₂₅₄ as the coating substance and a mixture of toluene-methanol-heptane-butanone (8 : 5 : 4 : 4) as the mobile phase. Apply separately to the plate (dried at room temperature for 24 hours) 10 μ l each of two solutions in acetone containing (1) 20 mg per ml (2) 0.4 mg per ml of the substance being examined. After developing and removal of the plate, dry in air and examine under ultraviolet light (254 nm). Any spot other than the principal spot obtained with solution (1) is not more intense than the principal spot obtained with solution (2).

Assay Dissolve about 0.2 g, accurately weighed, in 10 ml of acetone, add 10 ml of water and 3 drops of phenolphthalein IS. Titrate immediately with sodium hydroxide (0.1 mol/L) VS. Perform a blank determination and make any necessary correction. Each ml of sodium hydroxide (0.1 mol/L) VS is equivalent to 30.42 mg of $C_{14}H_{19}Cl_2NO_2$.

Category Antineoplastic.

Storage Preserve in tightly closed containers, protected from light.

Preparation Chlorambucil Chart Tablets

Chlorambucil Chart Tablets

Chlorambucil Chart Tablets contain not less than 85.0% and not more than 110.0% of the labelled amount of chlorambucil ($C_{14}H_{19}Cl_2NO_2$).

Description White or almost white chart tablets.

Identification (1) Add 5 ml of acetone to 5 squares of the chart tablets equivalent to about 10 mg of chlorambucil, shake to dissolve chlorambucil and filter. To the filtrate add 5 ml of water and mix well. Add 4 drops of nitric acid solution (1→2) and silver nitrate TS and heat on a water bath, an opalescence is produced.

(2) The light absorption of solution obtained in the Assay exhibits maxima at 257 nm and 320 nm, minima at 225 nm and 280 nm (Appendix IV A).

Content uniformity Comply with the requirements Appendix X E. To 1 square of the chart tablets add accurately 25 ml of a mixture of isopropyl ether-ethanol (1 : 9), shake and allow to stand. Carry out the procedure described under Assay using the supernatant solution, filter if necessary.

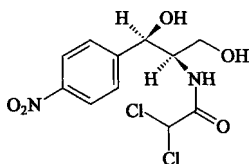
Assay Cut 20 squares of the chart tablets into small pieces and transfer to a stoppered conical flask. Add 50 ml of isopropyl ether, previously washed for 4 times with water and accurately measured, shake for 15 minutes, add 5 ml of 10% potassium dihydrogen phosphate solution. Stopper the flask tightly, shake vigorously for 15 minutes. Allow to stand for 5 minutes, measure accurately 5 ml of isopropyl ether solution to a 50 ml volumetric flask, dilute with ethanol to volume. Weigh accurately 40 mg of chlorambucil CRS to a 50 ml volumetric flask, add isopropyl ether (washed previously with water for 4 times) to volume and mix well. Measure accurately 5 ml to another 50 ml volumetric flask, dilute with ethanol to volume and mix well. Measure the absorbance of the two solutions at 302 nm (Appendix IV A) and calculate the content of $C_{14}H_{19}Cl_2NO_2$.

Category As described under Chlorambucil.

Strength 2 mg

Storage Preserve in tightly closed containers, protected from light and stored in a cool place.

Chloramphenicol



$C_{11}H_{12}Cl_2N_2O_5$ 323.13

[530-43-8]

Chloramphenicol is D-threo-(-)-2,2-dichloro-N-[β -hydroxy- α -(hydroxymethyl)-*p*-nitrophenethyl] acetamide. It contains not less than 98.0% and not more than 102.0% of $C_{11}H_{12}Cl_2N_2O_5$, calculated on the dried basis.

Description A white to slightly yellowish-green crystalline powder, needle crystals or elongated plates; taste, bitter. Freely soluble in methanol, ethanol, acetone or propylene glycol; slightly soluble in water.

Melting point 149-153°C (Appendix VI C).

Specific optical rotation +18.5° to +21.5°, in a solution of 50 mg per ml in dehydrated ethanol (Appendix VI E).

Identification (1) Dissolve 10 mg in 1 ml of dilute ethanol TS, add 3 ml of 1% calcium chloride solution and 50 mg of zinc powder, heat on a water bath for 10 minutes. To the supernatant liquid add about 0.1 ml of benzoyl chloride, shake thoroughly for one minute, add 0.5 ml of ferric chloride TS and 2 ml of chloroform, mix well; a reddish-violet colour is produced in the aqueous layer. Repeat the test omitting zinc powder; no reddish-violet colour is produced.

(2) The retention time of principal peak in the substance being examined in the chromatogram obtained in the Assay is identical with that of the principal peak of chloramphenicol CRS.

(3) The infrared absorption spectrum (Appendix IV C) is concordant with the reference spectrum of chloramphenicol (Appendix XVI).

Crystallinity Complies with the test for crystallinity (Appendix IX D).

Acidity or alkalinity A suspension of 25 mg per ml in water, pH 4.5-7.5 (Appendix VI H).

Relate substances Dissolve an accurately weighed quantity in methanol (add 1 ml of methanol per 10 mg of Chloramphenicol), dilute with mobile phase to produce the test solution of 0.1 mg per ml, mix well. Dissolve an accurately weighed quantity of 1-*p*-nitropheny-2-amino-1,3-prop CRS and *p*-nitrobenzaldehyde CRS in methanol (add 1 ml of methanol per 10 mg of 1-*p*-nitropheny-2-amino-1,3-prop), dilute with mobile phase to produce the mixture solution of 1 μ g per ml for 1-*p*-nitropheny-2-amino-1,3-prop and 0.5 μ g per ml for *p*-nitrobenzaldehyde (the reference solution). Carry out the method as described under Assay. Inject 10 μ l of the reference solution into the column and adjust the attenuation so that 1-*p*-nitropheny-2-amino-1,3-prop peak height in the chromatogram is 20%-25% of the full scale of the chart. Inject accurately 10 μ l of the test solution and the reference solution into the column separately, and record the chromatogram. Calculate the contents of 1-*p*-nitropheny-2-amino-1,3-prop and *p*-nitrobenzaldehyde by the external standard method. The contents of 1-*p*-nitropheny-2-amino-1,3-prop and *p*-nitrobenzaldehyde are not more than 1.0% and 0.5% respectively.

Loss on drying When dried to constant weight at 105°C, loses not more than 0.5% of its weight (Appendix VIII L).

Residue on ignition Not more than 0.1% (Appendix VIII N).

Assay Carry out the method for high performance liquid chromatography (Appendix V D), using a column packed with octadecylsilane bonded silica gel and a mixture of 0.1% sodium heptanesulfonate solution (mix 500 ml of 0.1% sodium heptanesulfonate solution, 5 ml of dimethylformamide and 0.5 ml of 1% sodium hydroxide solution) as the mobile phase. Detection wavelength is 272 nm. Dissolve Chloramphenicol CRS and 1-*p*-nitropheny-2-amino-1,3-prop CRS in methanol, dilute with mobile phase to produce mixture solution of 50 μ g per ml respectively. Inject 10 μ l into column and record the chromatogram. The number of theoretical plates of the column is less than 1500, calculated with reference to the peak of Chloramphenicol. The resolution factor between the peaks of Chloramphenicol and 1-*p*-nitropheny-2-amino-1,3-prop is not less than 2.0.

Procedure Dissolve about 50 mg, accurately weighed, in 5 ml of methanol, dilute with mobile phase to produce a solution of 0.1 mg per ml, mix well. Inject 10 μ l into column and record the chromatogram. Repeat the operations, using Chloramphenicol CRS instead of the substance being examined. Calculate the content of $C_{11}H_{12}Cl_2N_2O_5$ by the external standard method.

Category Amphenicols of Antibiotic.

Storage Preserve in tightly closed containers.

Preparation (1) Chloramphenicol Capsules
(2) Chloramphenicol Ear Drops
(3) Chloramphenicol Eye Drops
(4) Chloramphenicol Eye Ointment
(5) Chloramphenicol Tablets

Chloramphenicol Capsules

Chloramphenicol Capsules contain not less than 90.0% and not more than 110.0% of the labelled amount of chloramphenicol ($C_{11}H_{12}Cl_2N_2O_5$).

Description Contents containing white to slightly yellowish-green powder or granule.

Identification (1) The contents of the capsules comply with

the tests (1) for Identification described under Chloramphenicol.

(2) The retention time of principal peak in the substance being examined in the chromatogram obtained in the Assay is identical with that of the principal peak of chloramphenicol CRS.

Loss on drying When dried to constant weight at 105°C, the contents of the capsules lose not more than 1.0% of their weight (Appendix VIII L).

Dissolution Carry out the dissolution test (Appendix X C, method 1), using 900 ml of hydrochloric acid solution (9→1000) as the dissolution medium, adjust the rotational speed of the basket to 100 rpm. Withdraw the solution after exactly 30 minutes and filter. Dilute 5 ml of the successive filtrate, accurately measured, with hydrochloric acid solution (9→1000) to 50 ml, mix well. Measure the absorbance of the resulting solution at 278 nm (Appendix IV A). Calculate the dissolution of $C_{11}H_{12}Cl_2N_2O_5$ from each capsules, taking 298 as the value of A (1%, 1 cm). Not less than 70% of the labelled amount is dissolved.

Other requirements Comply with the general requirements for capsules (Appendix I E).

Assay Weigh accurately a quantity (equivalent to about 50 mg Chloramphenicol) of mixed contents obtained in the test for weight variation of contents, dissolve in methanol (add 1 ml of methanol per 10 mg of chloramphenicol), dilute with mobile phase to produce a solution of 0.1 mg per ml and filter. Carry out the Assay described under Chloramphenicol using an accurately measured quantity of the successive filtrate.

Category As described under Chloramphenicol.

Strength (1) 0.125 g (2) 0.25 g

Storage Preserve in tightly closed containers.

Chloramphenicol Ear Drops

Chloramphenicol Ear Drops contain not less than 85.0% of the labelled amount of chloramphenicol ($C_{11}H_{12}Cl_2N_2O_5$). Glycerin or propylene glycol may be added as solubilizing agent.

Description A clear colourless to slightly yellow viscous liquid; taste, extremely bitter; miscible with water.

Identification (1) To about 1 ml add 3 ml of 1% calcium chloride solution and 50 mg of zinc powder, heat on a water bath for 10 minutes. To the supernatant liquid add about 0.1 ml of benzoyl chloride, shake thoroughly for one minute, add 0.5 ml of ferric chloride TS and 2 ml of chloroform, mix well; reddish-violet colour is produced in the aqueous layer. (2) The retention time of principal peak in the substance being examined in the chromatogram obtained in the Assay is identical with that of the principal peak of Chloramphenicol CRS.

Related substances Dissolve an accurately weighed quantity in mobile phase to produce the test solution of 0.2 mg per ml. Dissolve an accurately weight of 1-p-nitropheny-2-amino-1,3-prop CRS and p-nitrobenzaldehyde CRS in methanol (and 1 ml of methanol per 10 mg of 1-p-nitropheny-2-amino-1,3-prop), dilute with mobile phase to produce the mixture solution of 8 µg per ml for 1-p-nitropheny-2-amino-1,3-prop and 2 µg per ml for p-nitrobenzaldehyde (the reference solution). Carry out the method as described under Assay. Inject 10 µl of the reference solution into the column and adjust the attenuation so that p-nitrobenzaldehyde peak

height in the chromatogram is 15% of the full scale of the chart. Inject accurately 10 µl of the test solution and the reference solution into the column separately, and record the chromatogram. Calculate the contents of 1-p-nitropheny-2-amino-1, 3-prop and p-nitrobenzaldehyde by the external standard method. The contents of 1-p-nitropheny-2-amino-1, 3-prop and p-nitrobenzaldehyde are not more than 5.0% and 0.5% respectively.

Other requirements Comply with the general requirements for ear preparations (Appendix I Q).

Assay Dissolve an accurately weighed quantity in mobile phase to produce a solution of 0.1 mg per ml and filter. Carry out the Assay described under Chloramphenicol.

Category As described under Chloramphenicol.

Strength 10 ml : 0.25 g

Storage Preserve in tightly closed containers.

Chloramphenicol Eye Drops

Chloramphenicol Eye Drops contain not less than 85.0% of the labelled amount of chloramphenicol ($C_{11}H_{12}Cl_2N_2O_5$). It may contain suitable buffers and preservatives.

Description A clear, colourless or almost colourless liquid.

Identification (1) To 4 ml add 3 ml of 1% calcium chloride solution and 50 mg of zinc powder, heat on a water bath for 10 minutes. To the supernatant liquid add about 0.1 ml of benzoyl chloride shake thoroughly for one minute, add 0.5 ml of ferric chloride TS and 2 ml of chloroform, mix well; a reddish-violet colour is produced in the aqueous layer.

(2) The retention time of principal peak in the substance being examined in the chromatogram obtained in the Assay is identical with that of the principal peak of Chloramphenicol CRS.

pH value 6.0-7.0 (Appendix VI H).

Related substances Dissolve an accurately weighed quantity in mobile phase to produce the test solution of 0.2 mg per ml. Dissolve an accurately weight of 1-p-nitropheny-2-amino-1,3-prop CRS and p-nitrobenzaldehyde CRS in methanol (add 1 ml of methanol per 10 mg of 1-p-nitropheny-2-amino-1,3-prop), dilute with mobile phase to produce the mixture solution of 8 µg per ml for 1-p-nitropheny-2-amino-1,3-prop and 2 µg per ml for p-nitrobenzaldehyde (the reference solution). Carry out the method as described under Assay. Inject 10 µl of the reference solution into the column and adjust the attenuation so that p-nitrobenzaldehyde peak height in the chromatogram is 15% of the full scale of the chart. Inject accurately 10 µl of the test solution and the reference solution into the column separately, and record the chromatogram. Calculate the contents of 1-p-nitropheny-2-amino-1, 3-prop and p-nitrobenzaldehyde by the external standard method. The contents of 1-p-nitropheny-2-amino-1, 3-prop and p-nitrobenzaldehyde are not more than 8.0% and 0.5% respectively.

Other requirements Comply with the general requirements for eye preparations (Appendix I G).

Assay Dissolve an accurately weighed quantity in mobile phase to produce a solution of 0.1 mg per ml and filter. Carry out the Assay described under Chloramphenicol.

Category As described under Chloramphenicol.

Strength (1) 5 ml : 12.5 mg (2) 8 ml : 20 mg
(3) 10 ml : 25 mg

Storage Preserve in tightly closed containers, stored in a cool place and protected from light.

Chloramphenicol Eye Ointment

Chloramphenicol Eye Ointment contains not less than 90.0% and not more than 110.0% of the labelled amount of chloramphenicol ($C_{11}H_{12}Cl_2N_2O_5$).

Description A pale yellow or yellow eye ointment.

Identification (1) Dissolve about 2 g with 10 ml of dilute ethanol TS by warming and stir in a water bath. Allow it to cool, filter, the filtrate complies with the test (1) for Identification described under Chloramphenicol.

(2) The retention time of principal peak in the substance being examined in the chromatogram obtained in the Assay is identical with that of the principal peak of Chloramphenicol CRS.

Other requirements Complies with the general requirements for eye preparations (Appendix I G).

Assay To about 4 g, accurately weighed, add 30 ml of petroleum ether in a separator, extract with 3 quantities of 20 ml each of phosphate BS (pH 6.0). Dilute the combined extracts to 100 ml with phosphate BS (pH 6.0), mix well. Dissolve an accurately weighed quantity in mobile phase to produce a solution of 0.1 mg per ml and filter. Carry out the Assay described under Chloramphenicol.

Category As described under Chloramphenicol.

Strength (1) 1% (2) 3%

Storage Preserve in tightly closed containers, stored in a cool place.

Chloramphenicol Tablets

Chloramphenicol Tablets contain not less than 90.0% and not more than 110.0% of the labelled amount of chloramphenicol ($C_{11}H_{12}Cl_2N_2O_5$).

Description Sugar-coated or film coated tablets with white to slightly yellowish-green cores.

Identification (1) Triturate and powder one tablet with coating removed. Shake with 10 ml of ethanol, filter and evaporate the filtrate to dryness. The residue complies with test (1) for Identification described under Chloramphenicol.

(2) The retention time of principal peak in the substance being examined in the chromatogram obtained in the Assay is identical with that of the principal peak of chloramphenicol CRS.

Dissolution Carry out the dissolution test (Appendix X C, method 1), using 900 ml of hydrochloric acid solution (9→1000) as the dissolution medium, adjust the rotational speed of the basket to 100 rpm. Withdraw a quantity of the solution after exactly 30 minutes and filter. Dilute 5 ml of the successive filtrate, accurately measured, with hydrochloric acid solution (9→1000) to 50 ml, mix well. Measure the absorbance of the resulting solution at 278 nm (Appendix IV A), calculate the dissolution of $C_{11}H_{12}Cl_2N_2O_5$ from each tablet, taking 298 as the value of A (1%, 1 cm). Not less than 70% of the labelled amount is dissolved.

Other requirements Comply with the general requirements for tablets (Appendix I A).

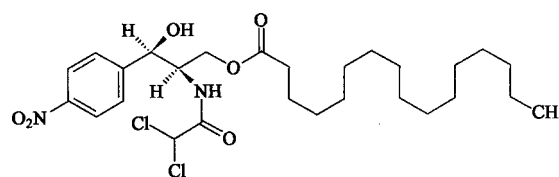
Assay Weigh accurately and powder 10 tablets. Dissolve an accurately weighed quantity of the powder equivalent to 50 mg Chloramphenicol in methanol (add 1 ml of methanol per 10 mg of chloramphenicol), dilute with mobile phase to produce a solution of 0.1 mg per ml and filter. Carry out the Assay described under Chloramphenicol using an accurately measured quantity of the successive filtrate.

Category As described under Chloramphenicol.

Strength (1) 0.05 g (2) 0.25 g

Storage Preserve in tightly closed containers.

Chloramphenicol Palmitate



$C_{27}H_{42}Cl_2N_2O_6$ 561.55

[530-43-8]

Chloramphenicol Palmitate is D-threo (-) -2,2-dichloro-N- [β-hydroxy-α- (hydroxymethyl) -p-nitrophenethyl] acetamide α-palmitate in the form of polymorph A or B. It contains not less than 56.5% and not more than 59.0% of chloramphenicol ($C_{11}H_{12}Cl_2N_2O_5$), calculated on the dried basis.

Description A white or almost white powder; almost odourless; tasteless.

Freely soluble in acetone or chloroform; sparingly soluble in ethanol; insoluble in water.

Melting range 89-95°C for polymorph A; 86-91°C for polymorph B, after dried at 60°C for 2 hours (Appendix VI C).

Specific optical rotation +22° to +25°, in a solution of 50 mg per ml in dehydrated ethanol (Appendix VI E).

Identification (1) The light absorption of a solution of 20 μg per ml in dehydrated ethanol exhibits a maximum at 271 nm. The absorbance is about 0.35 (Appendix IV A).

(2) The infrared absorption spectrum (Appendix IV C) of polymorph A or B is concordant with the reference spectrum of polymorph A or B of chloramphenicol palmitate (Appendix XVI, using mull method).

(3) Dissolve about 0.1 g in 2 ml of ethanolic potassium hydroxide TS, heat in a water bath for 15 minutes, avoid evaporation of ethanol; the solution yields the reactions characteristic of chlorides (Appendix III).

Free palmitic acid Dissolve 1 g in 30 ml of ethanol, previously neutralized to thymol blue, and titrate with sodium hydroxide (0.02 mol/L) VS until the colour changes to green, it contains not more than 2.0% of free palmitic acid ($C_{16}H_{32}O_2$). Each ml of sodium hydroxide (0.02 mol/L) VS is equivalent to 5.128 mg of $C_{16}H_{32}O_2$.

Free chloramphenicol Dissolve about 1 g, accurately weighed, in 80 ml of xylene in a 100 ml conical flask by heat in a water bath, cool, transfer to a separator and extract with three quantities, each of 15 ml, of water. Combine the aqueous extracts, wash with 10 ml of carbon tetrachloride.

Dilute the aqueous solution to 50 ml with water in a 50 ml volumetric flask, mix well and centrifuge. Measure the absorbance of the clear supernatant liquid at 278 nm (Appendix IV A), using a blank solution obtained by repeating the procedure without the substance being examined; the absorbance of the blank solution is not more than 0.05. Calculate the content of free chloramphenicol ($C_{11}H_{12}Cl_2N_2O_5$), taking 298 as the value of A (1%, 1 cm); not more than 0.045%.

Loss on drying When dried in vacuum over phosphorus pentoxide to constant weight at 60°C, loses not more than 1.0% of its weight (Appendix VIII L).

Residue on ignition Not more than 0.1% (Appendix VIII N).

Assay Dissolve an accurately weighed quantity in dehydrated ethanol to produce a solution of about 25 µg per ml, measure the absorbance at 271 nm (Appendix IV A). Calculate the content of $C_{27}H_{42}Cl_2N_2O_6$, taking 178 as the value of A (1%, 1 cm). The content of $C_{11}H_{12}Cl_2N_2O_5$ is obtained by multiplying the content of $C_{27}H_{42}Cl_2N_2O_6$ with 0.5754.

Category Amphenicols of Antibiotic.

Storage Preserve in tightly closed containers, protected from light.

Preparation (1) Chloramphenicol Palmitate (Polymorph B) Granules
(2) Chloramphenicol Palmitate Suspension
(3) Chloramphenicol Palmitate (Polymorph B) Tablets

Chloramphenicol Palmitate (Polymorph B) Granules

Chloramphenicol Palmitate (Polymorph B) Granules contain not less than 90.0% and not more than 110.0% of the labelled amount of chloramphenicol ($C_{11}H_{12}Cl_2N_2O_5$) with reference to chloramphenicol palmitate (polymorph B).

Description Suspensible granules; odour, fragrant; taste, sweet.

Identification To 1 g of powdered granules add 30 ml of water, shake thoroughly, filter, wash the residue with water several times and dry under reduced pressure at room temperature, triturate. The residue complies with the tests (2) and (3) for Identification described under Chloramphenicol Palmitate.

Acidity To a quantity add water to produce a suspension of 25 mg per ml, pH 4.5-7.0 (Appendix VI H).

Loss on drying When dried in vacuum over phosphorous pentoxide to constant weight at 60°C, loses not more than 2.0% of its weight (Appendix VIII L).

Other requirements Comply with the general requirements for granules (Appendix I N).

Assay Dissolve an accurately weighed quantity of the contents obtained from the test for weight variation of contents, equivalent to 25 mg of chloramphenicol palmitate, in a 100 ml volumetric flask with a quantity of dehydrated ethanol, shake thoroughly, dilute to volume with dehydrated ethanol, mix well and filter. Dilute an accurately quantity of the successive filtrate with dehydrated ethanol to produce a solution of 25 µg per ml. Carry out the method described under Chloramphenicol Palmitate.

Category As described under Chloramphenicol Palmitate.

Strength 0.1 g (calculated as $C_{11}H_{12}Cl_2N_2O_5$)

Storage Preserve in tightly closed containers, protected from light.

Chloramphenicol Palmitate Suspension

Chloramphenicol Palmitate Suspension contains not less than 90.0% and not more than 110.0% of the labelled amount of chloramphenicol ($C_{11}H_{12}Cl_2N_2O_5$).

Description A creamy white suspension; taste, sweet.

Identification (1) Shake about 5 ml with 20 ml of chloroform, separate the chloroform layer, filter and evaporate the filtrate to dryness. Wash the residue thoroughly with water, the residue complies with the tests (1) and (3) for Identification described under Chloramphenicol Palmitate.

(2) The infrared absorption spectrum (Appendix IV C) of the residue obtained in test for Polymorph A is concordant with the reference spectrum of polymorph B of chloramphenicol palmitate (Appendix XVI, using mull method).

Acidity pH 4.5-7.0 (Appendix VI H).

Polymorph A Preparation of reference substances (1) 20% polymorph A CRS: Mix thoroughly one part by weight of chloramphenicol palmitate polymorph A CRS and four parts by weight of chloramphenicol palmitate polymorph B CRS.

(2) 10% polymorph A CRS: Mix thoroughly one part by weight of chloramphenicol palmitate polymorph A CRS and nine parts by weight of chloramphenicol palmitate polymorph B CRS.

Preparation of the test substance To 20 ml of the suspension add 20 ml of water, mix well, centrifuge for 15 minutes, discard the supernatant liquid. Triturate the residue with 2 ml of water to form a paste, add 18 ml of water, shake thoroughly, centrifuge and discard the supernatant liquid. Wash the residue twice more in the same manner. Dry the residue under reduced pressure at room temperature for 14 hours and grind to a fine powder.

Procedure Triturate a small quantity of the test substance and the reference substances respectively with about twice its weight of liquid paraffin until smooth creamy pastes are obtained, mount a small portion of the mull between rock salt plates and record the infrared spectra (Appendix IV C) of each mull over the range of 780-900 cm^{-1} . The transmission of the test substance at 810 cm^{-1} is 20%-30%. On the spectrum of reference substance (1), determine the exact wave number of minimum absorption at about 885 cm^{-1} and 790 cm^{-1} and that of maximum absorption at about 858 cm^{-1} and 843 cm^{-1} . On the spectrum of reference substance (2), draw a straight baseline between the minima occurring at the wave numbers determined above, then draw two lines perpendicular to the baseline at the wave numbers of maxima determined above. Calculate the ratio of the peak height at the maximum at about 858 cm^{-1} to that at the maximum at about 843 cm^{-1} . Carry out the same procedure on the spectrum of the test substance. The ratio of absorbance of the test substance is greater than that of reference substance (2).

Other requirements Complies with the general requirements for suspension (Appendix I O).

Assay Measure accurately 5 ml of the suspension to a 125 ml separator, extract with 25 ml of chloroform, followed by four 20 ml portions. Evaporate the combined extracts to dryness. Dissolve and dilute the residue to 250 ml with dehydrated ethanol, mix well. Measure accurately 10 ml to a

200 ml volumetric flask, dilute with dehydrated ethanol to volume, mix well and carry out the Assay described under Chloramphenicol Palmitate.

Category As described under Chloramphenicol Palmitate.

Strength 1 ml : 25 mg (calculated as $C_{11}H_{12}Cl_2N_2O_5$)

Storage Preserve in tightly closed containers and protected from light.

Chloramphenicol Palmitate (Polymorph B) Tablets

Chloramphenicol Palmitate Tablets contain not less than 90.0% and not more than 110.0% of the labelled amount of chloramphenicol ($C_{11}H_{12}Cl_2N_2O_5$) in the form of polymorph B of chloramphenicol palmitate.

Description White tablets.

Identification (1) Shake thoroughly 5 powdered tablets with 10 ml of water in a centrifuge tube and centrifuge. Discard the supernatant liquid, wash the precipitate in the same manner until the supernatant liquid is practically clear. Dry the precipitate under reduced pressure at room temperature, grind to a fine powder. The infrared absorption spectrum (Appendix IV C) of the powder is concordant with the reference spectrum of polymorph B of chloramphenicol palmitate (Appendix XVI), using mull method.

(2) Comply with the test (3) for Identification described under Chloramphenicol Palmitate, using 1 powdered tablet.

Other requirements Comply with the general requirements for tablets (Appendix I A).

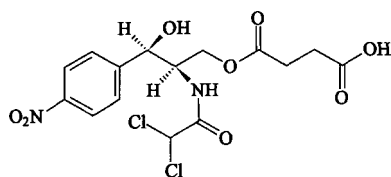
Assay Weigh accurately and powder 10 tablets. Weigh accurately a quantity of powder equivalent to about 25 mg of chloramphenicol palmitate, transfer to a 100 ml volumetric flask, shake and dilute to volume with dehydrated ethanol. Filter, dilute a quantity, accurately measured, of the successive filtrate with dehydrated ethanol to produce a solution of 25 μ g per ml. Carry out the Assay described under Chloramphenicol Palmitate.

Category As described under Chloramphenicol Palmitate.

Strength 50 mg (calculated as $C_{11}H_{12}Cl_2N_2O_5$)

Storage Preserve in tightly closed containers and protected from light.

Chloramphenicol Succinate



$C_{15}H_{16}Cl_2N_2O_8$ 423.21

Chloramphenicol Succinate is *D*-threo (-)-2,2-dichloro-*N*-[β -hydroxy- α -(hydroxymethyl)-*p*-nitrophenethyl] acetamide α -succinate. It contains not less than 75.0% and not more than 79.0% of chloramphenicol ($C_{11}H_{12}Cl_2N_2O_5$), calculated on the dried basis.

Description A white or almost white crystalline powder; odourless; taste, bitter.

Freely soluble in ethanol or acetone; slightly soluble in water; freely soluble in alkali solution.

Melting range 126-131°C (Appendix VI C).

Specific optical rotation +22° to +26° measured at 25°C, in a solution of 50 mg per ml in dehydrated ethanol (Appendix VI E).

Identification (1) To 50 mg add 5 ml of pyridine and 5 ml of sodium hydroxide TS, shake thoroughly, heat in a water bath for several minutes; the pyridine layer becomes deep red.

(2) The infrared absorption spectrum (Appendix IV C) is concordant with the reference spectrum of chloramphenicol succinate (Appendix XVI).

(3) Dissolve 50 mg in 2 ml of ethanolic potassium hydroxide TS, heat in a water bath for 15 minutes, avoid evaporation of ethanol; the solution yields the reactions characteristic of chlorides (Appendix III).

Clarity and colour of solution To 5 portions each of 1.32 g add 5 ml of 4% sodium carbonate solution respectively, the solution are clear and colourless. Any opalescence produced is not more pronounced than that of reference suspension I (Appendix IX B); any colour produced is not more intense than that of reference solutions YG₅ (Appendix IX A, method 1).

Ethanol insoluble substances Dissolve 0.5 g in 5 ml of ethanol, the solution is clear.

Sulfate Dilute the solution obtained in the test for clarity and colour of solution with 20 ml of water, add 6 ml of dilute hydrochloric acid TS dropwise with shaking, dilute to 50 ml with water, shake thoroughly and filter. Carry out the limit test for sulfates (Appendix VIII B), using 10 ml of the filtrate. Any opalescence produced is not more pronounced than that of a reference solution using 1.0 ml of potassium sulfate standard solution (0.05%).

Free chloramphenicol Carry out the method for thin-layer chromatography (Appendix V B), using silica gel GF₂₅₄ as the coating substance and a mixture of chloroform-methanol-water (9 : 1 : 0.1) as the mobile phase. Apply separately to the plate 10 μ l each of two solutions containing (1) 10 mg per ml of the substance being examined in 0.15% sodium carbonate solution and (2) 0.2 mg per ml of chloramphenicol CRS in water. After developing and removal of the plate, dry it in air and examine under ultraviolet light. The colour and the size of any spot other than the principal spot in the chromatogram obtained with solution (1) is not more intense or bigger than the principal spot obtained with solution (2).

Loss on drying When dried in vacuum over phosphorous pentoxide to constant weight at 60°C, loses not more than 0.5% of its weight Appendix VIII L.

Residue on ignition Not more than 0.1% (Appendix VIII N).

Sterility Complies with the test for sterility (Appendix XI H, membrane filtration method), dissolving each portion in suitable solvent. Transfer the solution into at least 500 ml of 0.9% sterile sodium chloride solutions.

Assay Dissolve an accurately weighed quantity in ethanol to produce a solution of 10 mg per ml, dilute with water to produce a solution of 20 μ g per ml, measure the absorbance at 276 nm (Appendix IV A). Calculate the content of $C_{11}H_{12}Cl_2N_2O_5$, taking 298 as the value of A (1%, 1 cm).

Category Amphenicols of antibiotic.

Storage Preserve in hermetically sealed containers.

Preparation Chloramphenicol Succinate for Injection

Chloramphenicol Succinate for Injection

Chloramphenicol Succinate for Injection is a sterile mixture of Chloramphenicol Succinate and anhydrous sodium carbonate. It contains not less than 95.0% and not more than 105.0% of the labelled amount of chloramphenicol ($C_{11}H_{12}Cl_2N_2O_5$), calculated on the basis of the average weight of contents.

Description A white or almost white powder.

Identification (1) Complies with the tests (1) for Identification described under Chloramphenicol Succinate. (2) The aqueous solution yields the reactions characteristic of sodium salts (Appendix III).

Acidity or alkalinity Dissolve a quantity in water to produce a solution containing 0.2 g of chloramphenicol per ml, pH 6.5-8.5 (Appendix VI H).

Clarity and colour of solution To each of 5 containers add water to produce solutions containing 0.2 g of chloramphenicol per ml by the labelled amount. The solution are clear and colourless; any opalescence produced is not more pronounced than that of reference suspension I (Appendix IX B); any colour produced is not more intense than that of reference solution YG₅ (Appendix IX A, method 1).

Loss on drying When dried in vacuum over phosphorous pentoxide to constant weight at 60°C, loses not more than 1.0% of its weight (Appendix VIII L).

Sterility Complies with the test for sterility (Appendix XI H), dissolving each portion in suitable solvent and transferring the solution into at least 500 ml of 0.9% sterile sodium chloride solution.

Other requirements Complies with the general requirements for injections (Appendix I B).

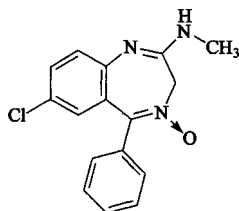
Assay Weigh accurately a quantity of the contents obtained from the test weight variation of contents, equivalent to about 50 mg of chloramphenicol, dissolve in water to produce a solution of 20 µg per ml. Measure the absorbance at 276 nm (Appendix IV A). Calculate the content of $C_{11}H_{12}Cl_2N_2O_5$, taking 298 as the value of A (1%, 1 cm).

Category As described under Chloramphenicol Succinate.

Strength Calculated as $C_{11}H_{12}Cl_2N_2O_5$
(1) 0.125 g (2) 0.25 g (3) 0.5 g

Storage Preserve in well closed containers.

Chlordiazepoxide



$C_{16}H_{14}ClN_3O$ 299.76

[58-25-3]

Chlordiazepoxide is 7-chloro-N-methyl-5-phenyl-3H-

1,4-benzodiazepine-2-amine-4-oxide. It contains not less than 99.0% of $C_{16}H_{14}ClN_3O$, calculated on the dried basis.

Description A pale yellow crystalline powder; odourless; taste, bitter.

Soluble in ether, chloroform or dichloromethane; slightly soluble in water.

Specific absorbance Measure the absorbance of a solution of 15 µg per ml in hydrochloric acid solution (9→1000) at 308 nm (Appendix IV A), the value of A (1%, 1 cm) is 309-329.

Identification (1) Dissolve 10 mg in 10 ml of hydrochloric acid solution (9→1000), add 1 drop of potassium iodobismuthate TS; an orangish-red precipitate is produced. (2) The light absorption of a solution of 7 µg per ml in hydrochloric acid solution (9→1000) exhibits maxima at 245 nm and 308 nm (Appendix IV A). (3) Dissolve 10 mg in 15 ml of hydrochloric acid solution (1→2), boil gently for 15 minutes and cool. The solution yields the reactions characteristic of primary aromatic amine (Appendix III).

Clarity of acidic solution A solution of 0.50 g in 25 ml of hydrochloric acid solution (9→1000) is clear; any opalescence produced is not more pronounced than that of a reference solution prepared by mixing 10 ml of standard lead solution with 1 ml of 5% sodium bicarbonate solution and 14 ml of water.

Loss on drying When dried to constant weight at 105°C, loses not more than 1.0% of its weight (Appendix VIII L).

Residue on ignition Not more than 0.1% (Appendix VIII N).

Assay Dissolve about 0.3 g, accurately weighed, in 20 ml of glacial acetic acid, add 1 drop of crystal violet IS, titrate with perchloric acid (0.1 mol/L) VS until the colour changes to blue. Perform a blank determination and make any necessary correction. Each ml of perchloric acid (0.1 mol/L) VS is equivalent to 29.98 mg of $C_{16}H_{14}ClN_3O$.

Category Antianxiety agent and anticonvulsant.

Storage Preserve in tightly closed containers, protected from light.

Preparation Chlordiazepoxide Tablets

Chlordiazepoxide Tablets

Chlordiazepoxide Tablets contain not less than 90.0% and not more than 110.0% of the labelled amount of chlordiazepoxide ($C_{16}H_{14}ClN_3O$).

Description Slightly yellow tablets.

Identification Triturate a quantity of powdered tablets equivalent to 0.5 g of chlordiazepoxide with 30 ml of chloroform to dissolve chlordiazepoxide, filter and evaporate the filtrate on a water bath to dryness; the residue complies with the tests for Identification described under Chlordiazepoxide.

Content uniformity Comply with the requirements for content uniformity (Appendix X E). Transfer 1 tablet to a 50 ml volumetric flask, add about 30 ml of hydrochloric acid solution (9→1000), shake thoroughly to disperse. Dilute with above hydrochloric acid solution to volume, mix well and filter. Measure accurately 3 ml of successive filtrate to 50 ml volumetric flask, dilute with above hydrochloric acid

solution to volume, mix well. Measure the absorbance of the resulting solution at 308 nm (Appendix IV A), calculate the content of $C_{16}H_{14}ClN_3O$, taking 319 as the value of A (1%, 1 cm).

Dissolution Carry out the dissolution test (Appendix X C, method 1), using 800 ml of hydrochloric acid solution (9→1000) as the dissolution medium, adjust the rotational speed of the basket to 100 rpm, withdraw 5 ml of the solution after exactly 30 minutes and filter. Measure the absorbance of the filtrate at 308 nm (Appendix IV A). Calculate the dissolution of $C_{16}H_{14}ClN_3O$ from each tablet, taking 319 as the value of A (1%, 1 cm), not less than 85% of the labelled amount is dissolved.

Other requirements Comply with the general requirements for tablets (Appendix I A).

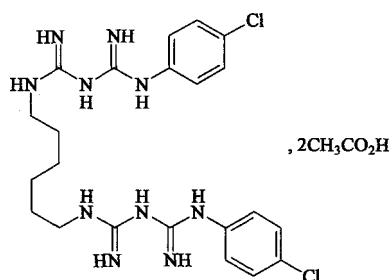
Assay Weigh accurately and powder 20 tablets. Transfer a quantity of powdered tablets equivalent to about 30 mg of chlordiazepoxide, accurately weighed, to a 100 ml volumetric flask, add 70 ml of hydrochloric acid solution (9→1000), shake vigorously to dissolve the chlordiazepoxide, dilute with hydrochloric acid solution (9→1000) to volume, mix and filter. Transfer 5 ml of the successive filtrate, accurately measured, to 100 ml volumetric flask, dilute with hydrochloric acid solution (9→1000) to volume and mix well. Measure the absorbance at 308 nm (Appendix IV A) and calculate the content of $C_{16}H_{14}ClN_3O$, taking 319 as the value of A (1%, 1 cm).

Category As described under Chlordiazepoxide.

Strength (1) 5 mg (2) 10 mg

Storage Preserve in tightly closed containers, protected from light.

Chlorhexidine Acetate



$C_{22}H_{30}Cl_2N_{10} \cdot 2C_2H_4O$ 625.56

[56-95-1]

Chlorhexidine Acetate is (*N,N'*-bis (4-chlorophenyl)-3,12-diimino-2,4,11,13-tetra-zatetra-decanecylimidamide, diacetate. It contains not less than 97.5% of $C_{22}H_{30}Cl_2N_{10} \cdot 2C_2H_4O$, calculated on the dried basis.

Description A white or almost white crystalline powder; odourless; taste, bitter. Soluble in ethanol; slightly soluble in water.

Identification (1) Dissolve about 10 mg in 5 ml of hot 1% cetrimonium bromide solution, add 1 ml of each of bromine TS and sodium hydroxide TS. A deep red colour is produced.

(2) Dissolve about 10 mg in 10 ml of water, add 2 drops of potassium dichromate TS. A yellow precipitate is produced; which dissolves on addition of a few drops of dilute nitric acid.

(3) The light absorption of a 10 μ g per ml solution in ethanol exhibits a maximum at 259 nm (Appendix IV A).

(4) Its aqueous solution yields the reactions characteristic of acetates (Appendix III).

***p*-Chloroaniline** Dissolve 0.20 g in 10 ml of hydrochloric acid solution (9→100) and 20 ml of water with shaking. Add in sequence 1 ml of 0.5 mol/L sodium nitrite solution and 2 ml of 5% ammonium sulfamate solution, mix well, allow to stand for 5 minutes. Add 5 ml of 0.1% *N*-(1-naphthyl)-ethylenediamine dihydrochloride solution, 1 ml of ethanol and sufficient water to produce 50 ml, mix well, allow to stand for 30 minutes. Any colour produced is not more intense than that of a reference solution prepared in the same manner, using 10 ml of *p*-chloroaniline solution [weigh accurately a quantity of *p*-chloroaniline CRS, add hydrochloric acid solution (9→100) to produce a solution of 10 μ g per ml] (0.05%).

Related substances Carry out the method for thin-layer chromatography (Appendix V B), using 8 g of silica gel GF₂₅₄ mixed with 22 ml of sodium formate solution (1→22) as the coating substance and a mixture of chloroform-dehydrated ethanol-formic acid (70 : 30 : 9) as the mobile phase. Apply separately to the plate 5 μ l each of three solutions in methanol containing (1) 6 mg per ml, (2) 60 μ g per ml and (3) 120 μ g per ml of the substance being examined. After developing and removal of the plate, dry it in air and examine under ultraviolet light (254 nm). Any spot in the chromatogram other than the principal spot obtained with solution (1) is not more intense than the principal spot obtained with solution (2) and not more than one such spot is more intense than the spot obtained with solution (3).

Loss on drying When dried to constant weight at 105°C, loses not more than 3.5% of its weight (Appendix VIII L).

Residue on ignition Not more than 0.1% (Appendix VIII N).

Assay Dissolve about 0.25 g, accurately weighed, in 30 ml of acetone with shaking, add 0.5-1 ml of a saturated solution of methyl orange in acetone. Titrate with perchloric acid (0.1 mol/L) VS until the colour changes to orange. Perform a blank determination and make any necessary correction. Each ml of perchloric acid (0.1 mol/L) VS is equivalent to 31.28 mg of $C_{22}H_{30}Cl_2N_{10} \cdot 2C_2H_4O_2$.

Category Antiseptic.

Storage Preserve in tightly closed containers.

Preparation Chlorhexidine Acetate Ointment

Chlorhexidine Acetate Ointment

Chlorhexidine Acetate Ointment contains not less than 90.0% and not more than 110.0% of the labelled amount of chlorhexidine acetate ($C_{22}H_{30}Cl_2N_{10} \cdot 2C_2H_4O_2$).

Formula	Chlorhexidine Acetate	5 g
	Borneol	5 g
	Anhydrous Lanolin	40 g
	White Vaseline	901 g
	Ethanol	a quantity
	To make	1000 g

Description A pale yellow or yellow ointment.

Identification (1) Heat about 2 g with 20 ml of ethanol in a water bath to melt the ointment base, stir, cool to room

temperature and filter. To 5 ml of the filtrate in a test tube add slowly alongside the wall the solution of vanillin in sulfuric acid (1→100), a red ring formed at the junction of the two layers.

(2) To 5 ml of the filtrate obtained in the test (1) for Identification add 5 ml of hot 1% cetrimonium bromide solution and 1 ml each of bromine TS and sodium hydroxide TS, an orange colour is produced.

Other requirements Complies with the general requirements for ointments (Appendix I F).

Assay Dissolve a quantity of the ointment equivalent to 10 mg of chlorhexidine acetate in 30 ml of slightly warm chloroform in a separator on shaking, extract twice with 20 ml of 1.5 mol/L acetic acid solution, followed by three portions of 15 ml. Combine the extracts to a 100 ml volumetric flask, add 1.5 mol/L acetic acid solution to volume and mix well. Measure accurately 5 ml to a 50 ml volumetric flask, dilute with ethanol to volume and mix well. Measure the absorbance of the resulting solution at 260 nm (Appendix IV A). Dissolve about 10 mg of chlorhexidine acetate CRS, accurately weighed, in a 100 ml volumetric flask in a quantity of 1.5 mol/L acetic acid solution and dilute to volume, mix well. Measure accurately 5 ml to a 50 ml volumetric flask, dilute with ethanol to volume and mix well. Measure the absorbance of the reference solution in the same manner. Calculate the content of $C_{22}H_{30}Cl_2N_{10} \cdot 2C_6H_{12}O_7$.

Category As described under Chlorhexidine Acetate.

Storage Preserve in well closed containers, stored in a cool and dark place.

Chlorhexidine Gluconate Gargle

Chlorhexidine Gluconate Gargle contains not less than 85.0% and not more than 115.0% of the labelled amount of chlorhexidine gluconate ($C_{22}H_{30}Cl_2N_{10} \cdot 2C_6H_{12}O_7$).

Description A colourless, clear liquid; odour, sweet.

Identification (1) Dissolve 10 ml in a 50 ml volumetric flask with dehydrated ethanol to volume and mix well. The light absorption of the resulting solution exhibits a maximum at 259 nm (Appendix IV A).

(2) To 2 ml add 0.5 ml of ferric chloride TS, heat on a water bath; an orange-yellow colour is produced which changes to yellow on addition of 1 ml of hydrochloric acid.

Assay The gargle is used as the test solution. Dissolve about 10 mg of chlorhexidine acetate CRS, accurately weighed, in 1.5 mol/L acetic acid solution in a 100 ml volumetric flask, dilute to volume and mix well. Measure accurately 25 ml of the test solution and 15 ml of the reference solution into two beakers separately, to the test solution in the beaker add 1.3 ml of glacial acetic acid. To each beaker add 10 ml of 10% cetrimide solution, 4 ml of 3 mol/L sodium hydroxide solution and 30 ml of water, mix well and allow to stand for 30 minutes. Filter into a 100 ml volumetric flask, wash the beaker with 30 ml of water in portions and filter, combine washings and the filtrate. Add 2 ml of a 1% solution of bromine in 10 mol/L sodium hydroxide solution and 1 ml of isopropanol, dilute with water to volume and mix well. Measure the absorbances of the resulting solutions exactly 30 minutes after adding the 1% bromine solution at 476 nm (Appendix IV A). Calculate the content of $C_{22}H_{30}Cl_2N_{10} \cdot 2C_6H_{12}O_7$, by multiplying the result by 1.43.

Category As described under Chlorhexidine Gluconate Solution.

Strength (1) 200 ml : 16 mg (2) 500 ml : 40 mg

Storage Preserve in well closed containers, stored in a cool place.

Chlorhexidine Gluconate Solution

Chlorhexidine Gluconate Solution is an aqueous solution of 1,6-bis [N^1 -(*p*-chlorophenyl)- N^5 -biguanido] hexane digluconate. It contains not less than 19.0% (g/ml) and not more than 21.0% (g/ml) of $C_{22}H_{30}Cl_2N_{10} \cdot 2C_6H_{12}O_7$.

Description A colourless to pale yellow, almost clear and slightly viscous liquid; odourless or almost odourless. Miscible with water, soluble in ethanol or acetone.

Relative density 1.060-1.070 (Appendix VI A).

Identification (1) To 1 ml add 40 ml of water, cool in an ice bath, add dropwise 20% sodium hydroxide solution to adjust the pH to 12-13 with stirring. Filter, wash the precipitate with cool water until the washings are neutral and recrystallise from 70% ethanol solution, dry at 105°C. The residue melts at 129-134°C, with decomposition (Appendix VI C).

(2) To 0.5 ml add 10 ml of water and 0.5 ml of cupric sulfate TS; a precipitate is produced. Boil to agglomerate the precipitate; a slightly purple colour is produced.

(3) To 0.5 ml add 10 ml of water and 0.5 ml of ferric chloride TS, heat gradually to boiling; a deep orange-red colour is produced which changes to yellow on addition of 1 ml of hydrochloric acid.

(4) To 0.05 ml add 5 ml of hot 1% cetrimide solution, 1 ml of bromine TS and 1 ml of sodium hydroxide TS; a deep red colour is produced.

Acidity Dilute 5 ml to 100 ml with water, pH 5.5-7.0 (Appendix VI H).

***p*-Chloroaniline** Dilute 2.0 ml to 50 ml with water. To 5 ml of the solution add 10 ml of hydrochloric acid solution (9→100) and 20 ml of water. Add 1 ml of 0.5 mol/L sodium nitrite solution and 2 ml of 5% ammonium sulphamate solution, mix well and allow to stand for 5 minutes. Add 5 ml of 0.1% naphthylethylenediamine dihydrochloride solution and 1 ml of ethanol, dilute to 50 ml with water, mix well and allow to stand for 30 minutes. Any colour in the solution is not greater than that in a standard prepared in the same manner using 10.0 ml of a 10 µg/ml solution of *p*-chloroaniline in hydrochloric acid solution (9→100) instead of the dilution of the solution to be examined (0.25%).

Related substances Carry out the method for thin-layer chromatography (Appendix V B), using 8 g of silica gel GF₂₅₄ mixed with 24 ml of sodium formate solution (1→24) as the coating substance and a mixture of chloroform-dehydrated ethanol-formic acid (60 : 30 : 9) as the mobile phase. Apply separately to the plate 5 µl of each of three solutions in 1.5 mol/L acetic acid solution containing (1) 6 mg per ml, (2) 30 µg per ml and (3) 120 µg per ml of the substance being examined. After developing and removal of the plate, dry it in air and examine under ultraviolet light (254 nm). Any spot in the chromatogram other than the principal spot obtained with solution (1) is not more intense than the principal spot obtained with solution (2), and not more than 1-2 such spots are more intense than the principal spot obtained with solution (3).

Residue on ignition Not more than 0.1% (Appendix VIII N).

Assay To about 1.0 g, accurately weighed, in a 200 ml volumetric flask, add water to volume and mix well. Transfer 1 ml of the solution, accurately measured, to a 100ml volumetric flask, add 5.3 ml of ethanol, dilute with 80% ethanol solution to volume and mix well. Measure the absorbance of the resulting solution at 259 nm (Appendix IV A). Calculate the content of $C_{22}H_{30}Cl_2N_{10} \cdot 2C_6H_{12}O_7$, taking 413 as the value of A (1%, 1 cm).

Category Disinfectant.

Strength 250 ml : 50 g

Storage Preserve in tightly closed containers, stored in a cool place and protected from light.

Preparation (1) Chlorhexidine Gluconate Gargle
(2) Dilute Chlorhexidine Gluconate Solution

Dilute Chlorhexidine Gluconate Solution

Dilute Chlorhexidine Gluconate Solution is an aqueous solution containing 20% Chlorhexidine Gluconate Solution and a quantity of sweetening agent and preservatives. It contains not less than 4.5% (g/ml) and not more than 5.5% (g/ml) of Chlorhexidine Gluconate ($C_{22}H_{30}Cl_2N_{10} \cdot 2C_6H_{12}O_7$).

Description A colourless to pale yellow liquid with a sweet odour.

Identification (1) To 2 ml add 5 ml of hot 1% cetrimide solution, 1 ml of bromine TS and 1 ml of sodium hydroxide TS; a deep red colour is produced.

(2) To 2 ml add 2 ml of water and 5 drops of cupric sulfate TS; a precipitate is produced. Boil to make the precipitate agglomerate; a slightly purple colour is produced.

(3) To 2 ml add 2 ml of water and 0.5 ml of ferric chloride TS, heat gradually to boiling; a deep orange-red colour is produced which changes to yellow on addition of 1 ml of hydrochloric acid.

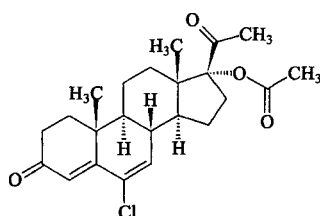
pH value pH 5.0-7.0 (Appendix VI H).

Assay Measure accurately 2 ml in a 100 ml volumetric flask, and carry out the Assay described under Chlorhexidine Gluconate Solution beginning at the words "add water to volume...". Calculate the content of $C_{22}H_{30}Cl_2N_{10} \cdot 2C_6H_{12}O_7$.

Category, Storage As described under Chlorhexidine Gluconate Solution.

Strength 250 ml : 12.5 g

Chlormadinone Acetate



$C_{23}H_{29}ClO_4$ 404.93

[302-22-7]

Chlormadinone Acetate is 6-chloro-17 α -hydroxy -pregna-4,6-diene-3,20-dione acetate. It contains not less than 96.0% and not more than 102.0% of $C_{23}H_{29}ClO_4$.

Description A white to pale yellow crystalline powder; odourless; tasteless.

Freely soluble in chloroform; slightly soluble in methanol; sparingly soluble in ethanol; insoluble in water.

Melting range 206-214.5°C (Appendix VI C).

Identification (1) Place a copper wire on flame until it imparts no green flame, cool, add about 1 mg on the copper wire and place on flame again, a green flame is observed.

(2) Dissolve about 0.1 mg on adding about 1 mg of isoniazide and 1 ml of methanol, add 1 drop of dilute hydrochloric acid TS; a yellow colour is produced.

(3) To about 3 mg add about 60 mg of hydroxylamine and 2 ml of methanol, shake to dissolve, add 1 ml of ethanolic solution of potassium hydroxide (2→25), heat in a warm water bath for 30 minutes. Allow it to cool, acidify by adding 5-7 drops of dilute hydrochloric acid TS and then 1 drop of ferric chloride TS; a purplish red colour is produced.

(4) Dissolve a quantity of the substance being examined and chlormadinone acetate CRS in chloroform to prepare solutions of about 20 mg per ml, respectively. Carry out the method for thin layer chromatography (Appendix V B), using silica gel G as the coating substance and a mixture of benzene-dehydrated ethanol (95 : 5) as the mobile phase. Apply 5 ml each of above two solutions to the same plate. After developing and removal of the plate, dry it in air, spray with a mixture of sulfuric acid-dehydrated ethanol (1 : 1) and heat at 105°C to observe the colour of the spots. The colour and position of the principal spots in the chromatograms of the two solutions are identical correspondingly.

(5) The infrared absorption spectrum (Appendix IV C) is concordant with the reference spectrum of chlormadinone acetate (Appendix XVI).

6 α -Chloro-17 α -hydroxyprogesterone acetate Measure the light absorption of solution obtained in Assay (Appendix IV A), the ratio of absorbance at 240 nm to that at 285 nm is not greater than 0.23.

Loss on drying When dried to constant weight at 105°C, loses not more than 0.5% of its weight (Appendix VIII L).

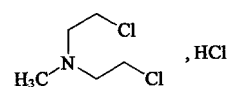
Residue on ignition Not more than 0.2% (Appendix VIII N).

Assay Dissolve a quantity, accurately weighed, to prepare a solution of 10 mg per ml in ethanol, measure the absorbance (Appendix IV A) at 285 nm, calculate the content of $C_{23}H_{29}ClO_4$, taking the value of A (1%, 1 cm) as 550.

Category Progesteroid.

Storage Preserve in tightly closed containers, protected from light.

Chlormethine Hyd. ochlo. ide



$C_5H_{11}Cl_2N \cdot HCl$ 192.52

[55-86-7]

Chlormethine Hydrochloride is 2-chloro-N-(2-chloroethyl)-N-methyl-ethanamine hydrochloride.

It contains not less than 98.0% of $C_5H_{11}Cl_2N \cdot HCl$, calculated on the dried basis.

Description A white crystalline powder, hygroscopic and corrosive.

Very soluble in water; freely soluble in ethanol.

Melting point 108-111 °C (Appendix VI C).

Identification (1) To 50 mg add 0.5 ml of sodium thiosulfate (0.1 mol/L) VS and 50 mg of sodium bicarbonate, heat the mixture carefully and allow to cool. Acidify with dilute hydrochloric acid, add 1 drop of iodine (0.05 mol/L) VS, the yellow colour does not disappear.

(2) The infrared absorption spectrum (Appendix IV C) is concordant with the reference spectrum of chlormethine hydrochloride (Appendix XVI).

(3) The aqueous solution yields the reactions characteristic of chlorides (Appendix III).

Acidity Dissolve 50 mg in 25 ml of water, pH 3.0-5.0 (Appendix VI H).

Loss on drying When dried in vacuum over phosphorous pentoxide to constant weight, loses not more than 0.5% of its weight (Appendix VIII L).

Assay Dissolve about 0.15 g, accurately weighed, in 20 ml of glacial acetic acid, add 5 ml of mercuric acetate TS and 1 drop of crystal violet IS, titrate with perchloric acid (0.1 mol/L) VS until the colour changes to blue. Perform a blank determination and make any necessary correction. Each ml of perchloric acid (0.1 mol/L) VS is equivalent to 19.25 mg of $C_5H_{11}Cl_2N \cdot HCl$.

Category Antineoplastic.

Storage Preserve in tightly closed containers, protected from light.

Preparation Chlormethine Hydrochloride Injection

Chlormethine Hydrochloride Injection

Chlormethine Hydrochloride Injection is a sterile solution of Chlormethine Hydrochloride in Water for Injection. It contains not less than 90.0% and not more than 110.0% of the labelled amount of chlormethine hydrochloride ($C_5H_{11}Cl_2N \cdot HCl$).

Description A clear, colourless or almost colourless, viscous liquid.

Identification (1) To 2 ml add 10 ml of water and 1 ml of sodium hydroxide TS, extract with ether. Separate the ether extract, add 1 ml of water and 2 drops of dilute hydrochloric acid, evaporate the ether, add 2 drops of mercuric potassium iodide TS, a white opalescence or precipitate is produced immediately.

(2) Yields the reactions characteristic of chlorides (Appendix III).

pH value Dilute 2 ml with 8 ml of water, pH 3.0-5.0 (Appendix VI H).

Other requirements Complies with the general requirements for injections (Appendix I B).

Assay Measure accurately with a "to contain" pipet a quantity equivalent to about 0.1 g of chlormethine hydrochloride to a stoppered conical flask, wash the inner wall of the pipet with a small amount of water, transfer the washings into the flask, add 0.1 g of sodium bicarbonate and 20 ml of sodium thiosulfate (0.1 mol/L) VS, accurately

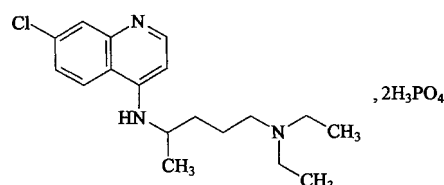
measured. Allow to stand for 2.5 hours, add starch IS and titrate with iodine (0.05 mol/L) VS until the colour changes to blue. Perform a blank determination and make any necessary correction. Each ml of sodium thiosulfate (0.1 mol/L) VS is equivalent to 9.626 mg of $C_5H_{11}Cl_2N \cdot HCl$.

Category As described under Chlormethine Hydrochloride.

Strength (1) 1 ml : 5 mg (2) 2 ml : 10 mg

Storage Preserve in well closed containers, protected from light.

Chloroquine Phosphate



$C_{18}H_{26}ClN_3 \cdot 2H_3PO_4$ 515.87

[50-63-5]

Chloroquine Phosphate is N^4 -(7-chloro-4-quinolinyl)- N' , N' -diethyl-1,4-pentanediamine phosphate (1 : 2). It contains not less than 98.0% of $C_{18}H_{26}ClN_3 \cdot 2H_3PO_4$, calculated on the dried basis.

Description A white crystalline powder; odourless; taste, bitter; discoloured slowly on exposure to light. The aqueous solution exhibits acid reaction.

Freely soluble in water; practically insoluble in ethanol, chloroform, ether or benzene.

Melting point 193-196°C, with decomposition (Appendix VI C).

Identification (1) The light absorption of a 10 µg per ml solution in 0.01 mol/L hydrochloric acid exhibits maxima at 222 nm, 257 nm, 329 nm and 343 nm (Appendix IV A).

(2) Dissolve about 0.5 g in 25 ml of water in a separator, add 5 ml of sodium hydroxide TS, extract with 50 ml of ether by shaking, wash the ether layer with water. Filter the ether extract via a filter funnel loaded with anhydrous sodium sulfate, and evaporate to dryness on a water bath. Dry the residue in vacuum over phosphorus pentoxide until the crystals are produced. The infrared absorption spectrum (Appendix IV C) of the crystals is concordant with the reference spectrum of chloroquine (Appendix XVI).

(3) Yields the reactions characteristic of phosphates (Appendix III).

Acidity Dissolve 1.0 g in 10 ml of water, pH 3.5-4.5 (Appendix VI H).

Clarity of solution A solution of 1.0 g in 10 ml of water is clear; or any opalescence produced is not more pronounced than that of the reference suspension II (Appendix IX B).

Related substances Carry out the method for thin-layer chromatography (Appendix V B), using silica gel GF₂₅₄ as the coating substance and a mixture of chloroform-cyclohexane-diethylamine (5 : 4 : 1) as the mobile phase. Apply separately to the plate 2 µl each of three solutions in water containing (1) 50 mg per ml, (2) 1.0 mg per ml and (3) 0.25 mg per ml of the substance being examined. After developing and removal of the plate, dry it in air and examine under ultraviolet light (254 nm). No spot other than the principal spot in the chromatogram obtained with

solution (1) is more intense than the spot obtained with solution (2) and not more than one such spot may be more intense than the spot obtained with solution (3).

Loss on drying When dried to constant weight at 120°C, loses not more than 3.0% of its weight (Appendix VIII L).

Heavy metals Moisten 1.0 g with 1 ml of sulfuric acid in a silica crucible. Ignite gently until no fumes of sulfur trioxide appear. Add 0.5 ml of nitric acid and again ignite until no fumes of nitrogen oxide appear. Then ignite at 500-600°C until all the carbon is burned off. Cool, carry out the limit test for heavy metals (Appendix VIII H, method 2): not more than 0.002%.

Arsenic Mix 0.40 g with 1.0 g of calcium hydroxide, triturate with small quantities of water. Allow to dry, ignite gently to carbonize and then ignite at 500-600°C until all the carbon is burned off. Cool, dissolve in 5 ml of hydrochloric acid and 23 ml of water. Carry out the limit test for arsenic (Appendix VIII J, method 1): not more than 0.0005%.

Assay Dissolve about 0.2 g, accurately weighed, in 20 ml of glacial acetic acid, add 1 drop of crystal violet IS, and titrate with perchloric acid (0.1 mol/L) VS until the colour changes to green. Perform a blank determination and make any necessary correction. Each ml of perchloric acid (0.1 mol/L) VS is equivalent to 25.79 mg of $C_{18}H_{26}ClN_3 \cdot 2H_3PO_4$.

Category Antimalarial and antiamebiasis.

Storage Preserve in tightly closed containers, protected from light.

Preparation (1) Chloroquine Phosphate Injection
(2) Chloroquine Phosphate Tablets

Chloroquine Phosphate Injection

Chloroquine Phosphate Injection is a sterile solution of Chloroquine Phosphate in Water for Injection. It contains not less than 95.0% and not more than 105.0% of the labelled amount of chloroquine phosphate ($C_{18}H_{26}ClN_3 \cdot 2H_3PO_4$).

Description A clear, colourless or almost colourless liquid.

Identification (1) To 1 ml add 20 ml of water and 10 ml of trinitrophenol TS; a precipitate is produced. The melting point of the precipitate, after washing with small portions of water and drying at 105°C, is about 207°C (Appendix IV C).

(2) Yields the reactions characteristic of phosphates (Appendix III).

pH value 3.5-4.5 (Appendix VI H).

Other requirements Complies with the general requirements for injections (Appendix I B).

Assay Dilute an accurately measured quantity equivalent to about 0.3 g of chloroquine phosphate to 30 ml with water, add 3 ml of 20% sodium hydroxide solution, mix well. Extract with four 20 ml portions of ether. Wash the combined ether extracts with 10 ml of water, and extract the aqueous layer with 15 ml of ether. Combine the ether extracts and evaporate to a volume of about 2-3 ml. Add 25 ml, accurately measured, of hydrochloric acid (0.1 mol/L) VS, heat gently to remove ether and to dissolve the residue, and cool. Add several drops of bromocresol green IS, and titrate with sodium hydroxide (0.1 mol/L) VS. Each ml of hydrochloric acid (0.1 mol/L) VS is equivalent to 25.79 mg of $C_{18}H_{26}ClN_3 \cdot 2H_3PO_4$.

Category As described under Chloroquine Phosphate.

Strength 5 ml : 322 mg

Storage Preserve in well closed containers, protected from light.

Chloroquine Phosphate Tablets

Chloroquine Phosphate Tablets contain not less than 93.0% and not more than 107.0% of the labelled amount of chloroquine phosphate ($C_{18}H_{26}ClN_3 \cdot 2H_3PO_4$).

Description White tablets or sugar-coated tablets with white core.

Identification Dissolve a quantity of the powdered tablets equivalent to about 0.5 g of chloroquine phosphate in 20 ml of water with shaking, filter. The filtrate complies with the test for Identification described under Chloroquine Phosphate.

Dissolution Carry out the dissolution test (Appendix X C, method 1), using 1000 ml of hydrochloric acid solution (9→1000) as the dissolution medium, adjust the rotational speed of the basket to 100 rpm. Withdraw the solution after exactly 45 minutes and filter, measure accurately 5 ml of the successive filtrate, dilute with the dissolution medium to produce a solution of 13 µg per ml and mix well. Measure the absorbance of the resulting solution at 343 nm (Appendix IV A). Calculate the dissolution of $C_{18}H_{26}ClN_3 \cdot 2H_3PO_4$ from each tablet, taking 371 as the value of A (1%, 1 cm). Not less than 75% of the labelled amount is dissolved.

Other requirements Comply with the general requirements for tablets (Appendix I A).

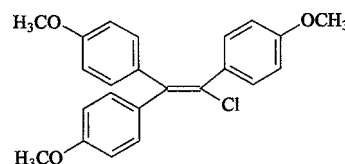
Assay Weigh accurately and powder 10 tablets. Weigh accurately a quantity of the powder equivalent to about 0.13 g of chloroquine phosphate into 200 ml volumetric flask, dissolve in 0.1 mol/L hydrochloric acid solution and dilute to volume, mix well and filter. Accurately measure 2 ml of the successive filtrate to a 100 ml volumetric flask, dilute with 0.1 mol/L hydrochloric acid solution to volume and mix well. Measure the absorbance of the resulting solution at 343 nm (Appendix IV A). Dissolve an accurately weighed quantity of chloroquine phosphate CRS in 0.1 mol/L hydrochloric acid solution and dilute to produce a solution of 13 µg per ml. Repeat the operation. Calculate the content of $C_{18}H_{26}ClN_3 \cdot 2H_3PO_4$.

Category As described under Chloroquine Phosphate.

Strength (1) 0.075 g (2) 0.1 g (3) 0.25 g

Storage Preserve in tightly closed containers, protected from light.

Chlorotrianisene



$C_{23}H_{21}ClO_3$ 380.87

[569-57-3]

Chlorotrianisene is 1, 1', 1''-(1-chloro-1-ethenyl)-

2-ylidene) tris (4-methoxybenzene). It contains not less than 98.0% and not more than 102.0% of $C_{23}H_{21}ClO_3$, calculated on the dried basis.

Description White or almost white crystals or a crystalline powder; odourless.

Freely soluble in chloroform, benzene or acetone; soluble in ether; slightly soluble in methanol or ethanol; practically insoluble in water.

Melting range 114-120°C, with decomposition (Appendix VI C).

Identification (1) Dissolve about 10 mg in a test tube in 2 ml of sulfuric acid, an intense violet colour is produced; the solution changes immediately to light red and becomes turbid on adding 5 ml of water; add cautiously 2 ml of sulfuric acid along the test tube wall, a violet-red colour is produced at the junction of the two layers and the colour changes into light red again after shaking.

(2) To about 5 mg add 0.2 ml of glacial acetic acid and 1 ml of phosphoric acid, heat on a water bath for 3 minutes, a pink colour is produced; the colour disappears immediately on adding 3 ml of glacial acetic acid again.

(3) The light absorption of a about 10 µg per ml solution in ethanol exhibits maxima at 247 nm and 307 nm, the absorbance is about 0.62 to 0.65 and 0.40 to 0.42, respectively (Appendix IV A).

(4) The infrared absorption spectrum (Appendix IV C) is concordant with the reference spectrum of Chlorotrianisene (Appendix XVI).

Chloride To 0.50 g add 20 ml of water, shake for 10 minutes, filter. Carry out the limit test for chlorides (Appendix VIII A), using 10 ml of the filtrate. Any opalescence produced is not more pronounced than that of a reference using 5.0 ml of sodium chloride standard solution (0.02%).

Loss on drying When dried to constant weight at 80°C, loses not more than 1.0% of its weight (Appendix VIII L).

Residue on ignition Not more than 0.1% (Appendix VIII N).

Assay Dissolve about 0.5 g, accurately weighed, in 15 ml of dehydrated ethanol by heating gently under reflux in a 250 ml conical flask. Add 2.0 g of metallic sodium, a small piece at a time, through the inlet of the condenser. Continue to reflux for 1 hour, shake occasionally. Add 25 ml of dehydrated ethanol and allow the excess metallic sodium to react completely. Heat for 15 minutes more, add 70 ml of water and allow to cool. To the solution add 15 ml of nitric acid and 25 ml of silver nitrate (0.01 mol/L) VS, accurately measured, shake well. Allow to stand for 10 minutes, filter, wash the flask and the precipitate with 80 ml of water in portions. Combine the filtrate and washings, add 3 ml of ferric ammonium sulfate IS and titrate with ammonium thiocyanate (0.1 mol/L) VS. Perform a blank determination and make any necessary correction. Each ml of silver nitrate (0.1 mol/L) VS is equivalent to 38.09 mg of $C_{23}H_{21}ClO_3$.

Category Estrogen.

Storage Preserve in tightly closed containers, protected from light.

Preparation Chlorotrianisene Pills

Chlorotrianisene Pills

Chlorotrianisene Pills contain not less than 85.0%

and not more than 115.0% of the labelled amount of chlorotrianisene ($C_{23}H_{21}ClO_3$).

Description White or creamy white dripping pills.

Identification (1) Comply with tests (1) and (2) for Identification described under Chlorotrianisene.

(2) The light absorption of the solution obtained in the Assay exhibits maxima at 247 nm and 307 nm (Appendix IV A).

Other requirements Comply with the general requirements for dripping pills (Appendix I H).

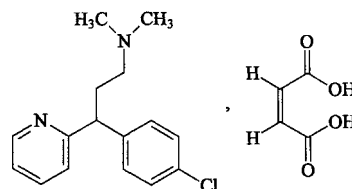
Assay Place 10 pills in a 200 ml volumetric flask, heat with a quantity of ethanol in a water bath at 65°C. Cool, dilute with ethanol to volume and mix well. Transfer 5 ml, accurately measured, into a 100 ml volumetric flask, dilute with ethanol to volume and mix well. Measure the absorbance at 307 nm (Appendix IV A). Calculate the content of $C_{23}H_{21}ClO_3$, taking 420 as the value of A (1%, 1 cm).

Category As described under Chlorotrianisene.

Strength 4 mg

Storage Preserve in tightly closed containers.

Chlorphenamine Maleate



$C_{16}H_{19}ClN_2 \cdot C_4H_4O_4$ 390.87 [113-92-8]

Chlorphenamine Maleate is 2-[p-chloro-α-[2-(dimethyl)ethyl]phenyl]pyridine maleate. It contains not less than 98.5% of $C_{16}H_{19}ClN_2 \cdot C_4H_4O_4$, calculated on the dried basis.

Description A white crystalline powder; odourless; taste, bitter.

Freely soluble in water, ethanol or chloroform; slightly soluble in ether.

Melting range 131.5-135°C (Appendix VI C).

Specific absorbance Measure the absorbance of a solution of 20 µg per ml in hydrochloric acid solution (1→100) at 264 nm (Appendix IV A), the value of A (1%, 1 cm) is 212-222.

Identification (1) To 10 mg add 1 ml of citric acid-acetic anhydride TS, heat on a water bath; a reddish-purple colour is produced.

(2) To about 20 mg add 1 ml of dilute sulfuric acid, add dropwise potassium permanganate TS; the solution remains colourless.

(3) The infrared absorbance spectrum (Appendix IV C) is concordant with the reference spectrum of chlorphenamine maleate (Appendix XVI).

Acidity Dissolve 0.1 g in 10 ml of water, pH 4.0-5.0 (Appendix VI H).

Related substances Carry out the method for gas chromatography (Appendix V E). The support is white diatomaceous earth, use 3% of phenyl (50%) methyl

silicone as the liquid stationary phase, and maintain the column temperature at 190°C, using a column with 1.2 m long. Dissolve 0.4 g of chlorphenamine maleate in 10 ml of methylene chloride, using as the test solution. Measure accurately 1 ml of above solution and dilute with methylene chloride to 100 ml, using as reference solution. Inject 1 µl of the reference solution into the column, adjust the attenuation so that the principal peak height in the chromatogram is 10%-20% of the full scale of the chart. Inject separately 1 µl each of the test and reference solution into the column and record the chromatogram for twice the retention time of the principal peak. The sum of peak areas due to impurities is not greater than twice of the principal peak area of the reference solution.

Tetrahydrofuran, dioxane pyridine and toluene Carry out the method for determination of organic solvent residue (Appendix VIII P, method 3). Use porous polymer beads of divinyl-ethylvinylbenzene cross-linked as the stationary phase; maintain the column temperature at 190°C. Measure accurately a quantity of benzene in methanol to produce a solution of 60 µg per ml as the internal solution. Measure accurately a quantity of tetrahydrofuran, dioxane, pyridine, and toluene in methanol to produce solutions of 720 µg per ml, 380 µg per ml, 200 µg per ml and 890 µg per ml as the reference preparation solutions respectively. Measure accurately 1 ml each of the internal and reference preparation solution in 10 ml volumetric flask, dilute with water to the volume and mix well, as the reference solution. Weigh accurately 1.0 g of chlorphenamine maleate to 10 ml volumetric flask, add 1 ml of internal solution and dilute with water to the volume, mix well as the test solution. The contents of solvent residue comply with the related requirements.

Readily carbonizable substances Carry out the limit test for readily carbonizable substances (Appendix VIII K), using 25 mg. Any colour produced is not more intense than that of reference solution Y₁.

Loss on drying when dried to constant weight at 105°C, loses not more than 0.5% of its weight (Appendix VIII L).

Residue on ignition Not more than 0.1% (Appendix VIII N).

Assay Dissolve about 0.15 g, accurately weighed, in 10 ml of glacial acetic acid, add 1 drop of crystal violet IS, titrate with perchloric acid (0.1 mol/L) VS until the colour changes to bluish-green. Perform a blank determination and make any necessary correction. Each ml of perchloric acid (0.1 mol/L) VS is equivalent to 19.54 mg of C₁₆H₁₉ClN₂ · C₄H₄O₄.

Category Antihistaminic agent.

Storage Preserve in tightly closed containers, protected from light.

Preparation (1) Chlorphenamine Maleate Injection
(2) Chlorphenamine Maleate Pills
(3) Chlorphenamine Maleate Tablets

Chlorphenamine Maleate Injection

Chlorphenamine Maleate Injection is a sterile solution of Chlorphenamine Maleate in Water for Injection. It contains not less than 95.0% and not more than 105.0% of the labelled amount of chlorphenamine maleate (C₁₆H₁₉ClN₂ · C₄H₄O₄).

Description A clear, colourless liquid.

Identification Evaporate a quantity equivalent to about 30 mg of chlorphenamine maleate on a water bath to dryness, the residue complies with tests (1) and (2) for Identification described under Chlorphenamine Maleate.

pH value 4.0-5.0 (Appendix VI H).

Other requirements Complies with the general requirements for injections (Appendix I B).

Assay Measure the absorbance of a solution containing 20 µg per ml in hydrochloric acid solution (1→100) at 264 nm (Appendix IV A), calculate the content of C₁₆H₁₉ClN₂ · C₄H₄O₄, taking 217 as the value of A (1%, 1 cm).

Category As described under Chlorphenamine Maleate.

Strength (1) 1 ml : 10 mg (2) 2 ml : 20 mg

Storage Preserve in well closed containers, protected from light.

Chlorphenamine Maleate Pills

Chlorphenamine Maleate Pills contain not less than 93.0% and not more than 107.0% of the labelled amount of chlorphenamine maleate (C₁₆H₁₉ClN₂ · C₄H₄O₄).

Formula	Chlorphenamine maleate	4 g
	Macrogl 6000	15.5 g
	to make	1000 pills or 2000 pills

Description White or almost white dripping pills.

Identification (1) To a quantity of pills equivalent to about 8 mg of chlorphenamine maleate add 1 ml of citric acid acetic anhydride TS, heat on a water bath, a reddish violet colour is produced.

(2) To a quantity of pills equivalent to about 20 mg of chlorphenamine maleate add 2 ml of dilute sulfuric acid, then add dropwise potassium permanganate TS, the solution remains colourless.

(3) Dissolve a quantity of pills equivalent to 4 mg of chlorphenamine maleate in 1 ml of chloroform (solution 1). Dissolve a quantity of chlorphenamine maleate CRS in chloroform to produce a solution of 4 mg per ml (solution 2). Carry out the method for thin-layer chromatography (Appendix V B), using silica gel GF₂₅₄ as the coating substance and a mixture of ethyl acetate-methanol-dilute acetic acid (5 : 3 : 2) as the mobile phase. Apply separately to the plate 3 µl each of the two solutions. After developing and removal of the plate, dry it in air and examine under ultraviolet light (254 nm). The colour and position of the principal spot in the chromatogram obtained with solution (1) corresponds to that of the principal spot obtained with solution (2).

Content uniformity Comply with the requirements (Appendix X E). Shake thoroughly 1 pill with 50 ml of water in a 200 ml volumetric flask to dissolve chlorphenamine maleate, add 2 ml of dilute hydrochloric acid, and dilute with water to volume, mix well, allow to stand, measure the absorbance of the lower layer of the solution at 264 nm, calculate the content of C₁₆H₁₉ClN₂ · C₄H₄O₄ in each pill, taking 217 as the value of A (1%, 1 cm).

Other requirements Comply with the general requirements for dripping pills (Appendix I H).

Assay Shake thoroughly a quantity of pills equivalent to about 40 mg of chlorphenamine maleate with 50 ml of water in a 100 ml volumetric flask to dissolve chlorphenamine

maleate, dilute with water to volume, mix well, allow to stand. Measure accurately 10 ml of the lower layer solution to a 200 ml volumetric flask, add 2 ml of dilute hydrochloric acid, dilute with water to volume, mix well. Measure the absorbance at 264 nm (Appendix IV A), calculate the content of $C_{16}H_{19}ClN_2 \cdot C_4H_4O_4$, taking 217 as the value of A (1%, 1 cm).

Category As described under Chlorphenamine Maleate.

Strength (1) 2 mg (2) 4 mg

Storage Preserve in tightly closed containers, protected from light, and stored in a cool place.

Chlorphenamine Maleate Tablets

Chlorphenamine Maleate Tablets contain not less than 93.0% and not more than 107.0% of the labelled amount of chlorphenamine maleate ($C_{16}H_{19}ClN_2 \cdot C_4H_4O_4$).

Description White tablets.

Identification (1) To a quantity of the powdered tablets equivalent to about 8 mg of chlorphenamine maleate add 4 ml of water, stir and filter. Evaporate the filtrate to dryness, the residue complies with test (1) for Identification described under Chlorphenamine Maleate.

(2) To a quantity of the powdered tablets equivalent to about 20 mg of chlorphenamine maleate add 2 ml of dilute sulfuric acid, stir and filter. To the filtrate add dropwise potassium permanganate TS, the solution remains colourless.

(3) Extract a quantity of the powdered tablets equivalent to about 5 mg of chlorphenamine maleate with chloroform and filter. Evaporate the filtrate to dryness and dissolve the residue in 1 ml of chloroform (solution 1). To a quantity of chlorphenamine maleate CRS add chloroform to produce a solution containing 5 mg per ml (solution 2). Carry out the method for thin-layer chromatography (Appendix V B), using silica gel GF₂₅₄ as the coating substance and a mixture of ethyl acetate-methanol-dilute acetic acid (5 : 3 : 2) as the mobile phase. Apply separately to the plate 10 μ l each of the two solutions. After developing and removal of the plate, dry it in air and examine under ultraviolet light (254 nm). The colour and position of the principal spot in the chromatogram obtained with solution (1) are identical to those of the principal spot obtained with solution (2).

Content uniformity Comply with the requirements (Appendix X E). Transfer 1 tablet to a 200 ml volumetric flask, add 50 ml of water, shake thoroughly to disperse, add 2 ml of dilute hydrochloric acid and dilute with water to volume. Proceed as directed under Assay. Calculate the content of $C_{16}H_{19}ClN_2 \cdot C_4H_4O_4$ in each tablet.

Dissolution Carry out the dissolution test (Appendix X C, method 3), using 2.5 ml of dilute hydrochloric acid diluted with water to 250 ml as the dissolution medium, adjust the rotational speed of the paddle to 50 rpm. Withdraw 10 ml of the solution after exactly 45 minutes and filter. Measure the absorbance of the successive filtrate at 264 nm (Appendix IV A). Calculate the dissolution of $C_{16}H_{19}ClN_2 \cdot C_4H_4O_4$ from each tablet, taking 217 as the value of A (1%, 1 cm), not less than 75% of the labelled amount is dissolved.

Other requirements Comply with the general requirements for tablets (Appendix I A).

Assay Weigh accurately and powder 10 tablets. Transfer an accurately weighed quantity equivalent to about 4 mg of

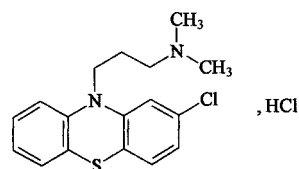
chlorphenamine maleate to a 200 ml volumetric flask, add 2 ml of dilute hydrochloric acid and a quantity of water with shaking to dissolve chlorphenamine maleate, dilute with water to volume and mix well. Allow to stand and filter. Measure the absorbance of the successive filtrate at 264 nm (Appendix IV A) and calculate the content of $C_{16}H_{19}ClN_2 \cdot C_4H_4O_4$, taking 217 as the value of A (1%, 1 cm).

Category As described under Chlorphenamine Maleate.

Strength 4 mg

Storage Preserve in tightly closed containers, protected from light.

Chlorpromazine Hydrochloride



$C_{17}H_{19}ClN_2S \cdot HCl$ 355.33

[69-09-0]

Chlorpromazine Hydrochloride is 2-chloro-*N*, *N*-dimethyl-10*H*-phenothiazine-10-propanamine monohydrochloride. It contains not less than 99.0% of $C_{17}H_{19}ClN_2S \cdot HCl$, calculated on the dried basis.

Description A white or creamy white crystalline powder; odour, slight; taste, very bitter; hygroscopic; discoloured slowly on exposure to light. The aqueous solution exhibits acid reaction.

Freely soluble in water, ethanol or chloroform; insoluble in ether or benzene.

Melting range 194-198°C (Appendix VI C).

Identification (1) To 10 mg add 1 ml of water and 5 drops of nitric acid; a red colour develops which turns to pale yellow on standing.

(2) The light absorption of a solution of 5 μ g per ml in hydrochloric acid solution (9→1000) exhibits maxima at 254 nm and 306 nm; the absorbance at 254 nm is about 0.46 (Appendix IV A).

(3) The infrared absorbance spectrum (Appendix IV C) is concordant with the reference spectrum of chlorpromazine hydrochloride (Appendix XVI).

(4) The aqueous solution yields the reactions characteristic of chlorides (Appendix III).

Clarity and colour of solution A solution of 0.50 g in 10 ml of water is clear and colourless. Any opalescence produced is not more pronounced than that of reference suspension I (Appendix IX B) and any colour produced is not more intense than that of reference solution Y₃ or YG₃ (Appendix IX A, method 1).

Related substances Protect from light throughout the procedure. Carry out the method for thin-layer chromatography (Appendix V B), using silica gel GF₂₅₄ as the coating substance and a mixture of cyclohexane-acetone-diethylamine (80 : 10 : 10) as the mobile phase. Apply separately to the plate 10 μ l each of two solutions in methanol containing (1) 10 mg per ml, (2) 0.1 mg per ml of the substance being examined. After developing and removal of the plate, dry it in air and view under an ultraviolet light (254 nm). Any spot other than the principal spot in the

chromatogram obtained with solution (1) is not more intense than the principal spot obtained with solution (2).

Loss on drying When dried to constant weight at 105°C, loses not more than 0.5% of its weight (Appendix VIII L).

Residue on ignition Not more than 0.1% (Appendix VIII N).

Assay Dissolve about 0.2 g, accurately weighed, in 10 ml of acetic anhydride, add 5 ml of mercuric acetate TS and 1 drop of orange IV IS, titrate with perchloric acid (0.1 mol/L) VS until the colour changes to rose-red. Perform a blank determination and make any necessary correction. Each ml of perchloric acid (0.1 mol/L) VS is equivalent to 35.53 mg of $C_{17}H_{19}ClN_2S \cdot HCl$.

Category Antipsychotic agent.

Storage Preserve in tightly closed containers, protected from light.

Preparation (1) Chlorpromazine Hydrochloride Injection
(2) Chlorpromazine Hydrochloride Tablets

Chlorpromazine Hydrochloride Injection

Chlorpromazine Hydrochloride Injection is a sterile solution of Chlorpromazine Hydrochloride in Water for Injection. It contains not less than 95.0% and not more than 105.0% of the labelled amount of chlorpromazine hydrochloride ($C_{17}H_{19}ClN_2S \cdot HCl$).

Description A clear, colourless or almost colourless liquid.

Identification (1) Complies with test (1) for Identification described under Chlorpromazine Hydrochloride, using a quantity equivalent to 10 mg of chlorpromazine hydrochloride.

(2) Complies with test (2) for Identification described under Chlorpromazine Hydrochloride, using the solution obtained in the Assay.

pH value 3.0-5.0 (Appendix VI H).

Related substances Protect from light throughout the procedure.

Carry out the method for thin-layer chromatography (Appendix V B), using silica gel GF₂₅₄ as the coating substance and a mixture of cyclohexane-acetone-diethylamine (80 : 10 : 10) as the mobile phase. Apply separately to the plate 10 µl each of three solutions in methanol containing (1) 20 mg per ml, (2) 1.0 mg per ml and (3) 0.1 mg per ml of the substance being examined. After developing and removal of the plate, dry it in air and examine under ultraviolet light (254 nm). Any spot other than the principal spot in the chromatogram obtained with solution (1) is not more intensely coloured than the principal spot obtained with solution (3) and not more than one spot in the chromatogram is more intense than the principal spot obtained with solution (2).

Other requirements Complies with the general requirements for injections (Appendix I B).

Assay Protect from light throughout the procedure. Measure accurately a quantity equivalent to 50 mg of chlorpromazine hydrochloride in a 250 ml volumetric flask, dilute with hydrochloric acid solution (9 → 1000) to volume and mix well. Place 10 ml, measure accurately, in a 50 ml volumetric flask, dilute with hydrochloric acid solution (9 → 1000) to volume. Measure the absorbance of the resulting solution at 306

nm (Appendix IV A). Calculate the content of $C_{17}H_{19}ClN_2S \cdot HCl$, taking 115 as the value of A (1%, 1 cm).

Category As described under Chlorpromazine Hydrochloride.

Strength (1) 1 ml : 10 mg (2) 1 ml : 25 mg
(3) 2 ml : 50 mg

Storage Preserve in well closed containers, protected from light.

Chlorpromazine Hydrochloride Tablets

Chlorpromazine Hydrochloride Tablets contain not less than 93.0% and not more than 107.0% of the labelled amount of chlorpromazine hydrochloride ($C_{17}H_{19}ClN_2S \cdot HCl$).

Description Sugar-coated tablets with white cores.

Identification Weigh a quantity of powdered tablets with coating removed, equivalent to 50 mg of chlorpromazine hydrochloride, dissolve in 5 ml of water and filter. The filtrate complies with tests (1) and (4) for Identification described under Chlorpromazine Hydrochloride.

Related substances Protect from light throughout the procedure. Dissolve a quantity of powdered tablets equivalent to 0.1 g of chlorpromazine Hydrochloride in 10 ml of methanol and filter, use the successive filtrate as solution (1). Dilute 1 volume of solution (1) to 100 volumes with methanol to produce solution (2). Comply with the test for Related substances described under Chlorpromazine Hydrochloride, beginning at the words "after developing and removal of the plate."

Dissolution Protect from light throughout the procedure. Carry out the dissolution test (Appendix X C, method 1), using 1000 ml of water as the dissolution medium and adjust the rotational speed of the basket to 100 rpm. Withdraw 10 ml of the solution after exactly 30 minutes and filter, measure accurately 5 ml of the successive filtrate to a 25 ml volumetric flask, dilute with hydrochloric acid solution (9 → 1000) to volume and mix well. Measure the absorbance at 254 nm (Appendix IV A). Calculate the dissolution of $C_{17}H_{19}ClN_2S \cdot HCl$ from each tablet, taking 915 as the value of A (1%, 1 cm). Not less than 70% of the labelled amount is dissolved.

Other requirements Comply with the general requirements for tablets (Appendix I A).

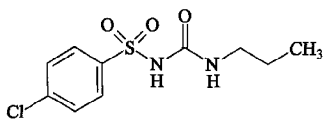
Assay Protect from light throughout the procedure. Weigh accurately and powder 10 tablets with coating removed. Weigh accurately a quantity of powder equivalent to about 10 mg of chlorpromazine hydrochloride into a 100 ml volumetric flask and dissolve with shaking in 70 ml of hydrochloric acid solution (9 → 1000), dilute to volume with the same solvent, shake well and filter. Measure accurately 5 ml of the successive filtrate into 100 ml volumetric flask, dilute to volume with the same solvent, mix well. Measure the absorbance of the resulting solution at 254 nm (Appendix IV A). Calculate the content of $C_{17}H_{19}ClN_2S \cdot HCl$, taking 915 as the value of A (1%, 1 cm).

Category As described under Chlorpromazine Hydrochloride.

Strength (1) 12.5 mg (2) 25 mg (3) 50 mg

Storage Preserve in tightly closed containers, protected from light.

Chlorpropamide



$C_{10}H_{13}ClN_2O_3S$ 276.74

[94-20-2]

Chlorpropamide is 4-chloro-*N* [(propylamino) carbonyl]-benzenesulfonamide. It contains not less than 99.0% of $C_{10}H_{13}ClN_2O_3S$, calculated on the dried basis.

Description A white crystalline powder; odourless, or almost odourless; taste, slightly bitter. Freely soluble in chloroform; soluble in ethanol; insoluble in water; freely soluble in alkali hydroxide solutions.

Melting range 125-130°C (Appendix VI C).

Identification (1) Boil about 0.1 g with 8 ml of 50% (g/g) sulfuric acid under a reflux condenser for 30 minutes, cool and filter. Render the filtrate alkaline with 20% sodium hydroxide solution and heat, an ammoniacal odour is perceptible.

(2) Heat 0.1 g with 1 g of anhydrous sodium carbonate to a dull red, continue to heat for 10 minutes. Cool, dissolve the residue in water, filter, acidify the filtrate with nitric acid and add 1 ml of silver nitrate TS; a white precipitate is produced.

(3) Dissolve 0.12 g in methanol to produce 50 ml, dilute 1 ml to 200 ml with 0.01 mol/L hydrochloric acid solution and mix well. The light absorption of the solution exhibits a maximum at 232 nm (Appendix IV A).

(4) The infrared absorption spectrum (Appendix IV C) is concordant with the reference spectrum of chlorpropamide (Appendix XVI).

Clarity and colour of alkaline solution Dissolve 1.0 g in 5 ml of sodium hydroxide TS, add 20 ml of water. The solution is clear and colourless; any opalescence produced is not more pronounced than that of reference suspension I (Appendix IX B); any colour produced is not more intense than that of reference solution Y₁ (Appendix IX A, method 1).

Loss on drying When dried to constant weight at 80°C, loses not more than 1.0% of its weight (Appendix VIII L).

Residue on ignition Not more than 0.1% (Appendix VIII N).

Heavy metals Carry out the limit test for heavy metals (Appendix VIII H, method 3), using 0.50 g; not more than 0.002%.

Assay Dissolve about 0.6 g, accurately weighed, in 20 ml of ethanol previously neutralized to phenolphthalein IS, add 3 drops of phenolphthalein IS, titrate with sodium hydroxide (0.1 mol/L) VS. Each ml of sodium hydroxide (0.1 mol/L) VS is equivalent to 27.67 mg of $C_{10}H_{13}ClN_2O_3S$.

Category Antidiabetic agent.

Storage Preserve in tightly closed containers, protected from light.

Preparation Chlorpropamide Tablets

Chlorpropamide Tablets

Chlorpropamide Tablets contain not less than 93.0% and not more than 107.0% of the labelled amount of chlorpropamide ($C_{10}H_{13}ClN_2O_3S$).

Description White tablets.

Identification Extract a quantity of powdered tablets equivalent to about 0.5 g of chlorpropamide with five quantities of 4 ml of acetone, filter, evaporate the filtrate to dryness on a water bath. The residue complies with the tests for Identification described under Chlorpropamide.

Other requirements Comply with the general requirements for tablets (Appendix I A).

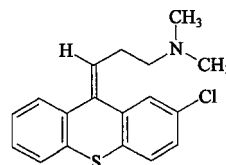
Assay Weigh accurately and powder 20 tablets, carry out the Assay described under Chlorpropamide, using a quantity of powdered tablets equivalent to about 0.3 g of chlorpropamide, accurately weighed. Each ml of sodium hydroxide (0.1 mol/L) VS is equivalent to 27.67 mg of $C_{10}H_{13}ClN_2O_3S$.

Category As described under Chlorpropamide.

Strength (1) 0.1 g (2) 0.25 g

Storage Preserve in tightly closed containers, protected from light.

Chlorprothixene



$C_{18}H_{18}ClNS$ 315.87

[113-59-7]

Chlorprothixene is (*Z*)-2-chloro-*N*, *N*-dimethylthioxanthene-1-propylamine. It contains not less than 98.0% of $C_{18}H_{18}ClNS$, calculated on the dried basis.

Description A pale yellow crystalline powder; odourless; tasteless.

Freely soluble in chloroform; insoluble in water.

Melting point 96-99°C (Appendix VI C).

Identification (1) To about 10 mg add 2 ml of nitric acid, a light red solution is produced. Dilute the solution with 5 ml of water, the solution exhibits a green fluorescence under ultraviolet light.

(2) The light absorption of a solution of about 50 µg per ml in hydrochloric acid solution (9→1000) exhibits a maximum at 324 nm (Appendix IV A).

(3) The infrared absorption spectrum (Appendix IV C) is concordant with the reference spectrum of chlorprothixene (Appendix XVI).

Loss on drying When dried over phosphorous pentoxide to constant weight, loses not more than 1.0% of its weight (Appendix VIII L).

Residue on ignition Not more than 0.1% (Appendix VIII N), using 1.0 g.

Heavy metals Carry out the limit test for heavy metals (Appendix VIII H, method 2), using the residue obtained in the test for Residue on ignition; not more than 0.002%.

Assay Dissolve about 0.25 g, accurately weighed, in 20 ml of glacial acetic acid, 1 ml of perchloric acid (0.1 mol/L) VS until the colour changes to blue. Perform a blank determination and make any necessary correction. Each ml of perchloric acid (0.1 mol/L) VS is equivalent to 31.59 mg of $C_{18}H_{18}ClNS$.

Category Antipsychotic.

Storage Preserve in tightly closed containers, protected from light.

Preparation Chlorprothixene Tablets

Chlorprothixene Tablets

Chlorprothixene Tablets contain not less than 90.0% and not more than 110.0% of the labelled amount of chlorprothixene ($C_{18}H_{18}ClNS$).

Description Sugar-coated tablets with almost white to pale yellow cores.

Identification To a quantity of powdered tablets, equivalent to about 0.1 g of chlorprothixene, add 5 ml of chloroform and stir to dissolve chlorprothixene. Filter and evaporate the filtrate to dryness. The residue complies with the tests (1) and (2) for Identification described under Chlorprothixene.

Dissolution Carry out the dissolution test (Appendix X C, method 1), using 900 ml of hydrochloric acid solution (9→1000) as the dissolution medium, adjust the rotational speed of the basket to 100 rpm. Withdraw 10 ml of the solution after exactly 30 minutes and filter, dilute an accurately measured quantity of the successive filtrate with the dissolution medium to produce a solution of about 50 µg per ml. Dissolve an accurately weighed quantity of chlorprothixene CRS in the dissolution medium to produce a solution of 50 µg per ml. Measure the absorbance of the two solutions at 324 nm (Appendix IV A). Calculate the dissolution of $C_{18}H_{18}ClNS$ from each tablet; not less than 75% of the labelled amount is dissolved.

Other requirements Comply with the general requirements for tablets (Appendix I A).

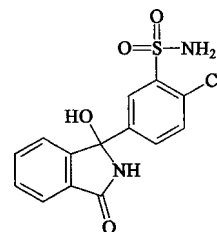
Assay Weigh accurately and powder 20 tablets. Transfer an accurately weighed quantity of the powder, equivalent to about 0.25 g of chlorprothixene, to a conical flask with stopper. Add 20 ml of chloroform and shake for 10 minutes, allow to stand for 30 minutes. Filter through a tared sintered glass funnel, wash the residue 3 times with chloroform, each of 10 ml. Combine the chloroform, add 1 drop of crystal violet IS, titrate with perchloric acid (0.1 mol/L) VS until the colour changes to blue. Perform a blank determination and make any necessary correction. Each ml of perchloric acid (0.1 mol/L) VS is equivalent to 31.59 mg of $C_{18}H_{18}ClNS$.

Category As described under chlorprothixene.

Strength (1) 12.5 mg (2) 15 mg (3) 25 mg (4) 50 mg

Storage Preserve in tightly closed containers, protected from light.

Chlortalidone



$C_{14}H_{11}ClN_2O_4S$ 338.76

[77-36-1]

Chlortalidone is 2-chloro-5-(2,3-dihydroxy-1-hydroxy-3-oxo-1H-indol-1-yl)-benzenesulphonamide. It contains not less than 98.0% of $C_{14}H_{11}ClN_2O_4S$, calculated on the dried basis.

Description A white or almost white crystalline powder; odourless; tasteless.

Soluble in methanol or acetone; slightly soluble in ethanol; practically insoluble in water, ether or chloroform.

Melting range 214–220°C, with decomposition (Appendix VI C)

Identification (1) To 50 mg add 3 ml of sulfuric acid, a deep yellow colour is produced immediately.

(2) The light absorption of a solution of 0.1 mg per ml in ethanol exhibits two maxima at 275 nm and 284 nm (Appendix IV A).

(3) The infrared absorption spectrum (Appendix IV C) is concordant with the reference spectrum of chlortalidone (Appendix XVI).

Chloride Shake 0.50 g with 50 ml of water for 5 minutes and filter, carry out the limit test for chlorides (Appendix VIII A), using 20 ml of the filtrate. Any opalescence produced is not more pronounced than that of a reference solution using 7.0 ml of sodium chloride standard solution (0.035%).

Related substances Carry out the method for thin-layer chromatography (Appendix V B), using silica gel GF₂₅₄ as the coating substance and a mixture of dioxane-isopropanol-toluene-concentrated ammonia solution (30 : 30 : 30 : 20) as the mobile phase. Apply separately to the plate 10 µl of each of two solutions in acetone containing (1) 20 mg per ml and (2) 0.20 mg per ml of the substance being examined. After developing and removal of the plate, dry it in air and examine under ultraviolet light (254 nm). Any spot other than the principal spot obtained with solution (1) is not more intense than the principal spot obtained with solution (2).

Loss on drying When dried to constant weight at 105°C, loses not more than 0.5% of its weight (Appendix VIII L).

Residue on ignition Not more than 0.1% (Appendix VIII N), using 1.0 g.

Heavy metals Carry out the limit test for heavy metals (Appendix VIII H, method 2), using the residue obtained in the test for Residue on ignition; not more than 0.002%.

Assay Carry out the method for high performance liquid chromatography (Appendix V D), using a column packed with octylsilane bonded silica gel and a mixture of 0.01 mol/L diammonium hydrogen phosphate solution-methanol (3 : 2) as the mobile phase (adjust to pH 5.5 with phosphoric acid). Detection wavelength is 254 nm and the number of the

theoretical plates of the column is not less than 1500, calculated with reference to the peak of chlortalidone.

Procedure Dissolve a quantity accurately weighed, in a small amount of methanol, dilute with a mixture of water-methanol (3 : 2) to produce a solution of 0.1 mg per ml. Inject 20 μ l into the column and record the chromatogram. Repeat the operation using chlortalidone CRS instead of the substance being examined, calculate the content of $C_{14}H_{11}ClN_2O_4S$ with respect to the peak area obtained in the chromatogram by the external standard method.

Category Diuretic.

Storage Preserve in tightly closed containers, protected from light.

Preparation Chlortalidone Tablets

Chlortalidone Tablets

Chlortalidone Tablets contain not less than 93.0% and not more than 107.0% of the labelled amount of chlortalidone ($C_{14}H_{11}ClN_2O_4S$).

Description White tablets.

Identification (1) To a quantity of powdered tablets, equivalent to about 20 mg of chlortalidone add 1 ml of sulfuric acid, a deep yellow colour is produced which is discoloured on diluting with water.

(2) To a quantity of powdered tablets, equivalent to about 50 mg of chlortalidone, add 1 g of sodium hydroxide, heat gently until melted, ammonia vapour is evolved which turns the moistened alkaline mercuric potassium iodide IP to brownish yellow colour. The residue yields the reactions characteristic of sulfites (Appendix III).

Dissolution Carry out the dissolution test (Appendix X C, method 2), using 900 ml of water as the dissolution medium. Adjust the rotational speed of the paddle to 100 rpm. Withdraw 10 ml of the solution after exactly 60 minutes and filter, use the successive filtrate as the test preparation. Dissolve an accurately weighted quantity of chlortalidone CRS in water to produce a solution of 0.1 mg per ml (for 100 mg strength) or 0.05 mg per ml (for 50 mg strength) as reference preparation. Measure the absorbance of the resulting solutions at 275 nm (Appendix IV A). Calculate the dissolution of $C_{14}H_{11}ClN_2O_4S$ from each tablet; not less than 70% of the labelled amount is dissolved.

Other requirements Comply with the general requirements for tablets (Appendix I A).

Assay Weigh accurately and powder 20 tablets. Boil a quantity of the powder containing 0.1 g of chlortalidone under a reflux condenser with 30 ml methanol for 5 minutes, shake vigorously for 15 minutes, cool and filter. Wash the residue with methanol and combine the filtrate and washings, dilute with methanol to 100 ml and mix well. Measure accurately 5 ml to a 50 ml volumetric flask, add 2 ml of hydrochloric acid solution (9 \rightarrow 100), dilute with methanol to volume and mix well. Measure the absorbance of the resulting solution at 275 nm (Appendix IV A). Dissolve an accurately weighed quantity of chlortalidone CRS in methanol to produce a solution of 1 mg per ml, repeat the operation beginning at the words "Measure accurately 5 ml to a 50 ml volumetric flask". Calculate the content of $C_{14}H_{11}ClN_2O_4S$.

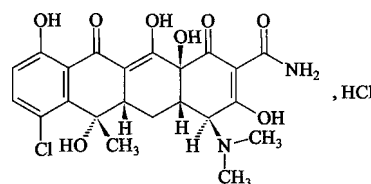
Category As described under Chlortalidone.

Strength (1) 50 mg (2) 100 mg

Storage Preserve in tightly closed containers, protected

from light.

Chlortetracycline Hydrochloride



$C_{22}H_{23}ClN_2O_8 \cdot HCl$ 515.35

[64-72-2]

Chlortetracycline Hydrochloride is 7-chloro-4-(dimethylamino)-1,4,4a,5,5a,6,11,12a-octahydro-3,6,10,12,12a-pentahydroxy-6-methyl-1,11-dioxo-2-naphthacene-carboxamide monohydro-chloride. It contains not less than 91.0% of $C_{22}H_{23}ClN_2O_8 \cdot HCl$, calculated on the dried basis.

Description Golden yellow or yellow crystals; odourless; taste, bitter; darkened on exposure to light. Slightly soluble in water or ethanol; practically insoluble in acetone, ether or chloroform.

Specific optical rotation -235° to -250° , measured at $25^\circ C$ in a solution of 5 mg per ml in water (Appendix VI E). Keep the solution in the dark for 30 minutes before measurement.

Identification (1) To about 0.5 mg add 2 ml of sulfuric acid, a blue colour is produced, which gradually becomes bluish-green; then add 1 ml of water, a golden yellow or brownish-yellow colour is produced.

(2) The retention time of principal peak of the substance being examined in the chromatogram obtained in the Assay is identical with that the principal peak of chlortetracycline hydrochloride CRS in the chromatogram.

(3) The infrared absorption spectrum (Appendix IV C) is concordant with the reference spectrum of Chlortetracycline (Appendix XVI).

(4) The aqueous solution yields the reactions characteristic of chlorides (Appendix III).

Acidity An aqueous solution of 5 mg per ml, pH 2.3-3.3 (Appendix VI H).

Related substances Carry out the method as described under Assay. Dissolve a quantity of the substance being examined, accurately weighed, in 0.01 mol/L hydrochloric acid solution to produce solutions of 1 mg per ml as test solution. Dissolve an accurately weighed quantity of tetracycline hydrochloride CRS and epimer of chlortetracycline in 0.1 mol/L hydrochloric acid to produce a solution of 0.08 mg tetracycline hydrochloride and 0.04 mg epimer of chlortetracycline per ml as reference solution. Inject 20 μ l of the reference solution into the column, adjust the attenuation so that the principal peak height in the chromatogram is 20%-25% of full scale of the chart. Inject separately 20 μ l each of test solution and reference solution into the column and record the chromatogram for 1.5 times the retention time of the principal peak. Each peak area of epimer of chlortetracycline and tetracycline hydrochloride is not greater than 4% and 8% of the area of the principal peak in the chromatogram obtained with reference solution respectively.

Light absorption of impurity The absorbance of a solution of 5 mg per ml in water at 460 nm (Appendix IV A) is not more than 0.40.

Loss on drying When dried to constant weight at 105°C, loses not more than 1.0% of its weight (Appendix VIII L).

Assay Carry out the method for high performance liquid (Appendix V D), using a column packed with octadecylsilane bonded silica gel (pH more than 8) and a mixture of 0.1 mol/L ammonium oxalate solution-dimethylformamide-0.2 mol/L diammonium hydrogen phosphate solution (68 : 27 : 5) (adjust to pH 8.3 with ammonia TS) as the mobile phase with a flow rate 1.3 ml per minute, maintain the column temperature at 40-50°C. Detection wavelength is 370 nm. The resolution factor between the peaks of epimer of chlortetracycline and tetracycline hydrochloride and that between tetracycline hydrochloride and chlortetracycline hydrochloride comply with related requirements. (elution sequence; epimer of chlortetracycline, tetracycline hydrochloride and chlortetracycline hydrochloride except solvent peak).

Procedure Dissolve about 25 mg, accurately weighed, in 0.01 mol/L hydrochloric acid and dilute to volume in a 50 ml volumetric flask, mix well. Inject 20 µl into the column and record the chromatogram. Repeat the operation, using chlortetracycline hydrochloride CRS instead of the substance being examined, calculate the content of $C_{22}H_{23}ClN_2O_8 \cdot HCl$.

Category Tetracycline antibiotic.

Storage Preserve in tightly closed containers, protected from light and stored in a dry place.

Preparation (1) Chlortetracycline Hydrochloride Eye Ointment
(2) Chlortetracycline Hydrochloride Ointment

Chlortetracycline Hydrochloride Eye Ointment

Chlortetracycline Hydrochloride Ointment contains not less than 90.0% and not more than 110.0% of the labelled amount of chlortetracycline, calculated as chlortetracycline hydrochloride ($C_{22}H_{23}ClN_2O_8 \cdot HCl$).

Description A yellow ointment.

Identification The retention time of principal peak of the substance being examined in the chromatogram obtained in the Assay is identical with that the principal peak of chlortetracycline hydrochloride CRS in the chromatogram.

Other requirements Complies with the general requirements for eye preparations (Appendix I G).

Assay Dissolve as completely as possible about 2 g, accurately weighed, in 25 ml of ether in a separator, extract with 3 portions each of 10 ml of 0.1 mol/L hydrochloric acid solution. Combine the extracts in 50 ml volumetric flask, dilute with water to volume. Dissolve 20 mg of chlortetracycline hydrochloride CRS, weighed accurately, in 0.01 mol/L hydrochloric acid solution and dilute to volume in a 100 ml volumetric flask, mix well. Carry out the Assay described under Chlortetracycline Hydrochloride with the resulting solutions.

Category As described under Chlortetracycline Hydrochloride.

Strength 0.5%

Storage Preserve in well closed containers, stored in a cool and dry place.

Chlortetracycline Hydrochloride Ointment

Chlortetracycline Hydrochloride Ointment contains not less than 90.0% and not more than 110.0% of the labelled amount of chlortetracycline, calculated on chlortetracycline hydrochloride ($C_{22}H_{23}ClN_2O_8 \cdot HCl$).

Description A yellow ointment.

Identification The retention time of principal peak of the substance being examined in the chromatogram obtained in the Assay is identical with that the principal peak of chlortetracycline hydrochloride CRS.

Other requirements Complies with the general requirements for ointments (Appendix I F).

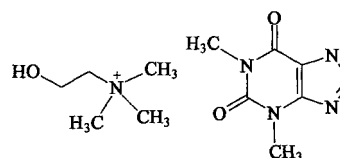
Assay Dissolve about 1 g, accurately weighed, in 25 ml of ether in a separator with shaking, extract with 3 portions each of 10 ml of 0.1 mol/L hydrochloric acid solution. Combine the extracts and dilute to volume in a 50 ml volumetric flask. Dissolve about 20 mg of chlortetracycline hydrochloride CRS, weighed accurately, in 0.01 mol/L hydrochloric acid solution and dilute to volume in a 100 ml volumetric flask, mix well. Carry out the Assay described under Chlortetracycline Hydrochloride with the resulting solutions.

Category As described under Chlortetracycline Hydrochloride.

Strength 1%

Storage Preserve in well closed containers, store in a cool and dry place.

Choline Theophyllinate



$C_{12}H_{21}N_5O_3$ 283.33

[13930-27-3]

Choline Theophyllinate is salt of 2-hydroxy-*N,N,N*-trimethyl-ethanamine with 3,7-dihydro-1,3-dimethyl-1*H*-purine-2,6-dione. It contains not less than 98.5% of $C_{12}H_{21}N_5O_3$, calculated on the dried basis.

Description A white, crystalline powder; odour, faintly amine-like; taste, salty and bitter. Freely soluble in water; soluble in ethanol; slightly soluble in chloroform or ether.

Melting range 187-192°C (Appendix VI C, regulate the rate of temperature rise to 3.0°C ± 0.5°C per minute).

Identification (1) Dissolve about 0.1 g in 1 ml of hydrochloric acid, add 0.1 g of potassium chlorate, evaporate to dryness on a water bath, the residue becomes purple on exposure to ammonia vapour, and then discharged on the addition of sodium hydroxide TS.

(2) Dissolve 0.5 g in 2 ml of water, add 3 ml of sodium hydroxide TS, boil, the odour of trimethylamine is perceptible.

(3) The light absorption of a solution of 15 µg per ml in sodium hydroxide (0.01 mol/L) VS exhibits a maximum at 275 nm (Appendix IV A).

Clarity and colour of solution A solution of 1.0 g in 10 ml of water is clear; any colour produced is not more intense than that of the reference solution (to 1.0 ml of standard potassium dichromate CS add water to produce 160 ml).

Loss on drying When dried to constant weight at 105°C, loses not more than 0.5% of its weight (Appendix VIII L).

Residue on ignition Not more than 0.1% (Appendix VIII N).

Assay Dissolve about 0.25 g, accurately weighed, in 50 ml of water and 8 ml of ammonia TS by heating gently on a water bath. Add accurately 20 ml of silver nitrate (0.1 mol/L) VS, mix well, heat again on a water bath for 15 minutes, cool to 5–10°C and allow to stand for 20 minutes. Filter through a sintered glass funnel, wash the residue with three 10 ml portions of water. Combine the filtrate and the washings, acidify with nitric acid and then add 3 ml more of nitric acid, cool, add 2 ml of ammonium ferric sulfate IS. Titrate with ammonium thiocyanate (0.1 mol/L) VS. Each ml of silver nitrate (0.1 mol/L) VS is equivalent to 28.33 mg of $C_{12}H_{21}N_5O_3$.

Category Smooth muscle relaxant.

Storage Preserve in tightly closed containers, stored in a dry place.

Preparation Choline Theophyllinate Tablets

Choline Theophyllinate Tablets

Choline Theophyllinate Tablets contain not less than 94.0% and not more than 106.0% of the labelled amount of choline theophyllinate ($C_{12}H_{21}N_5O_3$).

Description White tablets.

Identification Macerate a quantity of the powdered tablets with water, filter, the filtrate complies with tests (1) and (2) for Identification described under Choline Theophyllinate.

Other requirements Comply with the general requirements for tablets (Appendix I A).

Assay Weigh accurately and powder finely 20 tablets. Weigh accurately a quantity of the powder equivalent to about 0.5 g of choline theophyllinate to a 100 ml volumetric flask, add 70 ml of water, shake frequently for 30 minutes to dissolve choline theophyllinate, add water to volume and mix well. Filter, measure accurately 50 ml of the successive filtrate and add 8 ml of ammonia TS. Heat gently on a water bath, carry out the Assay described under Choline Theophyllinate, beginning at the words "Add accurately 20 ml...". Each ml of silver nitrate (0.1 mol/L) VS is equivalent to 28.33 mg of $C_{12}H_{21}N_5O_3$.

Category As described under Choline Theophyllinate.

Strength 0.1 g

Storage Preserve in tightly closed containers, stored in a dry place.

Chorionic Gonadotrophin

Chorionic Gonadotrophin is a gonad-stimulating hormone obtained from the urine of pregnant women. It has a potency not less than 2500 Units per mg, calculated on the dried basis.

The manufacturing process must have been shown to reduce any viral contamination such as hepatitis virus or HIV by appropriate validated methods.

Description A white or almost white powder.

Soluble in water; insoluble in ethanol, acetone or ether.

Oestrogens Three female mice weighing between 18 and 20 g are ovariectomized two to three weeks before the test. On the day of the test, inject subcutaneously into each of three mice a Sodium Chloride Injection containing 1250 Units per ml in four equally-divided doses, each of 0.2 ml, on three consecutive days. Inject the doses in the afternoon of the first day, in the morning and afternoon of the second day, and in the morning of the third day. The vaginal smears taken in the morning of the fourth, fifth and sixth days from each mouse by washing the vaginal wall with a small quantity of Sodium Chloride Injection show no signs of positive response under the low power microscope. The response is positive when most of the cells present in any of the smears are cornified or nucleated cells, but leucocytes are absent or scanty.

Loss on drying When dried in vacuum over phosphorus pentoxide to constant weight, loses not more than 3.0% of its weight (Appendix VIII L), use about 0.1 g.

Undue toxicity Complies with the test for undue toxicity by intravenous injection (Appendix XI C), using 2000 Units dissolved in 1 ml of Sodium Chloride Injection.

Bacterial endotoxin Carry out the test for bacterial endotoxin (Appendix XI E); less than 0.01 EU per unit.

Assay Carry out the biological assay of chorionic gonadotrophin (Appendix XIII E), the estimated potency is not less than 80% and not more than 125% of the labelled potency.

Category Gonad-stimulant.

Storage Preserve in tightly closed containers, stored in a cool and dark place.

Preparation Chorionic Gonadotrophin for Injection

Chorionic Gonadotrophin for Injection

Chorionic Gonadotrophin for Injection is a sterile, lyophilized preparation of chorionic gonadotrophin containing suitable excipient. It has a potency of not less than 80% and not more than 125% of the labelled potency.

Description A white, lyophilized mass or powder.

Loss on drying When dried in vacuum over phosphorus pentoxide to constant weight, loses not more than 5.0% of its weight (Appendix VIII L), use 0.1 g.

Sterility Dissolve the contents of 2 ampoules separately in sterile water to produce a solution of 250 Units per ml, the solution complies with the test for sterility (Appendix XI H).

Undue toxicity and Bacterial endotoxin Complies with the corresponding test described under Chorionic Gonadotrophin.

Other requirements Complies with the general requirements for injections (Appendix I B).

Assay Carry out the biological assay of chorionic gonadotrophin (Appendix XIII E), it complies with the requirement for potency.

Category As described under Chorionic Gonadotrophin.

Strength (1) 500 Units (2) 1000 Units (3) 2000 Units
(4) 3000 Units (5) 5000 Units

Storage Preserve in well closed containers, stored in a cool and dark place.

Chymotrypsin

Chymotrypsin is a proteolytic enzyme obtained by extraction of cattle or swine pancreas. It has a potency of not less than 800 Units per mg, calculated on the dried basis.

Description A white or almost white crystalline powder.

Identification Prepare an aqueous solution of 1 mg per ml. To 0.05 ml on a white spot plate add 0.2 ml of *N*-acetyl-L-tyrosin ethyl ester TS and mix well, a purple colour is produced.

Acidity An aqueous solution of 2 mg per ml, pH 5.5-7.0 (Appendix VI H).

Clarity of solution An aqueous solution of 2 mg per ml is clear.

Trypsin Prepare an aqueous solution of 10 mg per ml as the test solution. To 50 μ l of the test solution and 5 μ l of a solution of 0.1% trypsin CRS respectively in separate depressions on a white spot plate add 0.2 ml each of methyl *N*-tosyl-L-arginate hydrochloride TS. Allow it to stand, no purple colour appears in the test solution before that appears in the solution of trypsin CRS (1%).

Loss on drying When dried to constant weight over phosphorus pentoxide under reduced pressure at 60°C for 4 hours, loses not more than 5.0% of its weight (Appendix VIII L), using about 0.2 g.

Residue on ignition Not more than 2.5% (Appendix VIII N).

Assay *Test solution* Dissolve a quantity, accurately weighed, in 0.0012 mol/L hydrochloric acid solution to produce a solution of 12-16 Units per ml.

Substrate solution Transfer 23.7 mg of ethyl *N*-acetyl-L-tyrosin in a 100 ml volumetric flask, add 50 ml of phosphate buffer solution (mix 38.9 ml of 0.067 mol/L potassium dihydrogen phosphate solution with 61.1 ml of disodium hydrogen phosphate solution, adjust to pH 7.0), dissolve by warming, cool, dilute to volume and shake thoroughly. Store by freezing but avoid to thaw repeatedly.

Procedure Adjust the light absorption of a mixture of 0.2 ml of 0.0012 mol/L hydrochloric acid solution and 3.0 ml of the substrate solution to have an absorbance of 0.200, measured at 237 nm at 25°C \pm 0.5°C. Mix well 0.2 ml of the test solution with 3.0 ml of the substrate solution and measure the absorbance immediately. Measure the absorbance at an interval of 30 seconds for a period of 5 minutes. The changing rate of the absorbances is constant

within a period of not less than 3 minutes. Repeat the operation under the same condition. If the changing rate does not keep constant as required, repeat the measurement using the test solution of a lower concentration. The changing rate of the absorbance at an interval of 30 seconds should be kept in the range of 0.008-0.012. Plot a graph with absorbance as the ordinate and time as the abscissa, taking the linear part measured within 3 minutes. Calculate the activity from the following expression:

$$\text{Chymotrypsin Unit per mg } P = \frac{A_2 - A_1}{0.0075TW}$$

Where A_2 is the initial absorbance of the straight line;

A_1 is the final absorbance of the straight line;

T is the time taken in minutes from A_2 to A_1 ;

W is the quantity of the substance being examined in the test solution, mg;

0.0075 represents the change of absorbance equivalent to 1 Unit of chymotrypsin under the above condition.

Category Proteolytic enzyme.

Storage Preserve in tightly closed containers, protected from light and stored in a cool place.

Preparation Chymotrypsin for Injection

Chymotrypsin for Injection

Chymotrypsin for Injection is sterile, lyophilized chymotrypsin. It contains not less than 90.0% and not more than 120.0% of the labelled potency.

Description White lyophilized masses.

Identification An aqueous solution of 800 Units per ml complies with the test for Identification described under Chymotrypsin.

Acidity Dissolve the contents of each of 5 containers separately in 2 ml of water, combine the solutions and mix well, pH 5.5-6.5 (Appendix VI H).

Colour of solution Dissolve in 2 ml of water, the solution is almost colourless.

Loss on drying When dried to constant weight over phosphorus pentoxide under reduced pressure at 60°C for 4 hours, loses not more than 8.0% of its weight (Appendix VIII L), using about 0.2 g.

Other requirements Complies with the general requirements for injections (Appendix I B), except Weight variation of contents.

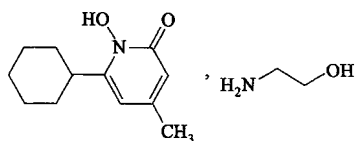
Assay Dissolve the contents of 3 containers separately in 0.0012 mol/L hydrochloric acid solution to produce solutions containing 12-16 Units per ml. Carry out the Assay described under chymotrypsin and calculate the activity. If one of them fails, repeat the assay using the other three containers, all of them comply with the requirement.

Category As described under Chymotrypsin.

Strength (1) 800 Units (2) 4000 Units

Storage Preserve in well closed containers, protected from light and stored in a cool place.

Ciclopirox Olamine



$C_{12}H_{17}NO_2 \cdot C_2H_7NO$ 268.36

[41621-49-2]

Ciclopirox Olamine is a double salt composed of 4-methyl-6-hexyl-1-hydroxyl-2(1*H*)-pyridone and 2-aminoethanol. It contains not less than 75.7% and not more than 78.0% of $C_{12}H_{17}NO_2$; not less than 22.3% and not more than 23.0% of C_2H_7NO , calculated on the dried basis.

Description A white crystalline powder; odourless; taste, bitter.

Freely soluble in methanol, ethanol or chloroform; sparingly soluble in dimethylformamide or water; slightly soluble in ethyl ether.

Identification (1) Dissolve 10 mg in 5 ml of water, add two drops of ninhydrin TS and boil; a bluish-violet colour is produced.

(2) Carry out the method for thin-layer chromatography (Appendix V B), using silica gel GF₂₅₄ as the coating substance and a mixture of benzene-ethanol-glacial acetic acid-dimethylformamide (90 : 8 : 1 : 1) as the mobile phase. Apply separately to the plate 10 μ l each of two solutions in methanol containing (1) 40 mg per ml of ciclopirox olamine CRS and (2) 40 mg per ml of substance being examined. After developing and removal of the plate, dry it in air, examine under ultraviolet light (254 nm). The fluorescence of the principal spot in the chromatogram obtained with solution (2) is identical in colour and position with that in the chromatogram obtained with solution (1).

(3) The light absorption of a solution of 20 μ g per ml in ethanol exhibits maxima at 304 nm and 231 nm (Appendix IV A).

(4) The infrared absorption spectrum (Appendix IV C) is concordant with the reference spectrum of ciclopirox olamine (Appendix XVI).

Alkalinity The pH value of a solution of 10 mg per ml in water is 8.0-9.0 (Appendix VI H).

Loss on drying When dried in vacuum over phosphorous pentoxide to constant weight, loses not more than 1.0% of its weight (Appendix VIII L).

Residue on ignition Not more than 0.1% (Appendix VIII N), using 1.0 g.

Heavy metals Carry out the limit test for heavy metals (Appendix VIII H, method 2), using the residue obtained in the test for residue on ignition; not more than 0.002%.

Assay *Ciclopirox* Dissolve about 0.3 g, accurately weighed, in 40 ml of dimethylformamide, add two drops of 1% thymol blue in methanol IS. Titrate with lithium methoxide (0.1 mol/L) VS until a blue colour is produced. Perform a blank determination and make any necessary correction. Each ml of lithium methoxide (0.1 mol/ml) VS is equivalent to 20.73 mg of $C_{12}H_{17}NO_2$.

2-Aminoethanol Dissolve about 0.3 g, accurately weighed, in 20 ml of methanol, add three drops of bromocresol green IS. Titrate with hydrochloric acid (0.1 mol/L) VS until a

yellow colour is produced. Perform a blank determination and make any necessary correction. Each ml of hydrochloric acid (0.1 mol/ml) VS is equivalent to 6.108 mg of C_2H_7NO .

Category Antifungal.

Storage Preserve in tightly closed containers, protected from light.

Preparation Ciclopirox Olamine Cream

Ciclopirox Olamine Cream

Ciclopirox Olamine Cream contains not less than 90.0% and not more than 110.0% of the labelled amount of ciclopirox olamine ($C_{12}H_{17}NO_2 \cdot C_2H_7NO$).

Description A creamy white cream.

Identification (1) To 0.1 g add 2 ml of ninhydrin TS, stir and boil; a bluish-violet colour is produced.

(2) To 4 g add 10 ml of methanol, warm on a water bath to dissolve ciclopirox olamine, then cool on water bath and filter. Carry out the method for thin-layer chromatography (Appendix V B), using silica gel GF₂₅₄ as the coating substance and a mixture of benzene-ethanol-glacial acetic acid-dimethyl formamide (90 : 8 : 1 : 1) as the mobile phase. Apply separately to the plate 10 μ l each of two solutions in methanol containing (1) 4 mg per ml of ciclopirox olamine CRS and (2) the filtrate of the substance being examined. After developing and removal of the plate, dry it in air, examine under ultraviolet light (254 nm). The fluorescence of the principal spot in the chromatography obtained with solution (2) is identical in colour and position with that in the chromatography obtained with solution (1).

(3) To 0.1 g add 50 ml of ethanol; shake and filter. The light absorption of the filtrate exhibits maxima at 304 nm and 231 nm (Appendix IV A).

Acidity and alkalinity To about 3.5 g add 15 ml of boiling water (pH = 6-7), stir and heat in water bath for 10 minutes, then cool. The pH value of the solution is 5.0-8.0 (Appendix VI H).

Assay *Reference preparation* Dissolve 30 mg of ciclopirox olamine CRS in a 100 ml volumetric flask with methanol and dilute to volume and mix well.

Test preparation To a quantity, weight accurately, equivalent to about 30 mg of ciclopirox olamine, add 25 ml methanol, warm on water bath to dissolve ciclopirox olamine; cool with ice water and filter. Extract for three times according to the procedure above mentioned. Combine the filtrate in a 100 ml volumetric flask and add methanol to volume.

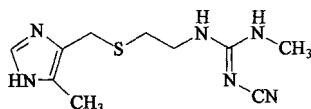
Procedure Transfer 5 ml of each of the two solutions, accurately measured, to two 25 ml of volumetric flasks, add 15 ml of methanol each and mix well. Add 1.5 ml of ferrous sulfate solution (Dissolve 0.6 g of ferrous sulfate in 0.6 ml of glacial acetic acid and a quantity of water, dilute to 25 ml and mix well) to each of the two flask and mix well; then add methanol to volume, mix well again, and protect from light for 1 hour. Measure the absorbance of the resulting solutions at 440 nm (Appendix IV A), calculate the content of $C_{12}H_{17}NO_2 \cdot C_2H_7NO$.

Category As described under Ciclopirox Olamine.

Strength (1) 10 g : 0.1 g (2) 15 g : 0.15 g

Storage Preserve in tightly closed containers, protected from light, stored at a cool place.

Cimetidine



$C_{10}H_{16}N_6S$ 252.34

[51481-61-9]

Cimetidine is *N*-cyano-*N'*-methyl-*N''*-[2-[(5-methyl-1*H*-imidazol-4-yl) methyl] thio] ethyl] guanidine. It contains not less than 99.0% of $C_{10}H_{16}N_6S$, calculated on the dried basis.

Description A white or almost white crystalline powder; almost odourless; taste, bitter.

Freely soluble in methanol; soluble in ethanol; sparingly soluble in isopropanol; slightly soluble in water; freely soluble in dilute hydrochloric acid.

Specific Absorbance Measure the absorbance of a solution of 8 μ g per ml in hydrochloric acid (0.9 \rightarrow 1000) at 218 nm (Appendix IV A), the value of *A* (1%, 1 cm) is 751-797.

Identification (1) Dissolve about 50 mg in 10 ml of water by warming, add 1 drop of ammonia TS and 2 drops of cupric sulphate TS, a bluish-grey precipitate is produced, which is soluble in an excess of ammonia TS.

(2) Ignite about 50 mg, fumes are evolved which stain lead acetate TP black.

(3) The infrared absorption spectrum (Appendix IV C) is concordant with the reference spectrum of cimetidine (Appendix XVI).

Chloride Carry out the limit test for chlorides (Appendix VIII A), using 1.0 g. Any opalescence produced is not more pronounced than that of a reference using 8 ml of sodium chloride standard solution (0.008%).

Related substances Carry out the method for thin-layer chromatography (Appendix V B), using silica gel G as the coating substance and a mixture of ethyl acetate-methanol-concentrated ammonia solution (5 : 1 : 1) as the mobile phase. Apply separately to the plate 5 μ l each of two solutions in methanol containing (1) 20 mg per ml and (2) 0.1 mg per ml of the substance being examined. After developing and removal of the plate, dry it in air and visualize with iodine vapour. Any spot other than the principal spot in the chromatogram obtained with solution (1) is not more intense than the principal spot obtained with solution (2).

Loss on drying When dried to constant weight at 105°C, loses not more than 0.5% of its weight (Appendix VIII L).

Residue on ignition Not more than 0.1% (Appendix VIII N), using 1.0 g.

Heavy metals Carry out the limit test for heavy metals, using the residue obtained in the test for Residue on ignition (Appendix VIII H, method 2); not more than 0.001%.

Assay Dissolve about 0.2 g, accurately weighed, in 20 ml of glacial acetic acid, add 1 drop of crystal violet IS. Titrate with perchloric acid (0.1 mol/L) VS until the solution changes to blue. Perform a blank determination and make any necessary correction. Each ml of perchloric acid (0.1 mol/L) VS is equivalent to 25.23 mg of $C_{10}H_{16}N_6S$.

Category Histamine H_2 receptor antagonist.

Storage Preserve in tightly closed containers.

Preparation (1) Cimetidine and Sodium Chloride Injection
(2) Cimetidine Capsules
(3) Cimetidine Tablets

Cimetidine and Sodium Chloride Injection

Cimetidine and Sodium Chloride Injection is a sterile solution of Cimetidine and Sodium Chloride in Water for Injections. It contains not less than 90.0% and not more than 110.0% of the labelled amount of cimetidine ($C_{10}H_{16}N_6S$), sodium chloride (NaCl).

Description A clear, colourless liquid.

Identification (1) To a quantity of the injection (equivalent to about 50 mg of cimetidine), add two drops of ammonia TS and two drops of copper sulfate TS, a bluish-grey precipitate is produced, add excessive ammonia TS; the precipitate is dissolved.

(2) The retention time of principal peaks of the substance being examined in the chromatogram obtained in the Assay is identical with that of cimetidine CRS in the chromatogram of the reference solution.

(3) Yield the reactions characteristic of sodium salts and chloride (Appendix III).

pH value 5.0-7.0 (Appendix VI H).

Particulate matter in Injection Complies with the requirements (Appendix IX C).

Bacterial endotoxin Carry out the test for bacterial endotoxin (Appendix XI E), less than 0.5 EU per ml.

Other requirements Complies with the general requirements for injection (Appendix I B).

Assay of Cimetidine Carry out the method for high performance liquid chromatography (Appendix V D), using a column packed with octadecylsilane bonded silica gel and a mixture of methanol-water-phosphoric acid-triethylamine (200 : 800 : 0.3 : 0.2) as mobile phase. Detection wavelength is 220 nm and the number of theoretical plates of the column is not less than 1000, calculated with reference to the peak of cimetidine.

Procedure Transfer an accurately measured 5 ml of the injection to a 100 ml volumetric flask and dilute with the mobile phase to volume, mix well, transfer 5 ml of the solution into a 20 ml volumetric flask, accurately measured, dilute with the mobile phase to volume and mix well. Inject 10 μ l of the resulting solution into the column. Dissolve an accurately weighed quantity of cimetidine CRS in the mobile phase to produce a solution of 50 μ g per ml, repeat the operation. Calculate the content of $C_{10}H_{16}N_6S$ with respect to the peak area obtained in the chromatogram by the external standard method.

Sodium chloride *Stock reference solution* Measure accurately a quantity of standard sodium solution, dilute with water to produce a solution of 100 μ g per ml.

The test solution Transfer an accurately measured 5 ml of the injection to a 50 ml volumetric flask and dilute with water to volume, mix well, transfer 1 ml of the solution to a 50 ml volumetric flask, accurately measured, dilute with water to volume, mix well.

Procedure Transfer separately 3.5 ml, 5.5 ml, 7.0 ml, 8.5 ml and 10.5 ml of the stock reference solution to five 100

ml volumetric flasks, accurately measured, dilute with water to volume, mix well. Carry out the method for flame spectrophotometry (Appendix IV F), measure the absorbance of above solutions and the test solution. Calculate the content of NaCl.

Category As described under cimetidine.

Strength (1) 50 ml : 0.2 g of cimetidine and 0.45 g of sodium chloride (2) 100 ml : 0.4 g of and 0.9 g of sodium chloride

Storage Preserve in well closed containers and protected from light.

Cimetidine Capsules

Cimetidine Capsules contain not less than 90.0% and not more than 110.0% of the labelled amount of cimetidine ($C_{10}H_{16}N_6S$).

Identification The contents of the capsules comply with the tests for Identification described under Cimetidine Tablets.

Dissolution Carry out the dissolution test (Appendix X C, method 1), using 900 ml of hydrochloric acid solution (0.9→1000) as the dissolution medium and adjust the rotational speed of the basket to 100 rpm. Withdraw 10 ml of the solution after exactly 20 minutes and filter. Dilute accurately measured 3 ml of the successive filtrate with dissolution medium to volume in a 100 ml volumetric flask. Measure the absorbance of the resulting solutions at 218 nm (Appendix IV A). Calculate the dissolution of $C_{10}H_{16}N_6S$ from each capsule, taking 774 as the value of A (1%, 1 cm), not less than 75% of the labelled amount is dissolved.

Other requirements Comply with the general requirements for capsules (Appendix I E).

Assay Dissolve an accurately weighed quantity, equivalent to about 0.1 g of cimetidine, of the mixed contents in the test for Weight variation of contents in 150 ml of hydrochloric acid solution (0.9→1000) with shaking and dilute with above hydrochloric acid solution to volume in a 200 ml volumetric flask, mix well and filter. Dilute accurately measured 2 ml of the successive filtrate to volume in a 200 ml volumetric flask with above hydrochloric acid solution and mix well. Measure the absorbance of the resulting solution at 218 nm (Appendix IV A), calculate the content of $C_{10}H_{16}N_6S$, taking 774 as the value of A (1%, 1 cm).

Category As described under Cimetidine.

Strength 0.2 g

Storage Preserve in tightly closed containers.

Cimetidine Tablets

Cimetidine Tablets contain not less than 93.0% and not more than 107.0% of the labelled amount of cimetidine ($C_{10}H_{16}N_6S$).

Description White tablets or faintly blue or greyish-green coloured tablets with the addition of pigment or film coated tablets.

Identification (1) Ignite a quantity of powdered tablets equivalent to about 0.1 g of cimetidine, fumes are evolved which stain lead acetate TP black.

(2) Carry out the method for thin-layer chromatography (Appendix V B), using silica gel G as the coating substance and a mixture of chloroform-methanol (5 : 1) as the mobile phase. Apply separately to the plate 5 μ l each of two solutions in methanol containing (1) 10 mg per ml of the substance being examined and (2) 10 mg per ml of cimetidine CRS. After developing and removal of the plate, dry it in air and visualize with iodine vapour. The principal spot in the chromatogram obtained with solution (1) is identical in position with the principal spot obtained with solution (2).

Dissolution Carry out the dissolution test (Appendix X C, method 1), using 900 ml of hydrochloric acid solution (0.9→1000) as the dissolution medium, and adjust the rotational speed of the basket to 100 rpm. Withdraw 10 ml of the solution after exactly 15 minutes and filter. Dilute a quantity of the successive filtrate, accurately measured, with dissolution medium to produce a solution of 5-10 μ g per ml. Measure the absorbance of the solution at 218 nm (Appendix IV A), calculate the dissolution of $C_{10}H_{16}N_6S$ from each tablet, taking 774 as the value of A (1%, 1 cm). Not less than 75% of the labelled amount is dissolved.

Other requirements Comply with the general requirements for tablets (Appendix I A).

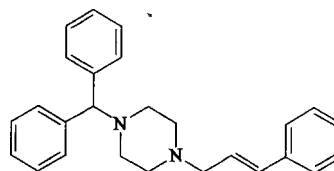
Assay Weigh accurately and powder 20 tablets. Dissolve an accurately weighed quantity of the powdered tablets equivalent to about 0.2 g in 150 ml of hydrochloric acid solution (0.9→1000) with shaking and dilute with above solvent to volume in a 200 ml volumetric flask, mix well and filter. Dilute accurately measured 2 ml of the successive filtrate to volume in a 200 ml volumetric flask with above solvent and mix well. Measure the absorbance of the resulting solution at 218 nm (Appendix IV A), calculate the content of $C_{10}H_{16}N_6S$, taking 774 as the value of A (1%, 1 cm).

Category As described under Cimetidine.

Strength (1) 0.2 g (2) 0.4 g (3) 0.8 g

Storage Preserve in tightly closed containers.

Cinnarizine



$C_{26}H_{28}N_2$ 368.52

[298-57-7]

Cinnarizine is 1-(diphenylmethyl)-4-(3-phenyl-2-propenyl)-piperazine. It contains not less than 98.0% of $C_{26}H_{28}N_2$, calculated on the dried basis.

Description White or almost white crystals or a crystalline powder; odourless; tasteless.

Freely soluble in chloroform or benzene; soluble in boiling ethanol; practically insoluble in water.

Melting range 117-121°C (Appendix VI C).

Specific absorbance Measure the absorbance of a solution of 7.5 μ g per ml in hydrochloric acid solution (9→1000) at 253 nm (Appendix IV A), the value of A (1%, 1 cm) is 558-592.

Identification (1) Dissolve about 20 mg in 5 ml of ethanol by warming, add 2 drops of potassium hydroxide TS, mix well. Add 2-3 drops of potassium permanganate TS, the violet colour is immediately discharged.

(2) To about 10 mg add several drops of a 2% solution of formaldehyde in sulfuric acid, a red colour is produced.

(3) Ignite about 50 mg in a test tube. Fumes are evolved which turn a piece of filter paper moistened with 2% trichloroacetic acid solution and 1 drop of a 5% solution of *p*-dimethylaminobenzaldehyde in hydrochloric acid to violet.

(4) The infrared absorption spectrum (Appendix IV C) is concordant with the reference spectrum of cinnarizine (Appendix XVI).

Alkalinity Shake 0.50 g with 20 ml of freshly boiled and cooled water for 5 minutes and filter. To the filtrate add 1 drop of methyl orange IS and 0.50 ml sulfuric acid (0.01 mol/L) VS, a red colour is produced.

Chloride Heat 0.20 g with 25 ml of water on a water bath for 10 minutes, shake thoroughly and filter. Collect the filtrate in a 50 ml volumetric flask, dilute with water to volume, mix well. Carry out the limit test for chlorides (Appendix VIII A), using 10 ml of the filtrate, accurately measured. Any opalescence produced is not more pronounced than that of a reference using 4.0 ml of sodium chloride standard solution (0.1%).

Loss on drying When dried to constant weight at 80°C, loses not more than 0.5% of its weight (Appendix VIII L).

Residue on ignition Not more than 0.1% (Appendix VIII N), using 1.0 g.

Heavy metals Carry out the limit test for heavy metals (Appendix VIII H, method 2), using the residue obtained in the test for Residue on ignition; not more than 0.002%.

Assay Dissolve about 0.15 g, accurately weighed, in 20 ml of glacial acetic acid and 4 ml of acetic anhydride, add 1 drop of crystal violet IS. Titrate with perchloric acid (0.1 mol/L) VS until the solution changes to green. Perform a blank determination and make any necessary correction. Each ml of perchloric acid (0.1 mol/L) VS is equivalent to 18.43 mg of $C_{26}H_{28}N_2$.

Category Vasodilator.

Storage Preserve in tightly closed containers, protected from light.

Preparation (1) Cinnarizine Capsules
(2) Cinnarizine Tablets

Cinnarizine Capsules

Cinnarizine Capsules contain not less than 93.0% and not more than 107.0% of the labelled amount of cinnarizine ($C_{26}H_{28}N_2$).

Identification To a quantity of the contents of the capsules, equivalent to about 0.25 g of cinnarizine, add 25 ml of ethanol to dissolve cinnarizine with warming. Filter and evaporate the filtrate to dryness, the residue complies with tests (1), (2) and (3) for Identification described under Cinnarizine.

Dissolution Comply with the dissolution test (Appendix X C, method 1). Complete the Dissolution as described under Cinnarizine Tablets.

Other requirements Comply with the general requirements for capsules (Appendix I E).

Assay Weigh accurately a quantity of the mixed contents obtained in the test for weight variation, equivalent to about 30 mg of cinnarizine. Carry out the Assay described under Cinnarizine Tablets, beginning at the words "in about 150 ml..."

Category As described under Cinnarizine.

Strength 25 mg

Storage Preserve in tightly closed containers, protected from light.

Cinnarizine Tablets

Cinnarizine Tablets contain not less than 95.0% and not more than 105.0% of the labelled amount of cinnarizine ($C_{26}H_{28}N_2$).

Description White or almost white tablets.

Identification (1) Dissolve a quantity of powdered tablets equivalent to about 0.25 g of cinnarizine in 25 ml of ethanol by warming and filter. Evaporate the filtrate to dryness, the residue complies with tests (1), (2) and (3) for Identification described under Cinnarizine.

Dissolution Carry out dissolution test (Appendix X C, method 1), using 1000 ml of hydrochloric acid solution (9→1000) as the dissolution medium, and adjust the rotational speed of the basket to 100 rpm. Withdraw 10 ml of the solution after exactly 45 minutes and filter. Dilute 5 ml of the successive filtrate, accurately measured, in a 10 ml volumetric flask with dissolution medium to volume, mix well. Measure the absorbance of the solution at 253 nm (Appendix IV A), calculate the dissolution of $C_{26}H_{28}N_2$, taking 575 as the value of A (1%, 1 cm). Not less than 70% of the labelled amount is dissolved.

Other requirements Comply with the general requirements for tablets (Appendix I A).

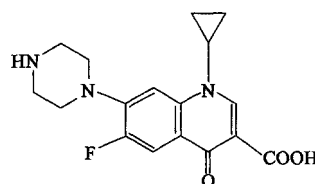
Assay Weigh accurately and powder 20 tablets. Dissolve an accurately weighed quantity equivalent to about 30 mg of cinnarizine in about 150 ml of hydrochloric acid solution (9→1000) in a 200 ml volumetric flask with shaking, and dilute to volume, shake well, filter. Dilute accurately measured 5 ml of the successive filtrate with hydrochloric acid solution (9→1000) in a 100 ml volumetric flask to volume, mix well. Measure the absorbance of the solution at 253 nm (Appendix IV A). Calculate the content of $C_{26}H_{28}N_2$, taking 575 as the value of A (1%, 1 cm).

Category As described under Cinnarizine.

Strength 25 mg

Storage Preserve in tightly closed containers, protected from light.

Ciprofloxacin



$C_{17}H_{18}FN_3O_3$ 331.34

Ciprofloxacin is 1-cyclopropyl-6-fluoro-1,4-dihydro-4-oxo-7-(1-piperazinyl)-3-quinolinecarboxylic acid. It contains not less than 98.5% and not more than 102.0% of $C_{17}H_{18}FN_3O_3$, calculated on the anhydrous basis.

Description White or slightly yellow crystalline powder; almost odourless; taste, bitter. Freely Soluble in acetic acid; very slightly soluble in ethanol and chloroform; practically insoluble in water.

Identification (1) The retention time of principal peak of ciprofloxacin in the substance being examined in the chromatogram obtained in the Assay is identical with that of the principal peak of the ciprofloxacin CRS in the chromatogram of the reference solution.

(2) The infrared absorption spectrum (Appendix IV C) is concordant with the reference spectrum of ciprofloxacin (Appendix XVI).

Crystallinity Complies with the test for crystallinity (Appendix IX D).

Clarity and colour of solution A solution of 0.1 g in 10 ml of hydrochloric acid (0.1 mol/L) is clear and colourless; if any colour is produced, its colour is not more intense than reference solution Y₄ or YG₄ (Appendix IX A, method 1).

Fluoroquinolinic acid Carry out the method for thin-layer chromatography (Appendix V B). Dilute a quantity with 0.1 mol/L hydrochloric acid to produce a solution containing 10 mg per ml as test solution; add about 5.0 mg Fluoroquinolinic acid in 50 ml measuring flask, then dissolve in 0.05 ml of 6 mol/L ammonia solution and water, dilute to volume. Shake thoroughly, dilute an accurately measured quantity with water to produce a solution containing 0.03 mg per ml as the reference solution. Carry out the method for thin-layer chromatography (Appendix V B), using silica gel GF₂₅₄ as the coating substance and chloroform: methanol: concentrated ammonia solution: Acetonitrile (4 : 4 : 2 : 1) as the mobile phase. Apply separately to the plate 5 μ l, put it into ammonia for 15 minutes. After developing and removal of the plate, allow it to dry in air and examine under ultra-violet light (254 nm). The spots of Fluoroquinolinic acid and ciprofloxacin are separated thoroughly. Any spot obtained with test solution is not more intense than the principal spot obtained with reference solution (0.3%).

Related substances Dissolve a quantity in 7% phosphate acid 0.2 ml, dilute with mobile phase to produce a test solution of 0.5 mg per ml. Dilute an accurately measured quantity with mobile phase to produce a reference solution of 1 μ g per ml. Carry out the method for Assay. Inject 50 μ l of the reference solution into the column, adjust the attenuation so that the principal peak height in the chromatogram is 20% full scale of the chart. Measure accurately 50 μ l of test solution and reference solution into the column respectively and record the chromatogram for twice the retention time of the principal peak. Each peak area and the sum of the areas of all peaks other than the principal peak in the chromatogram obtained from the test solution are not greater than 0.2% and 2.5 times (0.5%) of area of the principal peak in the chromatogram obtained with the reference solution. Disregard any peak with an area less than 0.05 times that of the principal peak in the chromatogram obtained with the reference solution.

Loss on drying When dried in vacuum over phosphorous pentoxide to constant weight at 120°C for 6 hours, loses not more than 1.0% of its weight (Appendix VIII L).

Residue on ignition Not more than 0.1% (Appendix VIII

N), using 1.0 g in a platinum crucible.

Heavy metals Carry out the limit test for heavy metals (Appendix VIII), using the residue obtained in the test for Residue on ignition; not more than 0.002%.

Assay Carry out the method for high performance liquid chromatography (Appendix V D), using a column packed with octadecylsilane bonded silica gel and a mixture of 0.05 mol/L citric acid solution-acetonitrile (82 : 18) with a pH value adjusted to pH 3.5 by triethylamine as the mobile phase. The flow rate is 1 ml per minute; maintain the column temperature at 30°C. The number of theoretical plate of the column is not less than 2000, calculated with reference to the peak of ciprofloxacin. Detection wavelength is 277 nm. The resolution factor between the peaks of ciprofloxacin and continuous impurity complies with the related requirements.

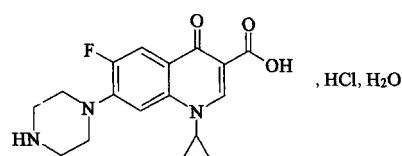
Procedure Dissolve about 25 mg of ciprofloxacin, accurately weighed, in 7% phosphate acid solution in a 50 ml volumetric flask, diluted with mobile phase to volume and mix well. Measure accurately 10 μ l into the column and record the chromatogram. Repeat the operation, using ciprofloxacin CRS instead of the substance. Calculate the content of ciprofloxacin ($C_{17}H_{18}FN_3O_3$) with respect to the peak area obtained in the chromatogram by the external standard method.

Category Aminoglycoside Antibiotic.

Storage Preserve in tightly closed containers, protected from light.

Preparation Ciprofloxacin Lactate and Sodium Chloride Injection.

Ciprofloxacin Hydrochloride



$C_{17}H_{18}FN_3O_3 \cdot HCl \cdot H_2O$, 385.82

Ciprofloxacin Hydrochloride is 1-cyclopropyl-6-fluoro-1,4-dihydro-4-oxo-7-(1-piperazinyl)-3-quinolinecarboxylic acid hydrochloride monohydrate. It contains not less than 88.5% of $C_{17}H_{18}FN_3O_3$, calculated on the anhydrous basis.

Description A white to slightly yellow crystalline powder; almost odourless; taste, bitter. Soluble in water; slightly soluble in methanol; very slightly soluble in ethanol; sparingly soluble in 0.1 mol/L hydrochloric acid.

Identification (1) The retention time of principal peak of the substance being examined in the chromatogram obtained in the Assay is identical with that of ciprofloxacin CRS.

(2) The infrared absorption spectrum (Appendix IV C) is concordant with the reference spectrum of ciprofloxacin hydrochloride (Appendix XVI).

(3) The aqueous solution yields the reactions characteristic of chlorides (Appendix III).

Acidity An aqueous solution of 25 mg per ml, pH 3.0-4.5 (Appendix VI H).

Clarity and colour of solution Dissolve 0.1 g in 10 ml of water, the solution is clear; any colour produced is not more intense than that of reference solution Y₄ or YG₄ (Appendix IX A, method 1).

Fluoroquinolonic acid Dissolve a quantity of the substance being examined in water to produce a solution of 10 mg per ml (solution 1). Dissolve 5.0 mg of fluoroquinolonic acid CRS in a mixture of 0.05 ml 6 mol/L ammonia solution and a quantity of water in a 50 ml flask, dilute to volume with water and mix well dilute an accurately measured quantity with water to produce a solution of 0.03 mg per ml (solution 2). The mixture of the above two solutions each of 1 ml is used to be solution (3). Carry out the method for thin layer chromatography (Appendix V B) using silica gel GF₂₅₄ as the coating substance and a mixture of methylene chloride-methanol-concentrated ammonia-acetonitrile (4 : 4 : 2 : 1) as mobile phase. Apply separately to the plate 5 µl each of three solutions and expose the plate to the ammonia vapour for 15 minutes. After developing and removal of the plate, dry it in air and examine under ultraviolet light (254 nm). Two spots in the chromatogram must be separated on the plate with solution (3), any spot corresponding to fluoroquinolonic acid in the chromatogram obtained with solution (1) is not more intense than the spot in the chromatogram obtained with solution (2) (0.3%).

Related substances Dissolve a quantity of the substance being examined in mobile phase to produce solutions of about 0.5 mg per ml (solution 1) and 1 µg per ml (solution 2). Carry out the method as described under the Assay. Inject 50 µl of solution (2) into the column, adjust the attenuation so that the principal peak height in the chromatogram is about 20% of the full scale of the chart. Inject separately 50 µl of above two solutions, and record the chromatogram for twice the retention time of the principal peak. Each peak area and the sum of the areas of all peaks other than the principal peak in the chromatogram obtained with solution (1) are not greater than twice and 3.5 times the area of the principal peak in the chromatogram obtained with solution (2) respectively. Disregard any peak with an area less than 0.05 times the area of principal peak in the chromatogram obtained with solution (2).

Toluene and ethanol Carry out the method for determination of residual solvents (Appendix VIII P), using a capillary column coated with 5% phenyl-95% methylpolysiloxane (or with the similar polarity stationary phase). Maintaining the temperature of the column at 50°C, use flame ionization detector (FID) with temperature at 200°C, the injector temperature is 150°C, use nitrogen as the carrier gas, the incubation temperature of headspace oven is 90°C, the incubation time of headspace vial is 30 min. Dissolve 0.2 g, accurately weighed, in headspace vial, in 5 ml of water, accurately measured, well closed, as the test solution. Measure accurately a quantity of toluene and ethanol, and dilute with water to produce a solution containing 0.05 mg of toluene and 0.1 mg of ethanol per ml. Measure accurately 5 ml into headspace vial, well closed, as the reference solution. Inject the reference solution, the resolution factor among the all-principal peaks complies with the related requirements. Inject the test solution and the reference solution separately, record the chromatogram. Calculate the content of toluene and ethanol respectively with respect to the peak area obtained in the chromatogram by the external standard method, the result complies with the related requirements.

Water 4.7%-6.7% (Appendix VIII M, method 1 A).

Residue on ignition Not more than 0.1% (Appendix VII N), using 1.0 g.

Heavy metals Carry out the limit test for heavy metals (Appendix VIII H, method 2), using the residue obtained in the test for Residue on ignition : not more than 0.002%.

Assay Carry out the method for high performance liquid chromatograph (Appendix V D), using a column packed with octadecylsilane bonded silica gel and a mixture of 0.05 mol/L citric acid solution-acetonitrile (82 : 18) as the mobile phase previously adjusted to pH 3.5 with triethylamine. The flow rate of the mobile phase is 1 ml per minute, detection wavelength is 277 nm and the column temperature is maintained at 30°C. The number of the theoretical plates of the column is not less than 2000, calculated with reference to the peak of ciprofloxacin. The resolution factor between the peaks of ciprofloxacin and the neighbour impurity complies with the related requirements.

Procedure Dissolve an accurately weighed quantity in mobile phase to produce a solution of about 0.5 mg per ml. Inject 10 µl of the solution into the column. Repeat the operation, using ciprofloxacin CRS instead of the substance being examined, calculate the content of C₁₇H₁₈FN₃O₃ with respect to the peak area obtained in the chromatogram by the external standard method.

Category Carbostyryl antibiotic

Storage Preserve in tightly closed containers, protected from light.

Preparation (1) Ciprofloxacin Hydrochloride Capsules
(2) Ciprofloxacin Hydrochloride Eye Drops
(3) Ciprofloxacin Hydrochloride Tablets

Ciprofloxacin Hydrochloride Capsules

Ciprofloxacin Hydrochloride Capsules contain not less than 90.0% and not more than 110.0% of the labelled amount of ciprofloxacin (C₁₇H₁₈FN₃O₃).

Description Capsules containing white to almost white granules or powder.

Identification (1) To a quantity of the contents of the capsules equivalent to about 0.1 g of ciprofloxacin add 20 ml of water, shake for 5 minutes to dissolve ciprofloxacin, filter, using the successive filtrate as a test solution. Dissolve a quantity of ciprofloxacin hydrochloride CRS in water to produce a reference solution of 5 mg of ciprofloxacin per ml. Carry out the method for thin-layer chromatography (Appendix V B), using silica gel G as the coating substance and a mixture of dichloromethane-methanol-concentrated ammonia solution-acetonitrile (4 : 4 : 2 : 1) as the mobile phase. Apply separately to the plate 1 µl each of the two solutions. Before developing, put the plate in ammonia for about 15 minutes. After developing and removal of the plate, dry it in air, examine under ultraviolet light (254 nm). The colour and position of the principal spot in the chromatogram obtained with the test solution correspond to the principal spot obtained with the reference solution.

(2) The retention time of principal peak of the substance being examined in the chromatogram obtained in the Assay is identical with that of ciprofloxacin CRS.

(3) To a quantity of the contents add water, shake and filter. The filtrate yields the reactions characteristic of chlorides (Appendix III).

Test (1) or (2) may be used alternative.

Dissolution Carry out the dissolution test (Appendix X C, method 2), using 900 ml of 0.1 mol/L hydrochloric acid solution as the dissolution medium, adjust the rotational speed of the paddle to 50 rpm. Withdraw 10 ml of the

solution after exactly 30 minutes and filter. Dilute 2 ml of the successive filtrate, accurately measured, with 0.1 mol/L hydrochloric acid solution to 100 ml and mix well. Measure the absorbance of the solution at 277 nm (Appendix IV A). Calculate the dissolution of $C_{17}H_{18}FN_3O_3$ from each capsule, taking 1278 as the value of A (1%, 1 cm). Not less than 80% of the labelled amount is dissolved.

Other requirements Comply with the general requirements for capsules (Appendix I E).

Assay Weigh accurately a quantity of the mixed contents obtained in the test for Weight variation of contents equivalent to 25 mg of ciprofloxacin to a 50 ml volumetric flask, add a quantity of mobile phase, shake thoroughly to dissolve ciprofloxacin hydrochloride, dilute to the volume, mix well and filter. Carry out the Assay described under Ciprofloxacin Hydrochloride, using the successive filtrate.

Category As described under Ciprofloxacin Hydrochloride.

Strength calculated as Ciprofloxacin ($C_{17}H_{18}FN_3O_3$) 0.25 g

Storage Preserve in tightly closed containers, protected from light.

Ciprofloxacin Hydrochloride Eye Drops

Ciprofloxacin Hydrochloride Eye Drops contain not less than 90.0% and not more than 110.0% of the labelled amount of ciprofloxacin ($C_{17}H_{18}FN_3O_3$).

Description A colourless to slightly yellow, clear solution.

Identification (1) Dissolve separately a quantity of the substance being examined and ciprofloxacin CRS in water to produce two solutions of about 3 mg of ciprofloxacin per ml as a test solution and a reference solution respectively. Carry out the method for thin-layer chromatography (Appendix V B), using silica gel G as the coating substance and a mixture of dichloromethane-methanol-concentrated ammonia solution-acetonitrile (4 : 4 : 2 : 1) as the mobile phase. Apply separately to the plate 1 μ l each of the two solutions. Before developing, put the plate in ammoniac for about 15 minutes. After developing and removal of the plate, dry it in air, examine under ultraviolet light (254 nm). The colour and position of the principal spot in the chromatogram obtained with the test solution correspond to the principal spot obtained with the reference solution.

(2) The retention time of principal peak of the substance being examined in the chromatogram obtained in the Assay is identical with that of ciprofloxacin CRS.

(3) Yield the reactions characteristic of chlorides (Appendix III).

pH value 4.0-5.0 (Appendix VI H).

Other requirements Comply with the general requirements for eye preparations (Appendix I G).

Assay Measure accurately 4 ml equivalent to about 12 mg of ciprofloxacin, to a 25 ml volumetric flask, dilute with mobile phase to volume, mix well. Carry out the Assay described under Ciprofloxacin Hydrochloride, using the resulting solution.

Category As described under Ciprofloxacin Hydrochloride.

Strength calculated as ciprofloxacin ($C_{17}H_{18}FN_3O_3$) (1) 5 ml : 15 mg (2) 8 ml : 24 mg

Storage Preserve in tightly closed containers, stored in a cool place and protected from light.

Ciprofloxacin Hydrochloride Tablets

Ciprofloxacin Hydrochloride Tablets contain not less than 90.0% and not more than 110.0% of the labelled amount of ciprofloxacin ($C_{17}H_{18}FN_3O_3$).

Description White or almost white tablets or film coated tablets with white to slightly yellow core.

Identification (1) To a quantity of the powdered tablets equivalent to about 0.1 g of ciprofloxacin add 20 ml of water, shake thoroughly for 5 minutes to dissolve ciprofloxacin, filter, using the successive filtrate as the test solution. Dissolve a quantity of ciprofloxacin hydrochloride CRS in water to produce a reference solution of 5 mg of ciprofloxacin per ml. Carry out the method for thin-layer chromatography (Appendix V B), using silica gel G as the coating substance and a mixture of dichloromethane-methanol-concentrated ammonia solution-acetonitrile (4 : 4 : 2 : 1) as the mobile phase. Apply separately to the plate 1 μ l each of the two solutions. Before developing, put the plate in ammoniac air for about 15 minutes. After developing and removal of the plate, dry it in air and examine under ultraviolet light (254 nm). The colour and position of the principal spot in the chromatogram obtained with the test solution correspond to the principal spot obtained with the reference solution.

(2) The retention time of principal peak of the substance being examined in the chromatogram obtained in the Assay is identical with that of ciprofloxacin CRS.

(3) To a quantity of the powdered tablets add water, shake thoroughly and filter, the filtrate yields the reactions characteristic of chlorides (Appendix III). Test (1) or (2) may be used alternative.

Dissolution Carry out the dissolution test (Appendix X C, method 2), using 900 ml of 0.1 mol/L hydrochloric acid solution as the dissolution medium, adjust the rotational speed of the paddle to 50 rpm. Withdraw 10 ml of the solution after exactly 30 minutes and filter. Dilute 2 ml of the successive filtrate, accurately measured, with 0.1 mol/L hydrochloric acid solution to 100 ml and mix well. Measure the absorbance of the resulting solution at 277 nm (Appendix IV A). Calculate the dissolution of $C_{17}H_{18}FN_3O_3$ from each tablet, taking 1278 as the value of A (1%, 1 cm). Not less than 80% of the labelled amount is dissolved.

Other requirements Comply with the general requirements for tablets (Appendix I A).

Assay Weigh accurately and powder 10 tablets. Weigh accurately a quantity of the powder equivalent to about 25 mg of ciprofloxacin to a 50 ml volumetric flask, add a quantity of water, shake thoroughly to dissolve, mix well and filter. Carry out the Assay described under Ciprofloxacin Hydrochloride, using the successive filtrate.

Category As described under Ciprofloxacin Hydrochloride.

Strength calculated as ciprofloxacin ($C_{17}H_{18}FN_3O_3$) 0.25 g

Storage Preserve in tightly closed containers, protected from light.

Ciprofloxacin Lactate and Sodium Chloride Injection

Ciprofloxacin Lactate and Sodium Chloride Injection is Ciprofloxacin in sterile Water for

Injection, sodium chloride prepared with the aid of Lactic Acid, or is a sterile solution of ciprofloxacin lactate and sodium chloride in Water. It contains not less than 90.0% and not more than 110.0% of the labelled amount of ciprofloxacin ($C_{17}H_{18}FN_3O_3$).

Description A clear, colourless or almost colourless liquid.

Identification (1) The retention time of principal peak of the substance being examined in the chromatogram obtained in the Assay is identical with that of ciprofloxacin CRS.

(2) The light absorption of a solution of 5 µg per ml in hydrochloric acid solution (9→1000) exhibits a maximum at 277 nm (Appendix IV A).

(3) Measure 50 ml, heat in a water bath to dryness, to the residue add 2.5 ml of hydrochloric acid solution (9→1000), stir to dissolve the residue, filter, the filtrate yields the reaction characteristic of lactate salts (Appendix III).

(4) Yields the reactions characteristic of sodium salts and chlorides (Appendix III).

pH value 3.5-4.5 (Appendix VI H).

Absorbance The absorbance at 430 nm (Appendix IV A) is not more than 0.03.

Related substances Dissolve a quantity of the substance being examined in mobile phase to produce solutions of 0.5 mg per ml (solution 1) and 5 µg per ml (solution 2). Carry out the method described under Ciprofloxacin. Each peak area other than the principal peak is not greater than 0.5 times the area of the principal peak in the chromatogram obtained with solution (2) (0.5%). The sum of the areas of all peaks other than the principal peak is not greater than the area of the principal peak in the chromatogram obtained with solution (2) (1.0%).

Particular matter Complies with the test for particular matter (Appendix IX D), using one container.

Heavy metals Evaporate 20 ml of the substance being examined to dryness, carry out the limit test for heavy metals (Appendix VIII H, method 2), using the residue. not more than 0.0001%.

Chloride Measure accurately 10 ml, add 40 ml of water, 5 ml of dextrin solution (1→50), 0.1 g of calcium carbonate and 5-8 drops of fluorescein IS, mix well, titrate with silver nitrate (0.1 mol/L) VS until the colour of the opalescent solution changes from yellow green to slightly red. The volume of silver nitrate (0.1 mol/L) VS consumed is not less than 14.6 ml and not more than 16.2 ml.

Pyrogens Complies with the test for pyrogens, (Appendix XI D), using 12 mg of ciprofloxacin per kg of rabbit's weight.

Other requirements Complies with the general requirements for injections (Appendix I B).

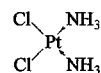
Assay Carry out the Assay described under Ciprofloxacin, using a solution of 0.5 mg of ciprofloxacin per ml in mobile phase.

Category As described under Ciprofloxacin.

Strength calculated as ciprofloxacin
(1) 100 ml : 0.1 g (2) 100 ml : 0.2 g
(3) 250 ml : 0.25 g.

Storage Preserve in well closed containers, protected from light.

Cisplatin



$Cl_2H_6N_2Pt$ 300.05

[15663-27-1]

Cisplatin is (Z) -diaminedichloroplatinum. It contains not less than 99.0% of $Cl_2H_6N_2Pt$.

Description A brilliant yellow to orange-yellow crystalline powder; odourless.

Freely soluble in dimethylsulfoxide; sparingly soluble in dimethylformamide; slightly soluble in water; insoluble in ethanol.

Identification (1) To about 5 mg add 1 ml of sulfuric acid, a greyish-green colour is produced.

(2) Heat a mixture of about 5 mg and a small amount of thiourea with water, a yellow colour is produced.

(3) The absorption spectrum of a solution of about 1 mg in 1 ml of sodium chloride physiological solution exhibits a maximum at 301 nm and a minimum at 247 nm (Appendix IV A).

(4) The infrared absorption spectrum (Appendix IV C) is concordant with the reference spectrum of cisplatin (Appendix XVI).

Clarity of solution A solution of 20 mg in 20 ml of normal saline is clear.

Acidity The solution obtained in the test for Clarity of solution, pH 5.0-7.0 (Appendix VI H).

Related substances Protect from light throughout the procedure.

Carry out the method for thin-layer chromatography (Appendix V B), using microcrystalline cellulose (activated one hour at 105°C) as the coating substance and a mixture of dimethylformamide-acetone (90 : 10) as the mobile phase. Apply separately to the plate 5 µl each of two solutions in dimethylformamide containing (1) 20 mg per ml and (2) 0.40 mg per ml of the substance being examined. After developing and removal of the plate, dry it in air, spray with stannous chloride solution [dissolve 5 g of stannous chloride in 100 ml of 1 mol/L hydrochloric acid solution, filter if necessary] and examine after one hour. The R_f values of any secondary spots in the chromatogram is not greater than the principal spot obtained with solution (1) and the secondary spots with R_f values greater than the principal spot obtained with solution (1) is not more intense in colour than the principal spot obtained with solution (2).

Chlorine content Carry out the method of oxygen flask combustion (Appendix VII C), using 30 mg, accurately weighed, of the substance being examined and 20 ml of sodium hydroxide TS as the absorbing liquid. Shake vigorously for a few minutes after the combustion is complete. Rinse the stopper and platinum wire with a small amount of water. Combine the washings with the absorbing liquid, add 1 drop of bromophenol blue IS, acidify with dilute nitric acid until the solution turns to yellow and then add 1 ml of dilute nitric acid, 20 ml of ethanol and 5 drops of ethanolic solution of 1% diphenylcarbazone. Titrate with mercuric nitrate (0.025 mol/L) VS, shake vigorously towards the end of titration and continue to titrate until the solution turns to rose red. Perform a blank determination and make any necessary correction. Each ml of mercuric nitrate (0.025 mol/L) VS is equivalent to 1.773 mg of Cl. The chlorine content is 23.0%-24.3%.

Loss on drying When dried to constant weight at 105°C, loses not more than 0.5% of its weight, using about 0.1 g (Appendix VIII L).

Assay Carry out the method for Residue on ignition (Appendix VIII N), using about 0.1 g, accurately weighed, without the addition of sulfuric acid. Ignite it at 400°C to constant weight. Calculate the content of $\text{PtCl}_2 (\text{NH}_3)_2$ by multiplying the weight of residue by 1.538.

Category Antineoplastic.

Storage Preserve in tightly closed containers, protected from light.

Preparation Cisplatin for Injection

Cisplatin for Injection

Cisplatin for Injection is the sterile powder of Cisplatin. It contains not less than 90.0% and not more than 110.0% of the labelled amount of cisplatin $\text{Cl}_2\text{H}_6\text{N}_2\text{Pt}$, calculated on the basis of average weight of content.

Description A brilliant yellow to orange yellow, crystalline powder.

Identification Complies with the tests for Identification described under Cisplatin.

Acidity, Related substances, Loss on drying Complies with the requirements described under Cisplatin.

Sterility Complies with the test for sterility (Appendix XI H), using a solution of 2 mg in 1 ml of sterile sodium chloride injection.

Pyrogens Complies with the test for pyrogens (Appendix XI D), using a solution of 1 mg in 1 ml of sterile sodium chloride injection, inject 2 ml per kg of the rabbit's weight.

Other requirements Complies with the general requirements for injections (Appendix I B).

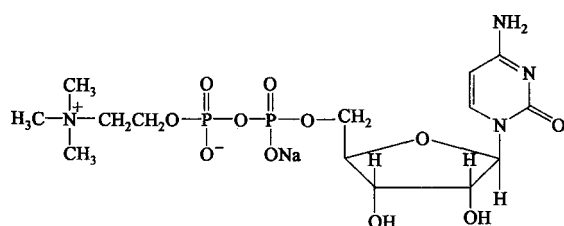
Assay Carry out the Assay described under Cisplatin, using about 0.1 g, accurately weighed, of the contents obtained in the test for Weight variation.

Category As described under Cisplatin.

Strength (1) 10 mg (2) 20 mg (3) 30 mg

Storage Preserve in well closed containers, protected from light.

Citicoline Sodium



$\text{C}_{14}\text{H}_{25}\text{N}_4\text{NaO}_{11}\text{P}_2$ 510.31

[33818-15-4]

Citicoline sodium is cytidine-5'-diphosphocholine monosodium salt. It contains not less than 98.0% of

$\text{C}_{14}\text{H}_{25}\text{N}_4\text{NaO}_{11}\text{P}_2$, calculated on the dried basis.

Description White crystals or a crystalline powder; odourless; freely soluble in water, insoluble in ethanol, acetone and chloroform.

Identification (1) To about 1 mg add 3 ml of dilute hydrochloric acid and 1 ml of bromine TS, heat on a water bath for 30 minutes, and remove the bromine with ventilation. Add 0.2 ml of 3,5-dihydroxy-methylbenzene ethanol solution (1→10) and 3 ml of ammonium ferric sulfate solution in hydrochloric acid (1→1000), and heat on a water bath for 20 minutes, a green colour is produced.

(2) The retention time of the principal peak in the substance being examined in the chromatogram obtained in the Assay is identical with that of the principal peak in the chromatogram of the reference solution.

(3) The infrared absorption spectrum (Appendix IV C) is concordant with the reference spectrum of citicoline sodium (Appendix XVI).

(4) Yields the flame reaction characteristic of sodium salts (Appendix III).

Acidity or alkalinity Dissolve 0.5 g in 10 ml of water, pH 6.0-7.5 (Appendix VI H).

Clarity and colour of solution A solution of 1.0 g in 8 ml of water is clear and colourless.

Related substances Dissolve a quantity in water to produce a solution of 2.5 mg per ml (test solution). Transfer 1 ml of the test solution measured accurately into a 100 ml volumetric flask, dilute with water to volume and mix well (reference solution 1). Transfer 2 ml of the reference solution 1 measured accurately into a 10 ml volumetric flask, dilute with water to volume and mix well (reference solution 2). Dissolve a quantity of 5'-cytidylate CRS, accurately weighed, in water to produce a solution of 7.5 µg per ml (reference solution). Carry out the method as described under Assay. Inject 10 µl of reference solution 1 into the column. Adjust the attenuation so that the principal peak height in the chromatogram is 20%-25% full scale of the chart. Inject separately 10 µl each of test solution, reference solution 1, reference solution 2 and reference solution into the column. In the chromatogram obtained with the test solution, the area of the peak corresponding to 5'-cytidylate is not greater than that of the principal peak of reference solution (0.3%), the area of any single peak other than the principal peak is not greater than that of the principal peak of reference solution 2 (0.2%), and the sum of the areas of all peaks other than the principal peak are not greater than that of the principal peak of reference solution 1.

Methanol and acetone Dissolve a quantity of ethanol, accurately measured, in water to produce a solution of 75 µg per ml (internal standard solution). To an accurately weighed quantity of methanol and acetone add internal standard solution to produce a solution of 150 µg each of methanol and acetone per ml (reference solution). Dissolve 0.5 g, accurately weighed, in the internal standard solution in a 10 ml volumetric flask, dilute with the internal standard solution to volume and mix well (test solution). Carry out the method for residual solvent (Appendix VIII P, method 3), using a packed column or a capillary column with appropriate polarity. Maintain the column temperature at 130°C. The contents of methanol and acetone comply with the requirement.

Chloride Carry out the limit test for chloride (Appendix VIII A), using 0.10 g. Any opalescence produced is not more pronounced than that of a reference solution using 5.0 ml of sodium chloride standard solution (0.05%).

Ammonium Carry out the limit test for ammonium (Appendix VIII K), using 0.20 g. Any colour produced is not more intense than that of a reference solution using 10.0 ml of ammonium chloride standard solution (0.05%).

Iron Carry out the limit test for iron (Appendix VIII G), using 0.20 g. Any colour produced is not more intense than that of a reference solution using 2.0 ml of iron standard solution (0.01%).

Phosphate Dissolve 0.10 g in 10 ml of water, add 1 ml of ammonium molybdate solution (Dissolve 1 g of ammonium molybdate in 40 ml of 0.5 mol/L sulphuric acid) and 0.5 ml of 1-amino-2-naphthol -4-sulfonic acid TS, react for 5 minutes. Any colour produced is not more intense than that of a reference solution using 5.0 ml of phosphorous standard solution (Transfer 0.286 g of potassium dihydrogen phosphate to 1000 ml volumetric flask, previously dried to constant weight at 105°C, dissolve in water and dilute to volume, mix well. Before use, transfer 10 ml, accurately measured, to 100 ml volumetric flask, dilute to volume with water and mix well, equivalent to 20 µg of PO₄ per ml) (0.1%).

Loss on drying When dried in vacuum over phosphorous pentoxide at 100°C for 5 hours, loses not more than 6.0% of its weight (Appendix VIII L).

Heavy metals Carry out the limit test for heavy metals, using 2.0 g (Appendix VIII H, method 1); not more than 0.002%.

Arsenic Carry out the limit test for arsenic, using 2.0 g (Appendix VIII J, method 1); not more than 0.0001%.

Bacterial endotoxin Carry out the limit test for bacterial endotoxin (Appendix XI E); less than 0.6 EU per mg.

Sterility Complies with the test for sterility (for injection) (Appendix XI H).

Assay Carry out the method for high performance liquid chromatography (Appendix V D), using a column packed with octadecylsilane bonded silica gel and phosphate BS [mix equal volumes of 0.1 mol/L potassium dihydrogen phosphate and tetrabutylammonium phosphate solution (adjust pH of 0.01 mol/L tetrabutylammonium hydroxide to 4.5 with phosphorous acid)]-methanol (95 : 5) as the mobile phase. Detection wavelength is 276 nm. Dissolve a quantity of 5'-cytidylate in water to produce a solution of 0.25 mg per ml, mix well a same amount with citicoline sodium reference solution and inject 20 µl into the column. The resolution factor between peaks of citicoline sodium and 5'-cytidylate complies with related requirements.

Procedure Dissolve an accurately weighed quantity in water to produce a solution of 0.25 mg per ml. Dissolve an accurately weighed quantity of citicoline sodium CRS in water to produce a solution of 0.25 mg per ml as reference solution. Inject 10 µl of each into the column, calculate the content of C₁₄H₂₅N₄NaO₁₁P₂ by the external standard method.

Category Medicines for improving cell metabolism.

Storage Preserve in tightly closed containers, protected from light.

Preparation (1) Citicoline sodium injection
(2) Citicoline sodium for injection

Citicoline Sodium for Injection

Citicoline sodium for injection is a sterile lyophilized powder. It contains not less than 90.0% and not more than 110.0% of the labelled

amount of citicoline sodium (C₁₄H₂₅N₄NaO₁₁P₂).

Description White or almost white loose pieces.

Identification A quantity complies with tests for Identification (1), (2) and (4) described under Citicoline Sodium.

Clarity and colour of solution Dissolve in 5 ml of water, the resulting solution is clear and colourless.

Acidity or alkalinity, Loss on drying and Related substances Comply with tests described under Citicoline Sodium.

Bacterial endotoxin A quantity complies with the test for Bacterial endotoxin described under Citicoline Sodium.

Other requirements Complies with the general requirements for injection (Appendix I B).

Assay To a quantity accurately add water to produce a solution of 0.25 mg per ml, carry out the method for Assay under Citicoline Sodium.

Category As described under Citicoline Sodium.

Strength 0.25 g

Storage preserve in well closed containers, protected from light.

Citicoline Sodium Injection

Citicoline sodium injection is a sterile solution of Citicoline sodium in Water for Injection. It contains not less than 90.0% and not more than 110.0% of the labelled amount of citicoline sodium (C₁₄H₂₅N₄NaO₁₁P₂).

Description A clear and colourless liquid.

Identification A quantity complies with tests for Identification (1), (2) and (4) described under Citicoline Sodium.

Acidity or alkalinity pH 6.0-8.0 (Appendix VI H).

Related substances Dissolve a quantity in water to produce a solution of 2.5 mg per ml (test solution). Transfer 1 ml of the test solution measured accurately into a 100 ml volumetric flask, dilute with water to volume and mix well (reference solution 1). Transfer 5 ml of the reference solution 1 measured accurately into a 10 ml volumetric flask, dilute with water to volume and mix well (reference solution 2). Dissolve a quantity of 5'-cytidylate CRS, accurately weighed, in water to produce a solution of 7.5 µg per ml (reference solution). Carry out the method as described under Citicoline Sodium. In the chromatogram obtained with the test solution, the area of the peak corresponding to 5'-cytidylate is not greater than that of the principal peak of reference solution (0.3%), the area of any single peak other than the principal peak is not greater than that of the principal peak of reference solution 2 and the sum of the areas of all peaks other than the principal peak are not greater than that of the principal peak of reference solution 1.

Bacterial endotoxin A quantity complies with the test for Bacterial endotoxin described under Citicoline Sodium.

Other requirements Complies with the general requirements for injection (Appendix I B).

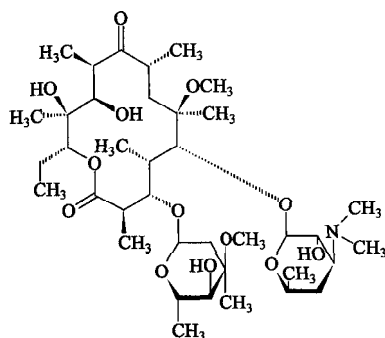
Assay Carry out the method for Assay under Citicoline Sodium.

Category As described under Citicoline Sodium.

Strength 2 ml : 0.25 g

Storage Preserve in well closed containers, protected from light.

Clarithromycin



$C_{38}H_{69}NO_{13}$ 747.96

[81103-11-9]

Clarithromycin is 6-O-methylethrythromycin. It contains not less than 94.0% of $C_{38}H_{69}NO_{13}$, calculated on the anhydrous basis.

Description A white or almost white crystalline powder; odourless; taste, bitter.

Freely soluble in chloroform; soluble in acetone or ethyl acetate; sparingly soluble in methanol or ethanol; insoluble in water.

Specific optical rotation -89° to -95° , in a solution of 10 mg per ml in chloroform (Appendix VI E).

Identification (1) Carry out the method for high performance liquid chromatography as described under Assay. The retention time of the principal peak of the substance being examined in the chromatogram corresponds to that of Clarithromycin CRS.

(2) The infrared absorption spectrum (Appendix IV C) is concordant with the reference spectrum of clarithromycin (Appendix XVI).

Alkalinity A suspension of 2 mg per ml in a mixture of water-methanol (19 : 1), pH 7.5-10.0 (Appendix VI H).

Crystallinity Complies with the test for crystallinity (Appendix IX D).

Related substances Dissolve an accurately weighed quantity in mobile phase to produce a test solution of about 1.0 mg per ml, measure accurately 5 ml to 100 ml volumetric flask, dilute with mobile phase to volume, mix well, as a reference solution. Carry out the method as described under Assay. Inject 20 μ l of the reference solution into the column. Adjust the attenuation so that the principal peak height in the chromatogram is about 40% of full scale of the chart. Inject separately 20 μ l into the column and record the chromatograms for 4 times of the retention time of the principal peak. The area of the individual impurity peak in the chromatogram obtained with the test solution is not greater than 1/2 times (2.5%) the area of the principal peak in the chromatogram obtained with the reference solution. The sum of the area of all impurity peaks in the chromatogram obtained with the test solution is not greater than 1.2 times (6.0%) area of the principal peak in the chromatogram obtained with the reference solution.

Water Dissolve a quantity in 10% imidazole solution in anhydrous methanol, carry out the method for determination of water (Appendix VIII M, method 1 A); not more than 2.0%.

Residue on ignition Not more than 0.3% (Appendix VIII N), using 1.0 g.

Heavy metals Carry out the limit test for heavy metals (Appendix VIII H, method 2), using the residue obtained in the test for Residue on ignition; not more than 0.002%.

Assay Carry out the method for high performance liquid chromatography (Appendix V D), using a column with octadecylsilane bonded silica gel and a mixture of phosphate buffer solution (dissolve 9.11 g potassium dihydrogen phosphate in water, and dilute with water to 1000 ml, add 2 ml of triethylamine, adjust pH to 5.5 with phosphoric acid)-acetonitrile (600 : 400) as the mobile phase. The detection wavelength is 210 nm. The flow rate is 1.0 ml/min. The column temperature is 45°C. The number of the theoretical plates of the column is not less than 3000, calculated with reference to the peak of Clarithromycin. The tailing factor is not more than 2.0. The resolution factor between peaks of Clarithromycin and the impurities complies with the related requirements.

Procedure Dissolve an accurately weighed quantity in mobile phase to produce a test solution of about 0.35 mg per ml. Inject 20 μ l into the column and record the chromatogram. Repeat the operation, using Clarithromycin CRS instead of the substance being examined, calculate the content of $C_{38}H_{69}NO_{13}$ with respect to the peak area obtained in the chromatogram by the external standard method.

Category Macrolide Antibiotic.

Storage Preserve in tightly closed containers, protected from light.

Preparation (1) Clarithromycin Capsules
(2) Clarithromycin Granules
(3) Clarithromycin Tablets

Clarithromycin Capsules

Clarithromycin Capsules contain not less than 90.0% and not more than 110.0% of the labelled amount of clarithromycin ($C_{38}H_{69}NO_{13}$).

Description Capsules containing white or almost white granules or crystalline powder.

Identification The retention time of principal peaks of the substance being examined in the chromatogram obtained in the Assay is identical with that of Clarithromycin CRS.

Related substances Dissolve a quantity of the contents of the capsules equivalent to 1.0 mg of Clarithromycin in 1 ml of mobile phase, centrifuge (3000 rpm) 5 minutes, use the supernatant fluid as a test solution, and carry out the Related Substances described under Clarithromycin. The area of the individual impurity peak in the chromatogram obtained with the test solution is not greater than 7/10 times the area of the principal peak in the chromatogram obtained with the reference solution (3.5%).

Dissolution Carry out the dissolution test (Appendix X C, method 2), using 0.1 mol/L acetate buffer solution (pH 5.0) (0.1 mol/L sodium acetate solution, adjust pH to 5.0 with glacial acetic acid) as the dissolution medium, adjust the rotational speed of the paddle to 50 rpm. Withdraw a quantity of the solution after exactly 30 minutes and filter, dilute the successive filtrate with 0.1 mol/L acetate buffer solution to produce a solution containing 0.15 mg of Clarithromycin per ml as a test solution. Dissolve an accurately weighed quantity of the mixed contents obtained in the test for weight variation of contents equivalent to about the average weight of one capsule in methanol (using 1 ml of methanol for 1 mg of clarithromycin), and dilute with 0.1

mol/L acetate buffer solution to produce a solution of 0.15 mg (for strength 125 mg) of clarithromycin per ml and filter as a reference solution. Measure accurately 4 ml each of the two solutions separately to two 25 ml volume flasks, add 8 ml of 0.1 mol/L acetate buffer solution, mix well, then add 10 ml of sulfuric acid solution (75→100), mix well, allow it to stand for 30 minutes, cool, dilute with 0.1 mol/L acetate buffer solution to volume, mix well. Measure the absorbance of the resulting solutions at 482 nm (Appendix IV A), calculate the dissolution of $C_{38}H_{69}NO_{13}$ from each tablet. Not less than 80% of the labelled amount is dissolved.

Other requirements Comply with the general requirements for capsules (Appendix I E)

Assay Weigh accurately a quantity of the mixed contents obtained in the test for weight variation of contents equivalent to about 35 mg of Clarithromycin to a 100 ml volumetric flask, dilute with the mobile phase to volume and mix well and filter, use the successive filtrate as a test solution, and carry out the Assay described under Clarithromycin.

Category As described under Clarithromycin.

Strength Calculated as $C_{38}H_{69}NO_{13}$
(1) 0.125 g (2) 0.25 g

Storage Preserve in tightly closed containers, stored in a cool and dry place and protected from light.

Clarithromycin Granules

Clarithromycin Granules contain not less than 90.0% and more than 110.0% of the labeled amount of clarithromycin ($C_{38}H_{69}NO_{13}$).

Description suspension granules; aromatic, taste sweet.

Identification A quantity of powdered granules complies with test (1) for Identification described under Clarithromycin.

Alkalinity A suspension of 2 mg per ml of water, pH 8.0-10.0 (Appendix VI C).

Water Dissolve about 0.2 g in 10% imidazole solution in anhydrous methanol, carry out the method for determination of water (Appendix VIII M, method 1 A); not more than 2.0%.

Other requirement Comply with the general requirement for granules (Appendix I N).

Assay Weigh accurately a quantity of the contents obtained in the test for weight variation of contents, triturate, equivalent to about 0.35 mg of Clarithromycin to a 1 ml volumetric flask, dilute with the mobile phase to volume and mix well and filter, use the successive filtrate as a test solution, and carry out the Assay described under Clarithromycin.

Category As described under Clarithromycin.

Strength Calculated as $C_{38}H_{69}NO_{13}$
(1) 0.05 g (2) 0.1 g (3) 0.125 g
4 . 2 g

Storage Preserve in tightly closed containers, stored in a cool and dry place and protected from light.

Clarithromycin Tablets

Clarithromycin Tablets contain not less than 90.0% and not more than 110.0% of the labelled

amount of clarithromycin ($C_{38}H_{69}NO_{13}$).

Description White or almost white tablets, or sugar coated, or film coated tablets with white or almost white core.

Identification A quality of powdered tablets comply with test (1) for Identification described under Clarithromycin.

Related Substances Dissolve a quantity of powdered tablets equivalent to 1.0 mg of Clarithromycin in 1 ml of mobile phase, centrifuge (3000 rpm) 5 minutes, use the supernatant fluid as a test solution, and carry out the Related Substances described under Clarithromycin. The area of the individual impurity peak in the chromatogram obtained with the test solution is not greater than 7/10 times the area of the principal peak in the chromatogram obtained with the reference solution (3.5%).

Dissolution Carry out the dissolution test (Appendix X C, method 1), using acetate buffer solution (pH5.0) (0.1 mol/L sodium acetate solution, adjust pH to 5.0 with glacial acetic acid) as the dissolution medium, adjust the rotational speed of the basket to 100 rpm. Withdraw a quantity of the solution after exactly 30 minutes and filter, dilute the successive filtrate with 0.1 mol/L acetate buffer solution to produce a solution containing 0.15 mg of Clarithromycin per ml as a test solution. Triturate 10 tablets dissolve an accurately weighed quantity equivalent to about the average weight of one tablet in methanol (using 1 ml of methanol for 1 mg of clarithromycin), dilute with 0.1 mol/L acetate buffer solution to produce a solution containing 0.15 mg of clarithromycin per ml as a reference solution. Measure accurately 4 ml each of the two solutions separately to two 25 ml volume flasks, add accurately 8 ml of 0.1 mol/L acetate buffer solution, mix well, then add 10 ml of sulfuric acid solution (75→100), mix well, allow to stand for 30 minutes, cool, dilute with 0.1 mol/L acetate buffer solution to volume, mix well. Measure the absorbance of the resulting solutions at 482 nm (Appendix IV A), calculate the dissolution of $C_{38}H_{69}NO_{13}$ from each tablet. Not less than 80% of the labeled amount is dissolved.

Other requirements Comply with the general requirements for tablets (Appendix I A).

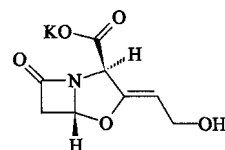
Assay Weigh accurately and triturate 10 tablets, weighed accurately a quantity equivalent to about 35 mg of clarithromycin to a 100 ml volumetric flask, dilute with the mobile phase to volume and mix well and filter, use the successive filtrate as a test solution, and carry out the Assay described under Clarithromycin.

Category As described under Clarithromycin.

Strength Calculated as $C_{38}H_{69}NO_{13}$
(1) 50 mg (2) 0.125 g (3) 0.25 g

Storage Preserve in tightly closed containers, stored in a cool and dry place and protected from light.

Clavulanate Potassium



$C_8H_8KNO_5$ 237.25

[61177-45-5]

Clavulanate Potassium is Potassium (Z)-(2R,5R)-3-(2-hydroxyethylidene)-7-oxo-4-oxo-1-azabi-

cyclo [3.2.0] heptane-2-carboxylate. It contains not less than 75.5% of clavulanic acid ($C_8H_9NO_5$), calculated on the anhydrous basis.

Description A white to slightly yellow crystalline powder; odour, faint; hygroscopic easily. Very soluble in water; freely soluble in methanol; slightly soluble in ethanol and insoluble in ether.

Specific optical rotation $+55^\circ$ to $+60^\circ$, in a solution of 10 mg per ml in water (Appendix VI E).

Identification (1) The retention time of principal peak of clavulanic acid in the substance being examined in the chromatogram obtained in the Assay is identical with that of the principal peak of clavulanic acid CRS in the chromatogram of the reference solution.

(2) The infrared absorption spectrum (Appendix VI C) is concordant with the reference spectrum of clavulanic acid (Appendix XVI).

(3) Yields the reaction characteristic of potassium salts (Appendix III).

Acidity or alkalinity To 200 mg add 20 ml of water, pH 6.0-8.0. (Appendix VI H).

Related substances Dissolve an accurately weighed quantity of the substance being examined in mobile phase A to produce a solution of 8 mg of clavulanic acid per ml as the test solution; measure accurately a quantity of the above solution and dilute with mobile phase A to produce a solution of 0.08 mg clavulanic acid per ml as the reference solution. Carry out the method for high performance liquid chromatography (Appendix V D), using a column packed with octadecylsilane bonded silica gel. 0.05 mol/L sodium dihydrogen phosphate solution (adjust the pH with phosphonic acid to 4.0) as mobile phase A; the mobile phase B is 0.05 mol/L sodium dihydrogen phosphate solution (adjust the pH with phosphoric acid to 4.0)-methanol (50 : 50). The flow rate is 1.0 ml per min and elute linear gradient, the column temperature is 40°C , detection wavelength is 230 nm. Inject $20\ \mu\text{l}$ of the system suitability solution (dissolve in mobile phase A to produce a solution of 0.1 mg amoxicillin and 0.1 mg clavulanic acid per ml separately) and record the chromatography. The relative retention time of clavulanic acid is about 1.0 and the relative retention time of amoxicillin is about 2.5. The resolution factor between the peaks of amoxicillin and clavulanic acid is not less than 13. Inject $20\ \mu\text{l}$ of the reference solution into the column, adjust the attenuation so that the principal peak height in the chromatogram is 20%-25% of full scale of the chart. Immediately inject separately $20\ \mu\text{l}$ each of the test solution and the reference solution and record the chromatogram. In the chromatogram obtained with the test solution; the area of any peak, apart from the principal peak, is not greater than the area of the principal peak in the chromatogram obtained with the reference solution (1 percent); the sum of the areas of all the peaks, apart from the principal peak, is not greater than twice the area of the principal peak in the chromatogram obtained with the reference solution (2 percent). Disregard any peak with an area less than 0.05 times that of the principal peak in the chromatogram obtained with the reference solution.

Time(min)	Mobile phase A(%)	Mobile phase B(%)
0	100	0
4	100	0
15	50	50
18	50	50
24	100	0
39	100	0

Water Not more than 1.5% (Appendix VIII M, method 1 A).

Heavy metals Dissolved 0.2 g in 23 ml of water, add 2 ml of acetate BS (pH 3.5). Carry out the limit test for heavy metals (Appendix VIII H, method 1), not more than 0.002%.

Sterility Complies with the test for sterility (Appendix XI H, membrane filtration method), dissolving each portion in not less than 500 ml of 0.9% sterile sodium chloride solution (used for injection).

Bacterial endotoxin Carry out the test for bacterial endotoxin (Appendix XI E): not more than 0.03 EU per mg of clavulanic acid.

Assay Carry out the method for high performance liquid chromatography (Appendix V D), using a column packed with octadecylsilane bonded silica gel and a mixture of phosphate buffer solution (dissolve 7.8 g of sodium dihydrogen phosphate in 900 ml of water, adjust the pH value to 4.4 with dilute phosphoric acid or 10 mol/L sodium hydroxide solution, dilute with water to 1000 ml)-methanol (95 : 5) as the mobile phase. The flow rate is 1.0 ml per min. Detection wavelength is 220 nm. Dissolve an accurately weighed quantity of amoxicillin CRS and clavulanic acid CRS in water to produce a mixture solution of 0.45 mg of amoxicillin and 0.25 mg of clavulanic acid per ml. Inject $20\ \mu\text{l}$ of the solution into the column and record the chromatogram. The resolution factor between the peaks of amoxicillin and clavulanic acid is not less than 3.5.

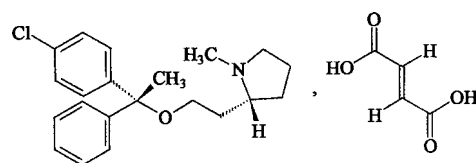
Procedure Dissolve about 25 mg, accurately weighed, in water in a 100 ml volumetric flask and dilute to volume, mix well, immediately inject $20\ \mu\text{l}$ of the resulting solution into the column and record the chromatogram. Dissolve an accurately weighed quantity of clavulanic acid CRS, equivalent to about 25 mg clavulanic acid in water in a 100 ml volumetric flask and dilute to volume, mix well. Repeat the operation, calculate the content of $C_8H_9NO_5$ with respect to the peak area obtained in the chromatogram by the external standard method.

Category β -lactamase inhibitor

Storage Preserve in hermetically sealed containers, stored in a dry place below -20°C .

Preparation (1) Amoxicillin Sodium and Clavulanate Potassium for Injection
(2) Amoxicillin Sodium and Clavulanate Potassium Tablets

Clemastine Fumarate



$C_{21}H_{26}ClNO \cdot C_4H_4O_4$ 459.97

[14976-57-9]

Clemastine Fumarate is (+)-2-[(2R)-2-[2-[(R)-p-chloro- α -methyl- α -phenylbenzyl]-oxy]ethyl]-1-methylpyrrolidine fumarate. It contains not less than 98.0% and not more than 102.0% of $C_{21}H_{26}ClNO \cdot C_4H_4O_4$, calculated on the dried basis.

Description A white or almost white crystalline powder; odourless; taste, slightly bitter. Slightly soluble in methanol; very slightly soluble in water or chloroform.

Specific optical rotation $+15^{\circ}$ to $+18^{\circ}$, in a solution of about 10 mg per ml in methanol (Appendix VI E).

Identification (1) Dissolve a quantity in warm ethanol solution (8→10) to produce a solution containing about 20 mg of clemastine fumarate per ml as test solution. Prepare reference solution of about 5 mg per ml of clemastine fumarate CRS. Carry out the method for thin-layer chromatography (Appendix V B), using silica gel GF₂₅₄ as the coating substance and a mixture of isopropyl ether-formic acid-water (70 : 25 : 5) as the mobile phase. Apply separately to the same plate 5 μ l each of above two solutions, after developing and removal of the plate, dry it in air and heat at 100°C for 30 minutes, allow to cool and examine under ultraviolet light (254 nm). The colour and position of the principal spot in the chromatogram obtained with the test solution correspond to the principal spot obtained with the reference solution.

(2). The infrared absorption spectrum (Appendix IV C) is concordant with the reference spectrum of clemastine fumarate (Appendix XVI).

Clarity and colour of methanol solution A solution of 100 mg in 10.0 ml of methanol is clear and colourless; any opalescence produced is not more pronounced than that of reference suspension [mix 2.5 ml of 0.00002 mol/L sodium chloride solution, 2.5 ml of water, 5.0 ml of 2.5 mol/L nitric acid solution and 1.0 ml of 0.1 mol/L silver nitrate solution, and use the solution within 5 minutes]; any colour produced is not more intense than that of reference solution [mix 1 volume of the solution of ferric chloride standard solution-cupric sulfate standard solution-cobaltic chloride standard solution-water (6 : 1 : 1 : 42) with 3 volumes of water].

Acidity To 1.0 g add 10 ml of water to produce a suspension; pH 3.2-4.2 (Appendix VI H).

Loss on drying When dried to constant weight at 105°C, loses not more than 0.5% of its weight (Appendix VIII L).

Heavy metals Carry out the limit test for heavy metals (Appendix VIII H, method 2), using 1.0 g; not more than 0.002%.

Related substances Carry out the method for thin-layer chromatography (Appendix V B), using silica gel G as the coating substance and a mixture of chloroform-methanol-concentrated ammonia solution (90 : 10 : 1) as the mobile phase. Apply separately to the plate 5 μ l of each of the following solutions in chloroform-methanol (1 : 1) containing (1) 20 mg per ml of the substance being examined, (2) 0.10 mg per ml, (3) 0.06 mg per ml and (4) 0.02 mg per ml; solution (2), (3) and (4) are prepared by diluting solution (1). After developing and removal of the plate, dry it in air, spray with dilute potassium iodobismuthate TS and hydrogen peroxide TS. The sum of any secondary spots obtained with solution (1) is not more than 1.0%; any spot, other than the principal spot obtained with solution (1) is not more intense than the principal spot obtained with solution (2).

Assay Dissolve about 0.35 g, accurately weighed, in 60 ml of glacial acetic acid, carry out the method for potentiometric titration (Appendix VII A), titrate with perchloric acid (0.1 mol/L) VS. Perform a blank determination and make any necessary correction. Each ml of perchloric acid (0.1 mol/L) VS is equivalent to 46.00 mg of $C_{21}H_{26}ClNO \cdot C_4H_4O_4$.

Category Antihistaminic.

Storage Preserve in tightly closed containers, protected from light.

Preparation Clemastine Fumarate Tablets

Clemastine Fumarate Tablets

Clemastine Fumarate Tablets contain not less than 90.0% and not more than 110.0% of the labelled amount of clemastine fumarate ($C_{21}H_{26}ClNO \cdot C_4H_4O_4$).

Description White tablets.

Identification Shake a quantity of the powdered tablets equivalent to about 2.5 mg of clemastine fumarate with 10 ml of a mixture of chloroform-methanol (1 : 1) in a conical flask with stopper for 20 minutes, filter and wash the residue twice with chloroform-methanol (1 : 1), each of 5 ml, combine the filtrate and washings, evaporate to dryness in vacuum and dissolve the residue in 1 ml of a mixture of chloroform-methanol (1:1) as the test solution. Prepare the reference solution of about 2.5 mg per ml of clemastine fumarate CRS in chloroform-methanol (1 : 1). Carry out the method for thin-layer chromatography (Appendix V B), using silica gel G as the coating substance and a mixture of chloroform-methanol-concentrated ammonia solution (90:10:1) as the mobile phase. Apply separately to the same plate 5 μ l each of above two solutions. After developing and removal of the plate, dry it in air, spray with dilute potassium iodobismuthate TS and hydrogen peroxide TS. The colour and position of the principal spot in the chromatogram obtained with the test solution corresponds to the principal spot obtained with the reference solution.

Content uniformity Comply with the requirements (Appendix X E). Triturate 1 tablet with 5 ml of methanol and transfer to a 50 ml volumetric flask, shake for 10 minutes to dissolve clemastine fumarate, dilute with acetic acid solution (dilute 333 ml of dilute glacial acetic acid with water to 1000 ml) to volume, shake for 20 minutes and filter. Carry out the procedure as described under Assay using the successive filtrate, calculate the content of $C_{21}H_{26}ClNO \cdot C_4H_4O_4$.

Dissolution Carry out the dissolution test (Appendix X C, method 2), using 500 ml of citrate BS (pH 4.0) [dissolve 20.0 g of citric acid monohydrate in 1000 ml of water, add 22.0 ml of sodium hydroxide solution (3→10) and 8.8 ml of hydrochloric acid, dilute with water to produce 2000 ml, adjust to pH 4.0] as the dissolution medium, adjust the rotational speed of the paddle to 50 rpm. Withdraw 50 ml of the solution after exactly 30 minutes and use it as test solution. Weigh accurately a quantity of clemastine fumarate CRS, dilute with the dissolution medium to produce a solution with same concentration as that of the test solution, using as reference solution. Transfer the test solution and 50 ml of each of the solvent and the reference solution in separators, respectively. Add 10 ml of methyl orange solution (dilute 20 ml of methyl orange IS with water to produce 100 ml) and 20 ml of chloroform to each separator, shake for 10 minutes, allow to stand, separate the chloroform layers and filter. Measure the absorbance of the filtrates at 420 nm (Appendix IV B). Calculate the dissolution of $C_{21}H_{26}ClNO \cdot C_4H_4O_4$ from each tablet; not less than 75% of the labelled amount is dissolved.

Other requirements Comply with the general requirements for tablets (Appendix I A).

Assay *Reference preparation* Dissolve about 27 mg of

clemastine fumarate CRS, accurately weighed, in a 100 ml volumetric flask with 10 ml of methanol, dilute with acetic acid solution (dilute 333 ml of dilute acetic acid with water to 1000 ml) to volume. Measure accurately 10 ml to a 100 ml volumetric flask, dilute with a mixture of acetic acid and methanol (dilute 100 ml of methanol with the acetic acid solution to produce 1000 ml) to volume and mix well.

Test preparation Weigh and powder 20 tablets. Transfer an accurately weighed quantity of the powder, equivalent to about 1.35 mg of clemastine fumarate, to a 50 ml volumetric flask, add 5 ml of methanol and shake for 10 minutes until clemastine fumarate is dissolved, dilute with the above acetic acid solution to volume, shake for 30 minutes and filter, using the successive filtrate as the test solution.

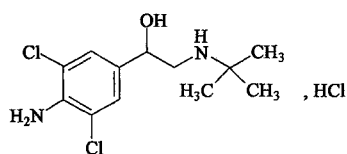
Procedure Measure accurately 15 ml of each of the two solutions and the mixture of acetic acid and methanol to separators, respectively. Add 25 ml of bromocresol purple solution (dissolve 100 mg of bromocresol purple in 1000 ml of above mentioned acetic acid solution) and 50 ml of chloroform, shake for 15 minutes, allow to stand, separate the chloroform layers and filter. Measure the absorbance of the filtrates at 406 nm (Appendix IV A). Calculate the content of $C_{21}H_{26}ClNO \cdot C_4H_4O_4$.

Category As described under Clemastine Fumarate.

Strength 1.34 mg

Storage Preserve in tightly closed containers, protected from light.

Clenbuterol Hydrochloride



$C_{12}H_{18}Cl_2N_2O \cdot HCl$ 313.65

Clenbuterol Hydrochloride is 4-amino- α -(tert-butylamino) methyl]-3,5-dichlorobenzyl alcohol hydrochloride. It contains not less than 98.5% of $C_{12}H_{18}Cl_2N_2O \cdot HCl$, calculated on the dried basis.

Description A white or almost white crystalline powder; odourless; taste, sparingly bitter. Soluble in water or ethanol; slightly soluble in chloroform or acetone; insoluble in ether.

Melting range 172-176°C, with decomposition (Appendix VI C).

Identification (1) Dissolve about 20 mg in 1 ml of water, add 5 ml of a saturated solution of potassium permanganate in 20% sulfuric acid solution. Shake for a few minutes then shake with a quantity of oxalic acid to decolorize and clarify the solution. Add 5 ml of water and a solution of dinitrophenyl hydrazine in perchloric acid, prepared by dissolving 1.2 g of 2,4-dinitrophenyl hydrazine in 50 ml of 30% perchloric acid, a precipitate is produced.

(2) The light absorption of a 30 μ g per ml solution in 0.1 mol/L hydrochloric acid solution exhibits maxima at 243 nm and 296 nm (Appendix IV A).

(3) The infrared absorption spectrum (Appendix IV C) is

concordant with the reference spectrum of clenbuterol hydrochloride (Appendix XVI).

(4) Yields the reaction characteristic of aromatic primary amines (Appendix III).

(5) The aqueous solution yields the reactions characteristic of chlorides (Appendix III).

Total chlorine Weigh accurately about 20 mg, carry out the method for oxygen flask combustion (Appendix VII C), using 10 ml of 0.4% sodium hydroxide solution as the absorbing liquid. When the fume is absorbed completely, shake for 5 minutes, allow to stand for a few minutes. Wash the stopper and platinum wire with a quantity of water. Add 5 ml of dilute nitric acid, 15 ml of silver nitrate (0.02 mol/L) VS, measured accurately, and 3 ml of nitrobenzene, shake vigorously. Then add 2 ml of ferric ammonium sulfate IS and titrate with ammonium thiocyanate (0.02 mol/L) VS. Perform a blank determination and make any necessary correction. Each ml of silver nitrate (0.02 mol/L) VS is equivalent to 0.709 mg of chlorine. It contains not less than 32.5% and not more than 35.0% of total chlorine.

Loss on drying When dried to constant weight at 105°C, loses not more than 0.5% of its weight (Appendix VIII L).

Residue on ignition Not more than 0.1% (Appendix VIII N), using 1.0 g.

Heavy metals Carry out the limit test for heavy metals (Appendix VIII H, method 2), using the residue obtained in the test for Residue on ignition; not more than 0.001%.

Assay Dissolve about 0.25 g, weighed accurately, in 25 ml of hydrochloric acid solution (1→2) in a 100 ml beaker, add 25 ml of water, carry out the method for potentiometric titration (Appendix VII A), titrate with sodium nitrite (0.05 mol/L) VS. Perform a blank determination and make any necessary correction. Each ml of sodium nitrite (0.05 mol/L) VS is equivalent to 15.68 mg of $C_{12}H_{18}Cl_2N_2O \cdot HCl$.

Category β_2 -adrenergic receptor activator.

Storage Preserve in well closed containers, protected from light.

Preparation Clenbuterol Hydrochloride Suppositories

Clenbuterol Hydrochloride Suppositories

Clenbuterol Hydrochloride Suppositories contain not less than 85.0% and not more than 115.0% of the labelled amount of clenbuterol hydrochloride ($C_{12}H_{18}Cl_2N_2O \cdot HCl$).

Description White or creamy white suppositories.

Identification Melt the fatty base of five suppositories with 10 ml of water by warming on a water bath, stir, cool and filter. The filtrate complies with the tests (4) and (5) for Identification described under Clenbuterol Hydrochloride.

Other requirements Comply with the general requirements for suppositories (Appendix I D).

Assay Weigh accurately, 20 suppositories, cut to chips. Dissolve an accurately weighed quantity equivalent to about 0.36 mg of clenbuterol hydrochloride in 20 ml of warm chloroform in a separator. Extract with 20, 15 and 10 ml of hydrochloric acid solution (9→100) successively. Combine the acid extracts in a 50 ml volumetric flask, dilute to volume with hydrochloric acid

solution (9→100), mix well. Filter and collect the successive filtrate as the test solution. Dissolve an accurately weighed quantity of clenbuterol hydrochloride CRS, in hydrochloric acid solution (9→100) to produce a solution of 7.2 µg per ml as the reference solution.

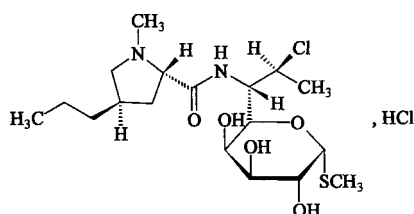
Transfer 15 ml each of the two solutions, accurately measured, to a 25 ml separator separately, add 5 ml of hydrochloric acid solution (9→100) and 1 ml of 0.1% sodium nitrite solution, mix well. Allow to stand for 3 minutes, add 1 ml of 0.5% ammonium sulfamate solution and mix well. Shake for 10 minutes, add 1 ml of 0.1% *N*-naphthylethylenediamine dihydrochloride solution and mix well. Allow to stand for 10 minutes, dilute to volume with hydrochloric acid solution (9→100) and mix well. Measure the absorbance (Appendix IV A) at 500 nm and calculate the content of $C_{12}H_{18}Cl_2N_2O \cdot HCl$.

Category As described under Clenbuterol Hydrochloride.

Strength 60 µg

Storage Preserve in tightly closed containers, protected from light and stored at a temperature below 30°C.

Clindamycin Hydrochloride



$C_{18}H_{33}ClN_2O_5S \cdot HCl$ 461.44 [21462-39-5]

Clindamycin Hydrochloride is (2*S*-trans) -methyl 7-chloro-6,7,8-trideoxy-6- [[(1-methyl-4-propyl-2-pyrrolidinyl) carbonyl] amino] -1-thio-L-threo-α-D-galactooctopyranoside monohydrochloride. It contains not less than 83.0% of $C_{18}H_{33}ClN_2O_5S$, calculated on the anhydrous basis.

Description A white crystalline powder; odourless.

Very soluble in water; freely soluble in methanol or pyridine; slightly soluble in ethanol; practically insoluble in acetone or chloroform.

Specific optical rotation +135°–+150°, in a solution of 40 mg per ml in water (Appendix VI E).

Identification (1) The retention time of the principal peak of the substance being examined in the chromatogram obtained in the Assay is identical with the principal peak in the chromatogram of clindamycin hydrochloride CRS.

(2) The infrared absorption spectrum (Appendix IV C) is concordant with the reference spectrum of clindamycin hydrochloride (Appendix XVI). If there are some difference found in the spectrum in the region of 1680–1050 cm^{-1} , repeat the operation by dissolving a quantity of the substance being examined in the small quantity of methanol, evaporating to dryness on a water bath and drying the residue under vacuum. The infrared absorption spectrum of the residue (Appendix IV C) is concordant with the reference spectrum of clindamycin hydrochloride (Appendix XVI).

(3) The aqueous solution yields reactions characteristic of chlorides (Appendix III).

Crystallinity Complies with the requirements of the test for crystallinity (Appendix IX D).

Acidity pH 3.0–5.5 (Appendix VI H), in a solution of 100 mg per ml in water.

Related substance Carry out the method described under Assay. Dissolve a quantity of the substance being examined, accurately weighed, in the mobile phase to produce solutions of 10.0 mg per ml (solution 1) and 0.4 mg per ml (solution 2). Inject 10 µl of the solution (2) into the column, adjust the attenuation so that the principal peak height in the chromatogram is 20% of the full scale of the chart. Inject 10 µl of the above solutions into the column and record the chromatogram for 1.5 times the retention time of the principal peak. The sum of all secondary peak areas in the chromatogram obtained with solution (1) is not greater than twice area of the principal peak in the chromatogram obtained with solution (2) (8.0%).

Water Not more than 6.0% (Appendix VIII M, method 1 A).

Residue on ignition Not more than 0.5% (Appendix VIII N).

Assay Carry out the method for high performance liquid chromatography (Appendix V D), using a column packed with octadecylsilane bonded silica gel and a mixture of ammonium dihydrogen phosphate solution (dissolve 2.88 g $y \quad g \quad p \quad p$ adjust to pH 3.0 with 80% phosphoric acid)-methanol (210 : 300) as the mobile phase. Detection wavelength is 214 nm and the number of theoretical plates of the column is not less than 1300, calculated with reference to the peak of clindamycin.

Procedure Dissolve about 50 mg, accurately weighed, in the mobile phase and dilute to volume in a 100 ml volumetric flask, mix well. Inject 10 µl of the solution into the column. Repeat the operation, using clindamycin hydrochloride CRS instead of the substance being examined, calculate the content of $C_{18}H_{33}ClN_2O_5S$.

Category Antibiotic.

Storage Preserve in tightly closed containers.

Preparation Clindamycin Hydrochloride Capsules

Clindamycin Hydrochloride Capsules

Clindamycin Hydrochloride Capsules contain not less than 90.0% and not more than 110.0% of the labelled amount of clindamycin hydrochloride, calculated with reference to clindamycin ($C_{18}H_{33}ClN_2O_5S$).

Identification To a quantity of the contents equivalent to about 0.2 g of clindamycin add 10 ml of methanol and allow to stand for 20 minutes, filter, and evaporate the filtrate to dryness on a water bath. The residue complies with the tests (1) and (3) for Identification described under Clindamycin Hydrochloride.

Water Not more than 7.0% (Appendix VIII M, method 1 A), using the mixed contents.

Other requirements Comply with the general requirements for capsules (Appendix I E).

Assay Carry out the Assay described under Clindamycin Hydrochloride using an accurately weighed quantity (equivalent to about 50 mg of clindamycin) of the mixed contents obtained from the test for Weight variation of

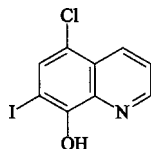
contents.

Category As described under Clindamycin Hydrochloride.

Strength Calculated as $C_{18}H_{13}ClN_2O_5S$
(1) 0.075 g (2) 0.15 g

Storage Preserve in tightly closed containers.

Clioquinol



C_9H_5ClINO 305.50 [130-26-7]
Clioquinol is 5-chloro-7-iodo-8-quinolinol. It contains not less than 38.0% and not more than 42.0% of iodine (I), and contains not less than 11.0% and not more than 12.4% of chloride (Cl), calculated on the dried basis.

Description A yellowish-white to brownish-yellow loose powder; odour, characteristic; tasteless; deteriorates easily on exposure to light. Slightly soluble in boiling dehydrated ethanol; insoluble in water or ethanol; soluble in hot glacial acetic acid.

Melting range 173-179°C, with decomposition (Appendix VI C).

Identification (1) To 0.5 g, add 5 ml of sulfuric acid and heat; violet vapours are evolved, which turn the moistened starch iodide TP bluish violet.

(2) To a solution in boiling ethanol, add a drop of ferric chloride TS; a deep green colour is produced.

(3) The infrared absorption spectrum (Appendix IV C) is concordant with the reference spectrum of clioquinol (Appendix XVI).

Free iodine and iodide Shake 1.0 g with 20 ml of water for 30 seconds, allow to stand for 5 minutes, and filter. To 10 ml of the successive filtrate add 1 ml of 1 mol/L sulfuric acid, then add 2 ml of chloroform, and shake; no violet colour appears in the chloroform layer (free iodine). To the mixture add 5 ml of 1 mol/L sulfuric acid and 1 ml of potassium dichromate TS, and shake for 15 seconds; the colour in the chloroform layer is not more intense than that of reference solution [dilute 2.0 ml of potassium iodide solution (1→6000) with water to 10 ml, add 6 ml of 1 mol/L sulfuric acid, 1 ml of potassium dichromate TS, and 2 ml of chloroform, and shake for 15 seconds] (0.05% of iodide).

Loss on drying When dried in vacuum over phosphorous pentoxide to constant weight, loses not more than 0.5% of its weight (Appendix VIII L).

Residue on ignition Not more than 0.3% (Appendix VIII N).

Assay Weigh accurately about 40 mg, carry out the method for oxygen flask combustion (Appendix VII C), using a mixture of 100 ml of sodium hydroxide solution (1→100) and 2 ml of saturated sulfur dioxide solution as the absorbing liquid. When the fume produced is completely absorbed, transfer to a beaker, wash the combustion flask with four 5 ml quantities of a buffer (dissolve 13.61 g of sodium acetate with 50 ml of water, and add 6 ml of glacial acetic acid, dilute with water to 100 ml, mix well). Combine the washings and the absorbing liquid in the beaker, add 25 ml

of acetone and a small quantity of polyethylene glycol 4000. Carry out the method for potentiometric titration (Appendix VII A), titrate with silver nitrate (0.1 mol/L) VS, using silver-glass electrode. The first potential jump corresponds to the consuming volume for iodine, and the second for chloride. Each ml of silver nitrate (0.1 mol/L) VS is equivalent to 12.69 mg of I, or 3.545 mg of Cl.

Category Antiamebiasis.

Storage Preserve in tightly closed containers, and protected from light.

Preparation Clioquinol cream

Clioquinol Cream

Clioquinol Cream contains not less than 90.0% and not more than 110.0% of the labelled amount of clioquinol (C_9H_5ClINO).

Description A yellow cream.

Identification (1) To a quantity of the cream, equivalent to about 0.1 g of clioquinol, add anhydrous sodium carbonate. Heat gently until it is charred, cool, add a quantity of water and stir, filter (add a quantity of active carbon to remove the colour of the solution if it is deeply coloured). Acidify the filtrate with nitric acid and then add silver nitrate TS; a pale yellow precipitate is produced. Filter, add ammonia TS to the precipitate to make alkaline, heat to gently boiling, cool and filter. Acidify the filtrate with nitric acid; a white precipitate is produced.

(2) To a quantity of cream add methyl cellosolve, stir to dissolve, add 1 drop of ferric chloride TS; a dark green colour is produced.

Other requirements Complies with the general requirements for ointment (Appendix I F).

Assay Weigh accurately a quantity equivalent to about 20 mg of clioquinol into a beaker, add 60 ml of methyl cellosolve-water (4 : 1), warm on a water bath to dissolve clioquinol, then cool in a water bath for 30 minutes. Filter, wash the beaker and filter with methyl cellosolve-water (4 : 1), transfer the combined filtrate and washings to a 100 ml amber-coloured volumetric flask, allow to warm to room temperature and dilute to volume with methyl cellosolve-water (4 : 1), mix well as the test solution. Dissolve a quantity, accurately weighed, of clioquinol CRS in methyl cellosolve-water (4 : 1) to produce a solution of 0.2 mg per ml as the reference solution.

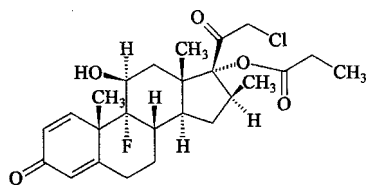
Transfer 10 ml of each of the two solutions, accurately measured, to two separate 25 ml volumetric flasks, add 10 ml of methyl cellosolve and 2 ml of ferric chloride TS (to 0.5 g of ferric chloride add 0.1 ml of hydrochloric acid and then dilute with methyl cellosolve to 100 ml, mix well), dilute to volume with methyl cellosolve, mix well. Measure the absorbance at 650 nm (Appendix IV A). Calculate the content of C_9H_5ClINO .

Category As described under clioquinol.

Strength 10 g : 0.3 g

Storage Preserve in tightly closed containers, stored in a cool place.

Clobetasol Propionate



$C_{25}H_{32}ClFO_5$ 466.99

[15122-46-7]

Clobetasol Propionate is 21-chloro-9 α -fluoro-11 β , 17 α -dihydroxy-16 α -methylpregna-1,4-diene-17-propionate. It contains not less than 97.0% and not more than 103.0% of $C_{25}H_{32}ClFO_5$, calculate on the dried basis.

Description An almost white to pale yellow crystalline powder.

Freely soluble in chloroform; soluble in ethyl acetate; sparingly soluble in methanol and ethanol; insoluble in water.

Melting range 190 - 197°C, with deposition (Appendix VI C).

Specific optical rotation +99° to 105°, in a solution of about 10 mg per ml in dioxane (Appendix VI E).

Identification (1) To a quantity, add 1 ml of ethanol, and mix well. Heat on water bath for 2 minutes, add 2 ml of nitric acid (1→2), mix well and add a few drops of silver nitrate, a white precipitate is produced.

(2) The infrared spectrum of clobetasol propionate (Appendix IV C) is concordant with the reference spectrum of clobetasol propionate (Appendix XVI).

(3) Yields the reaction characteristic of organic fluorides (Appendix III).

Related substances Carry out the method as described under Assay. Dissolve a quantity of the substance being examined in mobile phase to produce a solution of about 0.5 mg per ml (1). Measure accurately 2 ml of solution (1) into a 100 ml volumetric flask and dilute with mobile phase to the volume, shake well as solution (2). Inject 20 μ l of solution (2) into the column. Adjust the attenuation so that the principal peak height in the chromatogram is 10%-20% of full scale of the chart. Then inject separately 20 μ l of solution (1) and (2) into the column, and record the chromatogram for 2.5 times the retention time of the principal peak. If there are any other peaks in the chromatogram of solution (1), the area of any one is not greater than 1/2 of area of the principal peak of solution (2), the sum of the areas of all peaks other than the principal peak is not greater than 1.25 times area of the principal peak area of solution (2).

Loss on drying When dried to constant weight as 105°C, loses not more than 0.5% of its weight (Appendix VIII L).

Assay Carry out the method for high performance liquid chromatography (Appendix V D), using a column packed with octadecylsilane bonded silica gel and a mixture of 0.05 mol/L sodium dihydrogen phosphate solution (adjust pH 2.5 with 85% phosphoric acid solution)-acetonitrile-methanol (425 : 475 : 100) as the mobile phase. Detection wavelength is 240 nm and the number of theoretical plates of the column is not less than 5000, calculated with reference to the peak of clobetasol propionate. The resolution factor between the peaks of clobetasol propionate and internal standard complies with the related requirements.

Internal standard solution Dissolve a quantity of beclomethasone dipropionate in methanol to produce a solution of 0.40 mg per ml.

Procedure Dissolve a quantity of clobetasol propionate CRS, accurately weighed, in methanol to produce a solution of 0.20 mg per ml. Dilute 5 ml of the solution and the internal standard solution, both measured accurately, with methanol to volume in a 25 ml volumetric flask, mix well. Inject 10 μ l of the resulting solution into the column. Repeat the operation, using the substance being examined instead of clobetasol propionate CRS, calculate the content of $C_{25}H_{32}ClFO_5$ with respect to the peak area obtained in the chromatogram by the internal standard method.

Category Corticosteroid.

Storage Preserve in tightly closed containers, protected from light.

Preparation clobetasol propionate cream

Clobetasol Propionate Cream

Clobetasol Propionate Cream contains not less than 90.0% and not more than 110.0% of the labelled amount of clobetasol Propionate ($C_{25}H_{32}ClFO_5$).

Description A white cream.

Identification The retention time of principal peak of the substance being examined in the chromatogram obtained in the Assay is identical with that of clobetasol propionate CRS.

Other requirements Comply with the general requirements for ointments, Cream and Pastes (Appendix I F).

Assay Carry out the method for high performance liquid chromatography (Appendix V D). Using a column packed with octadecylsilane bonded silica gel and a mixture of methanol-water (65 : 35) as the mobile phase. Detection wavelength is 240 nm. The number of theoretical plates of the column is not less than 2000, calculated with reference to the peak of clobetasol propionate. The resolution factor between the peaks of clobetasol propionate and internal standard substance complies with the related requirements.

Internal standard solution To a quantity of fluocinonide, add methanol to produce a solution of 0.15 mg per ml.

Procedure Weigh accurately a quantity equivalent to about 1 mg of Clobetasol Propionate into a 50 ml volumetric flask, add accurately measured 5 ml of internal standard solution. Add 30 ml of methanol, heat in water bath at 60°C for 5 minutes, with intermittent stirring until the cream is completely dissolved and cool, dilute to volume with methanol, mix well, cool in ice-water bath more than 2 hours, filter immediately and cool to room temperature. Inject 20 μ l of the successive filtrate into the column, record the chromatogram. Dissolve an accurately weighed quantity of clobetasol propionate CRS in methanol and dilute to volume to produce a solution of 0.2 mg per ml. Measure accurately each 5 ml of this solution and 5 ml of the internal standard solution, into 50 ml volumetric flask, dilute to the volume with methanol, mix well. Inject 20 μ l into the column, record the chromatogram. Calculate the contents of $C_{25}H_{32}ClFO_5$ with respect to the peak area obtained in the chromatogram by the internal standard method.

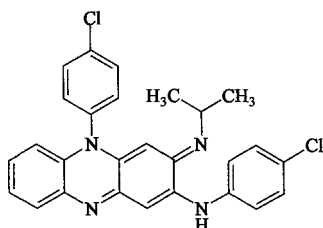
Category As described under Clobetasol Propionate.

Strength (1) 10 g : 2 mg (2) 10 g : 5 mg

Storage Preserve in tightly closed containers, stored in a

cool place.

Clofazimine



$C_{27}H_{22}Cl_2N_4$ 473.40

[2030-63-9]

Clofazimine is 3-(4-chloroanilino)-10-(4-chlorophenyl)-2,10-dihydro-2-(isopropylimino) phenazine. It contains not less than 98.0% of $C_{27}H_{22}Cl_2N_4$, calculated on dried base.

Description A brownish-red to reddish-brown crystal or crystalline powder; odourless.

Soluble in chloroform; slightly soluble in ether; very slightly soluble in ethanol; insoluble in water.

Melting range 211-215°C, with decomposition (Appendix VI C).

Identification (1) Dissolve 10 mg in 5 ml of sulfuric acid with shaking; a purplish red colour is produced and a cherry red colour develops after diluting with water.

(2) Dissolve about 15 mg in 100 ml of chloroform and shake well, to 5 ml of the resulting solution add 10 ml of 0.1 mol/L hydrochloric acid methanolic solution and dilute to 100 ml with sufficient chloroform. The light absorption of the resulting solution exhibits two maxima at 289 nm and 491 nm.

(3) The infrared absorption spectrum (Appendix IV C), is concordant with the reference spectrum of clofazimine (Appendix XVI).

Chloride Dissolve about 0.40 g in 5 ml of glacial acetic acid and add a quantity of water and 1 ml of nitric acid, dilute to 50 ml with sufficient water, and filter if necessary. Divide the filtrate into two equal portions. To one portion add 1 ml of silver nitrate TS, allow to stand for 15 minutes. Filter, if turbid to produce a clear solution and dilute to about 40 ml, add 2 ml of sodium chloride standard solution and make up to 50 ml with sufficient water, shake well, allow to stand in dark for 5 minutes, use the resulting solution as the reference solution. To another portion add water to about 40 ml, add 1 ml of silver nitrate TS and dilute to 50 ml with water, shake well, allow to stand in dark for 5 minutes. Any opalescence produced is not more pronounced than that of the reference solution.

Related substance Carry out the method for thin-layer chromatography (Appendix V B), using silica gel GF₂₅₄ as the coating substance and a mixture of dichloromethane-propanol (85 : 4) as the mobile phase. Apply separately to the same plate (previously saturated with 3% ammonia solution for 30 minutes) 5 µl of each of the following solutions. For solution of about 20 mg per ml of chloroform as test solution; dilute a quantity accurately measured with chloroform to solution of 0.16 mg and 0.10 mg per ml respectively as reference solution (1) and (2). After developing and removal of plate, allow it to dry in air. Develop once again, allow it to dry in air and examine under ultraviolet light (254 nm). Spray the plate with 50% sulphuric acid solution and examine again in daylight. In the

chromatogram obtained with the test solution, any secondary spot is not more intense than the principal spot in the chromatogram obtained with solution (1) and not more than two spots are more intense than the spot in the chromatogram obtained with solution (2).

Loss on drying When dried to constant weight at 105°C, loses not more than 0.5% of its weight (Appendix VIII L).

Residue on ignition Not more than 0.1% (Appendix VIII N), using 1.0 g.

Iron sal. Dissolve the residue obtained in the test for Residue on ignition in 2.5 ml of dilute hydrochloric acid and 10 ml of water and filter. Wash the crucible with water in portions and mix the filtrate and the washings, dilute to 25 ml, same weight. Dilute 10 ml of the resulting solution to 35 ml with water and carry out the test for Iron (Appendix VIII G). Any colour produced is not more intense than that produced in the same manner with 2.0 ml of standard iron solution (0.005%).

Assay Dissolve about 0.3 g accurately weighed, in 25 ml of glacial acetic acid and carry out the method for potentiometric titration (Appendix VII A), titrate with perchloric acid (0.1 mol/L) VS. Perform a blank titration and make any necessary correction. Each ml of perchloric acid (0.1 mol/L) VS is equivalent to 47.34 mg of $C_{27}H_{22}Cl_2N_4$.

Category Antileprosy.

Storage Preserve in tightly closed container, store in dry place and protected from light.

Preparation Clofazimine Soft Capsules

Clofazimine Soft Capsules

Clofazimine Soft Capsules contain not less than 90.0% and not more than 110.0% of labelled amount of clofazimine ($C_{27}H_{22}Cl_2N_4$).

Description Soft capsules containing brownish red to reddish brown oily liquid.

Identification (1) Comply with the test (1) for Identification described under Clofazimine using a quantity of the contents of about 10 mg of clofazimine.

(2) Dissolve a quantity of contents in chloroform to produce a solution containing 75 µg per ml of clofazimine, shake well and filter. To a quantity of 5 ml of successive filtrate add 0.1 mol/L methanolic hydrochloric acid solution and dilute to 50 ml with chloroform, shake well. The light absorption of the resulting solution exhibits a maximum at 491 nm (Appendix IV A).

Other requirements Comply with the general requirements for capsules (Appendix I E).

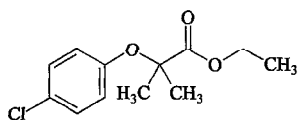
Assay Mix the contents obtained in the test for weight variation of contents and the washings of chloroform for shell of capsules, dilute to 100 ml with chloroform and shake well. Transfer 25 ml, measured accurately, to a 50 ml beaker and carry out the method for potentiometric titration (Appendix VII A), titrate with perchloric acid (0.1 mol/L) VS. Perform a blank determination and make any necessary correction. Each ml of perchloric acid (0.1 mol/L) VS is equivalent to 47.34 mg of $C_{27}H_{22}Cl_2N_4$.

Category As described under Clofazimine.

Strength 50 mg

Storage Preserve in tightly closed containers, stored in a dry place and protected from light.

Clofibrate



$C_{12}H_{15}ClO_3$ 242.70

[637-07-0]

Clofibrate is ethyl 2-(4-chlorophenoxy)-2-methylpropionate. It contains not less than 98.5% of $C_{12}H_{15}ClO_3$.

Description A clear, colourless to pale yellow, oily liquid; odour, characteristic; taste, acid then sweet; darkened gradually on exposure to light.

Freely soluble in ethanol, acetone, chloroform, ether or petroleum ether; practically insoluble in water.

Relative density 1.138-1.144 (Appendix VI A).

Refractive index 1.500-1.505 (Appendix VI F).

Identification (1) To a few drops of an ethereal solution (1→10) add a few drops of a saturated solution of hydroxylamine hydrochloride in ethanol and 2-3 drops of a saturated solution of potassium hydroxide in ethanol, heat for about 2 minutes on a water bath, and cool. Acidify with dilute hydrochloric acid, add 1-2 drops of 1% ferric chloride solution; a violet colour is produced.

(2) The light absorption of a solution of 0.10 mg per ml in dehydrated ethanol exhibits maxima at 280 nm and 288 nm; and the light absorption of a solution of 10 µg per ml in dehydrated ethanol exhibits a maximum at 226 nm (Appendix IV A).

(3) The infrared absorption spectrum (Appendix IV C) is concordant with the reference spectrum of clofibrate (Appendix XVI).

Acidity Dissolve 2.0 g in 10 ml of neutralized ethanol (to phenolphthalein IS) add a few drops of phenolphthalein IS and 0.15 ml of sodium hydroxide (0.1 mol/L) VS; a pink colour is produced.

p-Chlorophenol Extract 10.0 g with 20 ml of sodium hydroxide TS, wash the lower layer with 5 ml of water, add the washings to the aqueous layer and reserve the organic layer for the test for volatile related substances. Extract the combined aqueous layer and washings with two quantities of 5 ml of chloroform, discard the chloroform and acidify the aqueous layer with dilute hydrochloric acid. Extract with two quantities of 5 ml of chloroform, combine the organic extracts and dilute to 10 ml with chloroform as the test preparation, 0.0025% *p*-chlorophenol solution in chloroform is used as the reference preparation. Carry out the method for gas chromatography (Appendix V E), using a glass column of 2 m long coated with 5% dimethyl silicone fluid (SE-30), maintain the column temperature at 160°C, the content of *p*-chlorophenol is not more than 0.0025%.

Volatile related substance Dry a quantity of the organic layer obtained in the test for *p*-chlorophenol with anhydrous sodium sulfate and use it as the test preparation. Carry out the method for gas chromatography (Appendix V E), under the same conditions described above. Dilute a quantity of the test preparation with chloroform to produce a solution of 10 mg per ml and inject a quantity into the column, adjust the sensitivity of the detector or the amount injected so that the system is suitable for the test, then inject a quantity of the original test preparation into the column, record the

chromatogram for twice the retention time of the principal peak. The sum of secondary peak areas is not greater than 0.5% of the total peak area.

Assay Dissolve 2 g, accurately weighed, in 10 ml of ethanol neutralized to phenolphthalein IS in a conical flask, add a few drops of phenolphthalein IS. Add sodium hydroxide (0.1 mol/L) VS dropwise until a pink colour is produced. Add 20 ml of sodium hydroxide (0.5 mol/L) VS, accurately measured, heat under reflux for 1 hour until the oil drops disappear completely, and cool. Rinse the condenser with freshly boiled and cooled water, combine the washings to the conical flask, add a few drops of phenolphthalein IS, titrate with hydrochloric acid (0.5 mol/L) VS. Perform a blank determination and make any necessary correction. Each ml of sodium hydroxide (0.5 mol/L) VS is equivalent to 121.4 mg of $C_{12}H_{15}ClO_3$.

Category Serum cholesterol and triglycerides lowering agent.

Storage Preserve in tightly closed containers, protected from light.

Preparation Clofibrate Capsules

Clofibrate Capsules

Clofibrate Capsules contain not less than 90.0% and not more than 110.0% of the labelled amount of clofibrate ($C_{12}H_{15}ClO_3$).

Identification Comply with tests (1) and (2) for Identification described under Clofibrate using the contents of the capsules.

Acidity, p-Chlorophenol, Volatile related substance Comply with requirements described under Clofibrate.

Other requirements Comply with the general requirements for capsules (Appendix I E).

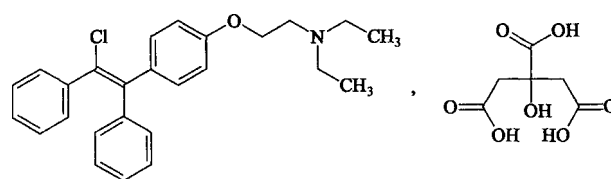
Assay Carry out the Assay described under Clofibrate, using about 2 g of the mixed contents of the capsules, accurately weighed, obtained in the test for weight variation. Each ml of sodium hydroxide (0.5 mol/L) VS is equivalents to 121.4 mg of $C_{12}H_{15}ClO_3$.

Category As described under Clofibrate.

Strength (1) 0.25 g (2) 0.5 g

Storage Preserve in tightly closed containers, protected from light.

Clomifene Citrate



$C_{26}H_{28}ClNO \cdot C_6H_8O_7$ 598.09

[50-41-9]

Clomifene Citrate is a mixture of the *E*- and *Z*-isomers of 2-[4-(2-chloro-1,2-diphenylethenyl)-phenoxy]-*N*, *N*-diethylethanamine citrate. It contains not less than 97.0% of $C_{26}H_{28}ClNO \cdot$

$C_6H_8O_7$, calculated on the anhydrous basis.

Description A white or almost white powder; odourless. Sparingly soluble in ethanol; slightly soluble in water and chloroform; practically insoluble in ether.

Identification (1) The light absorption of a 25 μ g per ml solution in hydrochloric solution (9 \rightarrow 1000) exhibits maxima at 233 nm and 290 nm; the absorbance is about 0.76-0.82 and 0.42-0.46, respectively (Appendix IV A).

(2) The infrared absorption spectrum (Appendix IV C) is concordant with the reference spectrum of clomifene citrate (Appendix XVI).

(3) Yields the reactions characteristic of citrates (Appendix III).

Related substances Carry out the method for high performance liquid chromatography (Appendix V D), using silica gel as the coating substance and a mixture of *n*-hexane-chloroform-triethylamine (80 : 20 : 0.1) as the mobile phase. The amount of triethylamine may be varied to meet system suitability requirements. Detection wavelength is 302 nm. Number of theoretical plates of the column is not less than 3000, calculated with reference to the peak of *Z*-clomifene; the resolution factor between the peaks of *E*- and *Z*-clomifene is not less than 1.3. Dissolve a quantity of the substance being examined in the mobile phase to produce a solution of 0.1 mg per ml, inject 20 μ l into the column. In the chromatogram obtained, a peak due to *E*-clomifene precedes the peak due to *Z*-clomifene. Measure the peak areas of *E*- and *Z*-clomifene, the percentage of *Z*-clomifene is 30%-50%, calculated by normalization method.

Clarity and colour of methanol solution Dissolve 1.0 g in 30 ml of methanol, the solution is clear; any colour produced is not more intense than that of reference solution Y_1 (Appendix IX A, method 1).

Water Not more than 1.0% (Appendix VIII M, method 1 A).

Heavy metals Carry out the limit test for heavy metals, using 1 g (Appendix VIII H, method 2); not more than 0.001%.

Assay Dissolve about 0.5 g, accurately weighed, in 20 ml of glacial acetic acid and add 1 drop of crystal violet IS. Titrate with perchloric acid (0.1 mol/L) VS until a bluish-green colour is produced. Perform a blank determination and make any necessary correction. Each ml of perchloric acid (0.1 mol/L) VS is equivalent to 59.81 mg of $C_{26}H_{28}ClNO \cdot C_6H_8O_7$.

Category Ovulation inducer.

Storage Preserve in tightly closed containers, protected from light.

Preparation (1) Clomifene Citrate Capsules
(2) Clomifene Citrate Tablets

Clomifene Citrate Capsules

Clomifene Citrate Capsules contain not less than 90.0% and not more than 110.0% of the labelled amount of clomifene citrate ($C_{26}H_{28}ClNO \cdot C_6H_8O_7$).

Identification (1) The light absorption of the solution obtained in the Assay exhibits maxima at 233 nm and 290 nm (Appendix IV A).

(2) The contents of the capsules yield the reactions characteristic of citrates (Appendix III).

Other requirements Comply with the general requirements for capsules (Appendix I E).

Assay Transfer an accurately weighed quantity of the mixed contents obtained in the test for weight variation equivalent to about 50 mg of clomifene citrate to a 100 ml volumetric flask. Add a quantity of hydrochloric acid solution (9 \rightarrow 1000), shake for 30 minutes to dissolve clomifene citrate, then dilute with the same solvent to volume, mix well. Filter, measure accurately 5 ml of the successive filtrate to another 100 ml volumetric flask, add hydrochloric acid solution (9 \rightarrow 1000) to volume and mix well. Dissolve a quantity of clomifene citrate CRS, accurately weighed, in hydrochloric acid solution (9 \rightarrow 1000) to produce a solution of 25 μ g per ml. Measure the absorbance of two solutions at 290 nm (Appendix IV A). Calculate the content of $C_{26}H_{28}ClNO \cdot C_6H_8O_7$.

Category As described under Clomifene Citrate.

Strength 50 mg

Storage Preserve in tightly closed containers, protected from light.

Clomifene Citrate Tablets

Clomifene Citrate Tablets contain not less than 90.0% and not more than 110.0% of the labelled amount of clomifene citrate ($C_{26}H_{28}ClNO \cdot C_6H_8O_7$).

Description White tablets.

Identification (1) The light absorption of the solution obtained in the Assay exhibits maxima at 233 nm and 290 nm (Appendix IV A).

(2) It yields the reactions characteristic of citrates (Appendix III).

Dissolution Carry out the dissolution test (Appendix X C, method 1), using 1000 ml hydrochloric acid solution (9 \rightarrow 1000) as the dissolution medium. Adjust the rotational speed of the basket to 100 rpm. After 45 minutes, filter a quantity of the solution, measure accurately 5 ml of the successive filtrate to a 10 ml volumetric flask, dilute with above acid solution to volume, mix well, using it as the test solution. Prepare the reference solution of clomifene citrate with a quantity of clomifene citrate CRS as described in the Assay. Measure the absorbances and calculate the dissolution of $C_{26}H_{28}ClNO \cdot C_6H_8O_7$ from each tablet, not less than 70% of the labelled amount is dissolved.

Other requirements Comply with the general requirements for tablets (Appendix III).

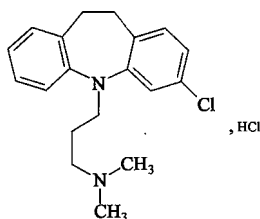
Assay Weigh and powder 10 tablets. Weigh accurately a quantity of the powder equivalent to 50 mg of clomifene citrate, carry out the Assay as described under Clomifene Citrate Capsules, beginning at the words "to a 100 ml volumetric flask...", calculate the content of $C_{26}H_{28}ClNO \cdot C_6H_8O_7$.

Category As described under Clomifene Citrate.

Strength 50 mg

Storage Preserve in tightly closed containers, protected from light.

Clomipramine Hydrochloride



$C_{19}H_{23}ClN_2 \cdot HCl$ 351.32

[17321-77-6]

Clomipramine Hydrochloride is *N*, *N*-dimethyl-10,11-dihydro-3-chloro-5*H*-dibenz[*b,f*]azepine-5-propanamine hydrochloride. It contains not less than 98.5% of $C_{19}H_{23}ClN_2 \cdot HCl$, calculated on the dried basis.

Description A white to pale yellow crystalline powder; odourless; taste, bitter; gradually changes to yellow on exposure to light.

Very soluble in glacial acetic acid or chloroform; freely soluble in water or ethanol; slightly soluble in acetone; practically insoluble in ether.

Melting range 190-196°C (Appendix VI C), melting range is not more than 2°C.

Specific absorbance Measure the absorbance of a solution of 20 µg per ml in hydrochloric acid (9→1000) at 252 nm (Appendix IV A), the value of *A* (1%, 1 cm) is 220-233.

Identification (1) To about 10 mg, add dropwise a small quantity of nitric acid, a dark blue colour is produced.

(2) Dissolve 1 g in 10 ml of water in a separator, add 5 ml of sodium hydroxide TS, extract twice with ether, each of 30 ml, combine the extracts, add a quantity of anhydrous sodium sulfate, shake and filter, expel the ether. To about 50 mg of the residue add 0.2 g of sodium carbonate, mix well. Ignite until it is completely carbonized, cool. Add 5 ml of water, boil, cool and filter, the filtrate yields the reactions characteristic of chlorides (Appendix III).

(3) The infrared absorption spectrum (Appendix IV C) is concordant with the reference spectrum of clomipramine hydrochloride (Appendix XVI).

(4) The aqueous solution extracted by ether obtained in test (2) yields the reactions characteristic of chlorides (Appendix III).

Colour of solution A solution of 1.0 g in 10 ml of water is colourless; any colour produced is not more intense than that of reference solution *Y*₃ (Appendix IX A, method 1).

Acidity An aqueous solution of 2.0 g in 20 ml, pH 3.5-5.0 (Appendix VI H).

Related substances Protect from light in the operation. Carry out the method for thin-layer chromatography (Appendix V B), using silica gel G (containing CMC) as the coating substance and a mixture of glacial acetic acid-ethyl acetate-hydrochloric acid-water (35 : 55 : 5 : 5) as the mobile phase. Apply separately to the plate 5 µl each of three solutions in methanol containing (1) 20 mg; (2) 40 µg of the substance being examined per ml and (3) 0.2 mg of imipramine hydrochloride CRS per ml. Place the plate into the chromatographic chamber which is saturated by the vapour of the mobile phase (line the inner walls of the chamber with filter paper moistened by the mobile phase), after developing and removal of the plate, dry it in air, spray with a solution of 0.5% potassium dichromate in

sulfuric acid solution (20% v/v) and examine immediately. Any spot in the chromatogram obtained with solution (1) corresponds to the principal spot obtained with solution (3) is not more intense than the principal spot of solution (3) and any other secondary spot is not more intense than the principal spot obtained with solution (2). The sum of secondary spots is not more than 3.

Loss on drying When dried to constant weight at 105°C, loses not more than 0.5% of its weight (Appendix VIII L).

Residue on ignition Not more than 0.1% (Appendix VIII N), using 1.0 g.

Heavy metals Carry out the limit test for heavy metals (Appendix VIII H, method 2), using the residue obtained in the test for Residue on ignition; not more than 0.001%.

Assay Dissolve about 0.4 g, accurately weighed, in 30 ml of glacial acetic acid and 5 ml of mercuric acetate TS, add 1 drop of crystal violet IS. Titrate with perchloric acid (0.1 mol/L) VS until the colour changes to blue. Perform a blank determination and make any necessary correction. Each ml of perchloric acid (0.1 mol/L) VS is equivalent to 35.13 mg of $C_{19}H_{23}ClN_2 \cdot HCl$.

Category Antidepressant.

Storage Preserve in tightly closed containers, protected from light.

Preparation (1) Clomipramine Hydrochloride Injection
(2) Clomipramine Hydrochloride Tablets

Clomipramine Hydrochloride Injection

Clomipramine Hydrochloride Injection is a sterile solution of Clomipramine Hydrochloride in Water for Injection. It contains not less than 95.0% and not more than 105.0% of the labelled amount of clomipramine hydrochloride ($C_{19}H_{23}ClN_2 \cdot HCl$).

Description A clear, colourless or almost colourless liquid.

Identification (1) To a quantity of the injection add nitric acid, a deep blue colour is produced immediately.

(2) Protect from light throughout the procedure. Dilute a quantity of the injection with methanol to produce a solution of 2.5 mg per ml as the test solution. Prepare a reference solution of 2.5 mg of clomipramine hydrochloride CRS per ml. Carry out the thin-layer chromatography (Appendix V B), using silica gel G as the coating substance and a mixture of glacial acetic acid-ethyl acetate-hydrochloric acid-water (35 : 55 : 5 : 5) as the mobile phase. Apply separately to the plate 5 µl each of above two solutions, after developing and removal of the plate, dry it in air, spray with a solution of 0.5% potassium dichromate in 20% sulfuric acid solution and examine immediately. The colour and position of the principal spot in the chromatogram obtained with the test solution correspond to the principal spot obtained with the reference solution.

(3) The retention time of principal peak of the clomipramine hydrochloride in the injection being examined in the chromatogram obtained in the Assay is identical with that of the principal peak of clomipramine hydrochloride CRS in the chromatogram of the reference solution.

pH 3.5-5.0 (Appendix VI H).

Colour The absorbance at 420 nm (Appendix IV A) is not more than 0.025.

Related substances Protect from light throughout the

procedure. Carry out the method as described under Assay. Dilute a quantity of the injection with the mobile phase to produce a solution of 1 mg per ml as the test solution. Dilute a quantity of the test solution with the mobile phase to produce a solution of 0.04 mg per ml as the reference solution. Inject 20 μ l of the reference solution into the column, adjust the attenuation so that the principal peak height in the chromatogram is 20% of the full scale of the chart. And then inject separately 20 μ l each of the test solution and the reference solution into the column, record the chromatogram for twice the retention time of the principal peak. In the chromatogram obtained with the test solution, the sum of the areas of all peaks other than the principal peak is not greater than 3/10 of area of the principal peak in the chromatogram obtained with the reference solution (Disregard any peak with a relative retention time to clomipramine hydrochloride less than 0.25).

Other requirements Complies with the general requirements for injections (Appendix I B).

Assay Protect from light throughout the procedure. Carry out the method for high performance liquid chromatography (Appendix V D), using a column packed with octadecylsilane bonded silica gel and a mixture of 1.25% sodium heptanesulfonate solution-1.0% trichloroacetic acid solution-2.5% potassium dihydrogen phosphate solution-methanol (80 : 50 : 40 : 330) as the mobile phase. The temperature of the column is 40°C and detection wavelength is 251 nm. The number of the theoretical plates of the column is not less than 2000, calculated with reference to the peak of clomipramine. The resolution factor between the peak of clomipramine and the adjacent impurity peaks complies with the related requirements.

Procedure Dilute a quantity of the injection, accurately measured, with the mobile phase to produce a solution of 0.1 mg per ml. Inject 20 μ l of the resulting solution into the column. Repeat the operation, using clomipramine hydrochloride CRS instead of the injection being examined. Calculate the content of $C_{19}H_{23}ClN_2 \cdot HCl$ with respect to the peak area obtained in the chromatogram by the external standard method.

Category As described under Clomipramine Hydrochloride.

Strength 2 ml : 25 mg

Storage Preserve in well closed containers, protected from light.

Clomipramine Hydrochloride Tablets

Clomipramine Hydrochloride Tablets contain not less than 90.0% and not more than 110.0% of the labelled amount of clomipramine hydrochloride ($C_{19}H_{23}ClN_2 \cdot HCl$).

Description Sugar coated tablets with white to pale yellow core.

Identification (1) Comply with the tests (1), (2) and (4) for Identification described under Clomipramine Hydrochloride, using a quantity of powdered tablets. (2) The light absorption of the solution obtained in Assay exhibits a maximum at 252 nm and a shoulder peak between 270-280 nm (Appendix IV A).

Content uniformity Comply with the requirements (Appendix X E). Shake 1 tablet with 40 ml of 0.1 mol/L hydrochloric acid solution in a 50 ml volumetric flask for 1 hour, dilute to volume, mix well and filter. Proceed as

described under Assay, beginning at the words "Measure accurately a quantity of successive filtrate...". Calculate the content of $C_{19}H_{23}ClN_2 \cdot HCl$.

Other requirements Comply with the general requirements for tablets (Appendix I A).

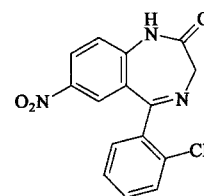
Assay Triturate 20 tablets with a small quantity of 0.1 mol/L hydrochloric acid solution. Transfer to a 250 ml volumetric flask with 0.1 mol/L hydrochloric acid solution in portions, shake thoroughly to dissolve clomipramine hydrochloride, dilute to volume and mix well, filter. Measure accurately a quantity of the successive filtrate, dilute with 0.1 mol/L hydrochloric acid solution to produce a solution of 20 μ g per ml, mix well. Measure the absorbance at 252 nm (Appendix IV A), calculate the content of $C_{19}H_{23}ClN_2 \cdot HCl$, taking 226 as the value of A (1%, 1cm).

Category As described under Clomipramine Hydro-chloride.

Strength (1) 10 mg (2) 25 mg

Storage Preserve in tightly closed containers, protected from light.

Clonazepam



$C_{15}H_{10}ClN_3O_3$ 315.72

[1622-61-3]

Clonazepam is 5-(O-chlorophenyl)-1,3-dihydro-7-nitro-2H-1,4-benzodiazepin-2-one. It contains not less than 99.0% of $C_{15}H_{10}ClN_3O_3$, calculated on the dried basis.

Description A slightly yellow or pale yellow crystalline powder; almost odourless; tasteless. Sparingly soluble in acetone or chloroform; slightly soluble in methanol or ethanol; practically insoluble in water.

Melting point 237-240°C (Appendix VI C).

Identification (1) Dissolve 10 mg in 1 ml of dilute hydrochloric acid, add potassium iodobismuthate TS dropwise, an orange red precipitate is produced immediately, which darkens on standing.

(2) The light absorption of a solution of 10 μ g per ml in ethanol containing 0.5% sulfuric acid exhibits two maxima at 252 nm and 307 nm (Appendix IV A).

(3) The infrared absorption spectrum (Appendix IV C) is concordant with the reference spectrum of clonazepam (Appendix XVI).

Related substances Carry out the method for thin-layer chromatography (Appendix V B), using silica gel GF₂₅₄ as the coating substance and a mixture of ethyl acetate-carbon tetrachloride (1 : 1) as the mobile phase. Apply separately to the plate 25 μ l each of two solutions in acetone containing (1) 20 mg per ml of the substance being examined and (2) 100 μ g per ml of 2-amino-2-chloro-5-nitrobenzophenone CRS. After developing and removal of the plate, dry it in air and spray with dilute sulfuric acid, heat at 105°C for 20-30 minutes, cool and spray in sequence with 0.1% sodium nitrite solution, 0.5% ammonium sulfamate solution and 0.1% N-naphthylenediamine dihydrochloride solution, allow

it to dry in air after each spraying. Any spot, other than the principal spot, obtained with solution (1) is not more intense than the principal spot obtained with solution (2).

Loss on drying When dried to constant weight at 105°C, loses not more than 0.5% of its weight (Appendix VIII L).

Residue on ignition Not more than 0.1% (Appendix VIII N), using 1.0 g.

Heavy metals Carry out the limit test for heavy metals (Appendix VIII H, method 2), using the residue obtained in the test for Residue on ignition; not more than 0.002%.

Assay Dissolve about 0.25 g, accurately weighed, in 35 ml of acetic anhydride, add 2 drops of Nile blue IS. Titrate with perchloric acid (0.1 mol/L) VS until the colour changes to yellowish green. Perform a blank determination and make any necessary correction. Each ml of perchloric acid (0.1 mol/L) VS is equivalent to 31.57 mg of $C_{15}H_{10}ClN_3O_3$.

Category Anxiolytic and Anticonvulsant agent.

Storage Preserve in tightly closed containers, protected from light.

Preparation (1) Clonazepam Injection
(2) Clonazepam Tablets

Clonazepam Injection

Clonazepam Injection is a sterile solution of Clonazepam in Water for Injection. It contains not less than 90.0% and not more than 110.0% of the labelled amount of clonazepam ($C_{15}H_{10}ClN_3O_3$).

Description A clear, colourless or slightly yellowish green liquid.

Identification (1) To 3 ml add 1 ml of dilute hydrochloric acid, and add potassium iodobismuthate TS dropwise, an orange red precipitate is produced immediately, which darkens on standing.

(2) The light absorption of a solution obtained in the Assay exhibits a maximum at 310 nm (Appendix IV A).

pH value 4.0-6.0 (Appendix IV H).

Colour Not more intense than that of reference solution YG₅ (Appendix IX A, method 1).

Related substances Measure accurately a quantity, equivalent to about 10 mg of clonazepam, in a separator and extract with 5 ml each of chloroform for 4 times. Combine the chloroform extracts, evaporate on a water bath to about 5 ml, dilute with chloroform to produce 10 ml and mix well (test solution). Dissolve 2-amino-2-chloro-5-nitrobenzophenone CRS in chloroform to produce a solution of 30 µg per ml (reference solution). Carry out the method for thin-layer chromatography (Appendix V B), using silica gel GF₂₅₄ as the coating substance and a mixture of ethyl acetate-carbon tetrachloride (1 : 1) as the mobile phase. Apply separately to the plate 50 µl of each of two resulting solutions. After developing and removal of the plate, dry it in air and spray with dilute sulfuric acid, heat at 105°C for 20 minutes, cool and spray in sequence with 0.1% sodium nitrite solution, 0.5% ammonium sulfamate solution and 0.1% *N*-naphthylenediamine dihydrochloride solution, allow it to dry in air after each spraying. Any spot, other than the principal spot, obtained with test solution is not more intense than the principal spot obtained with reference solution.

Other requirements Complies with the general requirements

for Injections (Appendix I B).

Assay Measure accurately a quantity, equivalent to about 10 mg of clonazepam, to produce a solution of 10 µg per ml in ethanol. Dissolve an accurately weighed quantity of clonazepam CRS in ethanol to produce a solution of 10 µg per ml. Measure the absorbances of the two solutions at 310 nm (Appendix IV A). Calculate the content of $C_{15}H_{10}ClN_3O_3$.

Category As described under Clonazepam.

Strength 1 ml : 1 mg

Storage Preserve in well closed containers, protected from light.

Clonazepam Tablets

Clonazepam Tablets contain not less than 90.0% and not more than 110.0% of the labelled amount of clonazepam ($C_{15}H_{10}ClN_3O_3$).

Description White or almost white tablets.

Identification (1) To a quantity of powdered tablets, equivalent to about 10 mg of clonazepam, add 10 ml of acetone, shake to dissolve clonazepam and filter. Evaporate the filtrate on a water bath to dryness. The residue complies with the test (1) for Identification described under Clonazepam.

(2) The light absorption of solution obtained in the Assay exhibits a maximum at 307 nm (Appendix IV A).

Content uniformity Comply with the requirements (Appendix X E).

Triturate 1 tablet in a mortar with a quantity of ethanol solution containing 0.5% sulfuric acid. Transfer to a 50 ml (for strength 0.5 mg) or 200 ml (for strength 2 mg) volumetric flask with the same solvent in portions. Shake for 30 minutes to dissolve clonazepam, dilute to volume and mix well. Filter and use the successive filtrate as the test preparation. Proceed as described under Assay. Calculate the content of $C_{15}H_{10}ClN_3O_3$.

Dissolution Carry out the dissolution test (Appendix X C, method 2), using 900 ml of water as the dissolution medium, adjust the rotatory speed of the paddle to 100 rpm. Withdraw the solution after exactly 60 minutes and filter, taking the successive filtrate as the test solution. Carry out the method for high performance liquid chromatography (Appendix V D), using a column packed with octadecylsilane bonded silica gel and a mixture of water-methanol-acetonitrile (40 : 30 : 30) as the mobile phase. Detection wavelength is 254 nm, and the number of the theoretical plates of the column is not less than 1000, calculated with reference to the peak of clonazepam. Inject 100 µl of the test solution, accurately measured, into the column and record the chromatogram. Dissolve a quantity of clonazepam CRS, accurately weighed in methanol to produce a solution of 2 µg per ml. Repeat the operation. Calculate the dissolution of $C_{15}H_{10}ClN_3O_3$ from each tablet with respect to the peak area obtained in the chromatogram by the external standard method, not less than 70% of the labelled amount is dissolved.

Other requirements Comply with the general requirements for tablets (Appendix I A).

Assay Weigh accurately and powder 80 tablets (for strength 0.5 mg) or 20 tablets (for strength 2 mg). To an accurately weighed quantity of the powder, equivalent to about 10 mg of clonazepam, in a 100 ml volumetric flask add 75 ml of ethanol solution containing 0.5% sulfuric acid, shake for 45 minutes to dissolve clonazepam, dilute with the

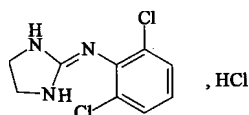
same solvent to the volume and mix well. Filter, measure accurately 5 ml of the successive filtrate to a 50 ml volumetric flask, and dilute to volume and mix well. Dissolve an accurately weighed quantity of clonazepam CRS in the same solvent to produce a solution of 10 µg per ml. Measure the absorbances of the resulting solutions at 307 nm (Appendix IV A). Calculate the content of $C_{15}H_{10}ClN_3O_3$.

Category As described under Clonazepam.

Strength (1) 0.5 mg (2) 2 mg

Storage Preserve in tightly closed containers, protected from light.

Clonidine Hydrochloride



$C_9H_9Cl_2N_3 \cdot HCl$ 266.56

[4205-91-8]

Clonidine Hydrochloride is 2,6-dichloro-*N*-2-imidazolidinylidene benzenamine monohydrochloride. It contains not less than 99.0% of $C_9H_9Cl_2N_3 \cdot HCl$, calculated on the dried basis.

Description A white crystalline powder; odourless. Soluble in water or ethanol; very slightly soluble in chloroform; practically insoluble in ether.

Identification (1) Dissolve 1 mg in 2 ml of water, add 1 ml of freshly prepared 5% sodium nitroprusside solution, 2 ml of sodium hydroxide TS and 1 g of sodium bicarbonate, shake thoroughly, a violet colour is produced, which darkens on standing.

(2) The light absorption of a solution of 0.30 mg per ml in 0.01 mol/L hydrochloric acid solution exhibits maxima at 272 nm and 279 nm; the absorbance is about 0.55 and 0.47, respectively (Appendix IV A).

(3) The infrared absorption spectrum (Appendix IV C) is concordant with the reference spectrum of clonidine hydrochloride (Appendix XVI).

(4) The aqueous solution yields the reactions characteristic of chlorides (Appendix III).

Acidity Dissolve 0.10 g in 10 ml of water, pH 4.0-5.0 (Appendix VI H).

Clarity of solution A solution of 0.10 g in 10 ml of water is clear.

Related substances Carry out the method for thin-layer chromatography (Appendix V B), using silica gel G as the coating substance and the filtered upper layer of a mixture of *n*-butanol-water-glacial acetic acid (4 : 5 : 1) as the mobile phase. Apply separately to the plate 3 µl each of two solutions in methanol containing (1) 10 mg per ml and (2) 50 µg per ml of the substance being examined. After developing and removal of the plate, dry it in air and spray with dilute potassium iodobismuthate TS and followed with sodium nitrite solution. Any spot other than the principal spot in the chromatogram obtained with solution (1) is not more intense in colour than that of the principal spot obtained with solution (2).

Loss on drying When dried to constant weight at 105°C, loses not more than 0.5% of its weight (Appendix VIII L).

Heavy metals Dissolve 1.0 g in 2 ml of acetate BS (pH

3.5) and sufficient water to produce 25 ml, carry out the limit test for heavy metals (Appendix VIII H, method 1); not more than 0.002%.

Assay Dissolve about 0.15 g, accurately weighed, in 10 ml of glacial acetic acid and 3 ml of mercuric acetate TS by warming, cool, add 1 drop of crystal violet IS, titrate with perchloric acid (0.1 mol/L) VS until the colour changes to bluish-green. Perform a blank determination and make any necessary correction. Each ml of perchloric acid (0.1 mol/L) VS is equivalent to 26.66 mg of $C_9H_9Cl_2N_3 \cdot HCl$.

Category Antihypertensive agent.

Storage Preserve in tightly closed containers, protected from light.

Preparation (1) Clonidine Hydrochloride Eye Drops
(2) Clonidine Hydrochloride Injection
(3) Clonidine Hydrochloride Tablets

Clonidine Hydrochloride Eye Drops

Clonidine Hydrochloride Eye Drops contain not less than 90.0% and not more than 110.0% of the labelled amount of clonidine hydrochloride ($C_9H_9Cl_2N_3 \cdot HCl$).

Description A clear, colourless liquid.

Identification (1) To 0.5 ml add 2 ml of water and mix well, the solution complies with test (1) for Identification described under Clonidine Hydrochloride.

(2) The light absorbance of a solution of 0.30 mg per ml in hydrochloric acid solution (0.9→1000) exhibits two maxima at 272 nm and 279 nm (Appendix IV A).

pH value 5.0-7.0 (Appendix VI H).

Other requirements Comply with the general requirements for eye preparations (Appendix I G).

Assay Carry out the method for high performance liquid chromatography (Appendix V D), using a column packed with octylsilane bonded silica gel and a mixture of 0.22% sodium octanesulfonate-methanol-phosphoric acid (500 : 500 : 1, adjust the pH with 1 mol/L sodium hydroxide solution or phosphate to 3.0) as the mobile phase. Detection wavelength is 220 nm and the number of theoretical plates of the column is not less than 3500, calculated with reference to the peak of clonidine hydrochloride. The tail factor of the column is not more than 1.5.

Procedure Dilute an accurately measured quantity of the eye drops with mobile phase to produce a solution of 2.5 µg per ml. Inject accurately measured 50 µl into the column. Dilute an accurately weighed quantity of clonidine hydrochloride CRS with mobile phase to produce a solution of 2.5 µg per ml. Repeat the operation, calculate the content of $C_9H_9Cl_2N_3 \cdot HCl$ with respect to the peak area obtained in the chromatogram by the external standard method.

Category Ophthalmic.

Strength 5 ml : 12.5 mg

Storage Preserve in well closed containers, protected from light.

Clonidine Hydrochloride Injection

Clonidine Hydrochloride Injection is a sterile

solution of Clonidine Hydrochloride in Water for Injection. It contains not less than 90.0% and not more than 110.0% of the labelled amount of clonidine hydrochloride ($C_9H_9Cl_2N_3 \cdot HCl$).

Description A clear, colourless liquid.

Identification (1) Evaporate 6 ml to about 2 ml on a water bath, the remaining solution complies with test (1) for Identification described under Clonidine Hydrochloride.

(2) The light absorption of a solution containing 5 ml of the injection and 1 drop of 1 mol/L hydrochloric acid solution exhibits maxima at 272 nm and 279 nm (Appendix IV A).

pH value 4.0-6.0 (Appendix VI H).

Other requirements Complies with the general requirements for injections (Appendix I B).

Assay Carry out the method for high performance liquid chromatography (Appendix V D), using a column packed with octylsilane bonded silica gel and a mixture of 0.22% sodium octanesulfonate-methanol-phosphoric acid (500 : 500 : 1, adjust the pH with 1 mol/L sodium hydroxide solution or phosphate to 3.0) as the mobile phase. Detection wavelength is 220 nm and the number of theoretical plates of the column is not less than 3500, calculated with reference to the peak of clonidine hydrochloride. The tail factor of the peak is not more than 1.5.

Procedure Measure accurately 2 ml of the injection in 100 ml volumetric flask. Dilute with mobile phase to volume, mix well. Inject accurately measured 50 μ l into the column. Dilute an accurately weighed quantity of clonidine hydrochloride CRS with mobile phase to produce a solution of 3 μ g per ml. Repeat the operation, calculate the content of $C_9H_9Cl_2N_3 \cdot HCl$ with respect to the peak area obtained in the chromatogram by the external standard method.

Category As described under Clonidine Hydrochloride.

Strength 1 ml : 0.15 mg

Storage Preserve in well closed containers, protected from light.

Clonidine Hydrochloride Tablets

Clonidine Hydrochloride Tablets contain not less than 90.0% and not more than 110.0% of the labelled amount of clonidine hydrochloride ($C_9H_9Cl_2N_3 \cdot HCl$).

Description White tablets.

Identification (1) To a quantity of powdered tablets equivalent to about 0.25 mg of clonidine hydrochloride, add 5 ml of water to dissolve clonidine hydrochloride. Add 1 ml of 30% sodium hydroxide solution, shake, then add 5 ml of ether and shake again. Separate the ether layer and evaporate to about 0.5 ml. Add 1 drop of the ether extract to a dry filter paper previously moistened with freshly prepared alkaline sodium nitroprusside solution (mix 0.2 g of sodium nitroprusside with 4 ml of water and 1 ml of sodium hydroxide TS), then add 1 drop of 8% sodium bicarbonate solution; a violet spot is produced.

(2) The retention time of principal peaks of the substance being examined in the chromatogram obtained in the Assay is identical with that of clonidine hydrochloride CRS.

(3) To a quantity of powdered tablets equivalent to about 0.75 mg of clonidine hydrochloride add 30 ml of water, shake to dissolve clonidine hydrochloride. Add 5 ml of

sodium hydroxide TS, extract with 20 ml of chloroform and centrifuge. Filter the chloroform layer through anhydrous sodium sulfate and evaporate the filtrate to dryness. Dissolve the residue in 5 ml of 0.01 mol/L hydrochloric acid solution. The light absorption of the solution exhibits maxima at 272 nm and 279 nm (Appendix IV A).

Content uniformity Comply with the requirements (Appendix X E). Dissolve 1 tablet with mobile phase in a 25 ml volumetric flask, shake thoroughly for 30 minutes, dilute to volume with mobile phase, mix well and filter. proceed as described under the Assay, using the successive filtrate.

Other requirements Comply with the general requirements for tablets (Appendix I A).

Assay Carry out the method for high performance liquid chromatography (Appendix V D), using a column packed with octylsilane bonded silica gel and a mixture of 0.22% sodium octanesulfonate-methanol-phosphoric acid (500 : 500 : 1, adjust the pH with 1 mol/L sodium hydroxide solution or phosphate to 3.0) as the mobile phase. Detection wavelength is 220 nm and the number of theoretical plates of the column is not less than 3500, calculated with reference to the peak of clonidine hydrochloride. The tailing factor of the peak is not more than 1.5.

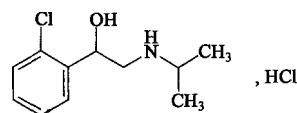
Procedure Weigh accurately and powder 20 tablets. Dissolve an accurately weighed quantity of the powdered tablets equivalent to about 0.15 mg of clonidine hydrochloride in 50 ml volumetric flask with a quantity of the mobile phase, shake thoroughly for 30 minutes. Dilute with the mobile phase to volume, filter with 0.45 μ m pore size membrane. Inject accurately measured 50 μ l of the successive filtrate into the column. Dilute an accurately weighed quantity of clonidine hydrochloride CRS with mobile phase to produce a solution of 3 μ g per ml. Repeat the operation, calculate the content of $C_9H_9Cl_2N_3 \cdot HCl$ with respect to the peak area obtained in the chromatogram by the external standard method.

Category As described under Clonidine Hydrochloride.

Strength 75 μ g

Storage Preserve in tightly closed containers, protected from light.

Clorprenaline Hydrochloride



$C_{11}H_{16}ClNO \cdot HCl$ 250.17

[5588-22-7]

Clorprenaline Hydrochloride is α -[[[(1-methyl-ethyl) amino] methyl] -2-chloro-benzenemethanol hydrochloride. It contains not less than 98.5% of $C_{11}H_{16}ClNO \cdot HCl$, calculated on dried basis.

Description A white or almost white crystalline powder; odourless; taste, bitter.

Freely soluble in water or ethanol; soluble in chloroform; slightly soluble in acetone; insoluble in ether.

Melting range 165-169°C (Appendix VI C).

Identification (1) To 1 ml of 1% solution in water, add 5 ml of 20% saturated potassium permanganate solution in

sulfuric acid, shake for several minutes, add a quantity of oxalic acid, mix well, to make a clear solution, add 5 ml of water and dinitrophenylhydrazine TS; a precipitate is produced immediately.

(2) The infrared absorption spectrum (Appendix IV C) is concordant with the reference spectrum of clorprenaline hydrochloride (Appendix XVI).

(3) The aqueous solution yields the reactions characteristic of chlorides (Appendix III).

Total chlorine Weigh accurately about 20 mg, carry out the method for oxygen flask combustion (Appendix VII C), using 10 ml of sodium hydroxide (0.1 mol/L) solution as the absorbing liquid. When the combustion is complete, shake for 5 minutes. Allow to stand for a few minutes. Wash the stopper and the platinum wire with a quantity of water, add 5 ml of dilute nitric acid, 15 ml of silver nitrate (0.02 mol/L) VS, measured accurately, 3 ml of nitrobenzene and 2 ml of ferric ammonium sulfate IS, titrate with ammonium thiocyanate (0.02 mol/L) VS. Perform a blank determination and make any necessary correction. Each ml of silver nitrate (0.02 mol/L) VS is equivalent to 0.709 mg of Cl. The content of total chlorine (Cl) is not less than 27.5% and not more than 29.5%, calculated on dried basis.

Loss on drying When dried to constant weight at 105°C, loses not more than 1.0% (Appendix VIII L).

Residue on ignition Not more than 0.1% (Appendix VIII N), using 1.0 g.

Heavy metals Carry out the limit test for heavy metals (Appendix VIII H, method 2), using the residue obtained in the test for Residue on ignition; not more than 0.001%.

Assay Dissolve about 0.15 g, accurately weighed, in 20 ml of glacial acetic acid, warm to dissolve if necessary, add 3 ml of mercuric acetate TS and 1 drop of crystal violet IS, titrate with perchloric acid (0.1 mol/L) VS until the solution becomes bluish-green. Perform a blank determination and make any necessary correction. Each ml of perchloric acid (0.1 mol/L) VS is equivalent to 25.02 mg of $C_{11}H_{16}ClNO \cdot HCl$.

Category β -Andrenergic receptor activating agent

Storage Preserve in tightly closed containers protected from light.

Preparation Clorprenaline Hydrochloride Tablets

Clorprenaline Hydrochloride Tablets

Clorprenaline Hydrochloride Tablets contain not less than 90.0% and not more than 110.0% of the labelled amount of clorprenaline hydrochloride ($C_{11}H_{16}ClNO \cdot HCl$).

Description White tablets.

Identification To a quantity of the powdered tablets equivalent to about 50 mg clorprenaline hydrochloride, add 5 ml of water, stir and filter. The filtrate complies with the tests (1) and (3) for Identification described under clorprenaline hydrochloride.

Content uniformity Comply with the requirements (Appendix X E). To 1 tablet in a 50 ml conical flask with stopper, add 5 ml of water, shake to dissolve clorprenaline hydrochloride. Add 5 ml of acetic acid-sodium acetate BS (Dissolve 4 g of anhydrous sodium acetate in 800 ml of water, add 155 ml of glacial acetic acid and adjust to pH 2.8

with acetic acid), 20 ml of chloroform and 0.8 ml of a mixture of dimethyl yellow-solvent blue 19 IS. Titrate with 0.1% dioctyl sodium sulfosuccinate solution, shake vigorously towards the end of titration, continue the titration until the colour of chloroform layer turns from green to reddishgrey. Measure accurately 5 ml of reference solution of clorprenaline hydrochloride CRS (dissolve about 50 mg of clorprenaline hydrochloride CRS accurately weighed, in a 50 ml volumetric flask with water and dilute to volume, mix well) to a 50 ml conical flask with stopper, carry out the method as described above beginning at the words "shake to dissolve the clorprenaline hydrochloride", calculate the content of $C_{11}H_{16}ClNO \cdot HCl$, according to the two volumes consumed of 0.1% dioctyl sodium sulfosuccinate solution (ml).

Other requirements Comply with the general requirements for tablets (Appendix I A).

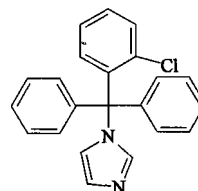
Assay Weigh accurately and powder 20 tablets. Transfer a quantity of the powdered tablets equivalent to about 20 mg of clorprenaline hydrochloride, accurately weighed, to a conical flask with stopper, add 20 ml of water, shake to dissolve clorprenaline hydrochloride. Add 15 ml of acetic acid-sodium acetate BS as described under the content uniformity, then 1 ml of a mixture of dimethyl yellow-solvent blue 19 IS and 20 ml of chloroform. Titrate with 0.45% dioctyl sodium sulfosuccinate solution, shake vigorously towards the end of titration, continue the titration until the colour of chloroform layer turns from green to reddish-grey. Weigh accurately about 20 mg of clorprenaline hydrochloride CRS, carry out the method as described above beginning at the words "to a conical flask with stopper", calculate the content of $C_{11}H_{16}ClNO \cdot HCl$, according to the two volumes consumed of 0.45% dioctyl sodium sulfosuccinate solution (ml).

Category As described under Clorprenaline Hydrochloride.

Strength 5 mg

Storage Preserve in tightly closed containers, protected from light.

Clotrimazole



$C_{22}H_{17}ClN_2$ 344.84

[23593-75-1]

Clotrimazole is 1-[(2-chlorophenyl) diphenylmethyl]-1H-imidazole. It contains not less than 98.5% of $C_{22}H_{17}ClN_2$, calculated on the dried basis.

Description A white to faintly yellow crystalline powder; odourless; tasteless.

Freely soluble in methanol or chloroform; soluble in ethanol or acetone; practically insoluble in water.

Melting range 141-145°C (Appendix VI C).

Identification (1) Dissolve about 0.1 g in 10 ml of acetone, add trinitrophenol TS until it precipitates completely, allow to stand and filter. The residue, after washing with water

and drying at 105°C for 1 hour, melts at about 170°C, with decomposition (Appendix VI C).

(2) Dissolve about 10 mg in 1 ml of sulfuric acid, an orange-yellow colour is produced; the colour disappears on adding 3 ml of water, and reappears on adding 3 ml of sulfuric acid.

(3) The infrared absorption spectrum (Appendix IV C) is concordant with the reference spectrum of clotrimazole (Appendix XVI).

Imidazole Prepare a solution of 100 mg per ml in chloroform as the test solution, and a solution of imidazole CRS of 0.50 mg per ml in chloroform as the reference solution. Carry out the method for thin-layer chromatography (Appendix V B), using silica gel G as the coating substance and a mixture of xylene-propanol-concentrated ammonia solution (180 : 20 : 1) as the mobile phase. Apply separately to the plate 5 µl each of the two solutions. After developing and removal of the plate, dry it in air and visualize in iodine vapour. Any spot other than the principal spot in the chromatogram obtained with the test solution is not more intense than the principal spot obtained with the reference solution (0.5%).

Diphenyl-(2-chlorophenyl)-methanol Prepare a solution of 200 mg per ml in chloroform as the test solution, and a solution of diphenyl-(2-chlorophenyl)-methanol CRS of 1.0 mg per ml in chloroform as the reference solution. Carry out the method for thin-layer chromatography (Appendix V B), using silica gel GF₂₅₄ as the coating substance and a mixture of xylene-propanol-concentrated ammonia solution (180 : 20 : 1) as the mobile phase. Apply separately to the plate 10 µl each of the two solutions. After developing and removal of the plate, dry it in air, examine under an ultraviolet light (254 nm). The fluorescence of any secondary spot in the chromatogram obtained with the test solution is not more intense than that of the principal spot obtained with the reference solution (0.5%).

Loss on drying When dried to constant weight at 105°C, loses not more than 0.5% of its weight (Appendix VIII L).

Residue on ignition Not more than 0.1% (Appendix VIII N), using 1.0 g.

Heavy metals Carry out the limit test for heavy metals, using the residue obtained in the test for Residue on ignition (Appendix VIII H, method 2); not more than 0.002%.

Assay Dissolve about 0.3 g, accurately weighed, in 20 ml of glacial acetic acid and add 1 drop of crystal violet IS. Titrate with perchloric acid (0.1 mol/L) VS until a bluish-green colour is produced. Perform a blank determination and make any necessary correction. Each ml of perchloric acid (0.1 mol/L) VS is equivalent to 34.48 mg of C₂₂H₁₇ClN₂.

Category Antifungal.

Storage Preserve in tightly closed containers, protected from light and stored in a cool place.

Preparation (1) Clotrimazole Cream
(2) Clotrimazole Oral Pellicles
(3) Clotrimazole Pellicles
(4) Clotrimazole Solution
(5) Clotrimazole Suppositories
(6) Compound Clotrimazole Cream

Clotrimazole Cream

Clotrimazole Ointment contains not less than 90.0% and not more than 110.0% of the labelled amount of clotrimazole (C₂₂H₁₇ClN₂).

Description A White Cream.

Identification (1) To a quantity of ointment equivalent to about 20 mg of clotrimazole add 10 ml of 0.5 mol/L sulfuric acid, warm on water bath and stir to dissolve clotrimazole, cool and filter. Add a few drops of trinitrophenol TS to the filtrate, a pale yellow precipitate is formed.

(2) To a quantity of ointment equivalent to about 20 mg of clotrimazole add 10 ml of dehydrated ethanol, warm on a water bath, cool, filter and evaporate the filtrate to dryness on water bath. Dissolve the residue with 1 ml of sulfuric acid, an orange-yellow colour is produced; the colour disappears on adding 3 ml of water, and reappears on adding 3 ml of sulfuric acid.

Other requirements Complies with the general requirements for cream (Appendix I F).

Assay Carry out the method for high performance liquid chromatography (Appendix V D), using a column packed with octadecylsilane bonded silica gel and a mixture of phosphate solution (Dissolve 4.35 g dipotassium hydrogen phosphate and dilute to 1000 ml with water, shake well) - methanol (25 : 75) as the mobile phase. Detection wavelength is 254 nm and the number of theoretical plates of the column is not less than 2500. The resolution factor between the peaks of clotrimazole and adjacent impurity should agree with the requirement.

Procedure Mix well the cream of 5 pieces. Dissolve a quantity of the cream, accurately weighed, with proper quantity of methanol into a 25 ml volumetric flask on the water bath at 50°C until clotrimazole is dissolved, cool to room temperature, dilute with methanol to the volume, shake well, put in an ice water bath for 2 hours, immediately filter, take the successive filtrate and cool to room temperature as the test solution. Inject 20 µl into the column and record the chromatogram. Dissolve a quantity of clotrimazole CRS, accurately weighed, and dilute with methanol to produce a solution of about 0.5 mg per ml, repeat the operation of the test solution, calculate the content of C₂₂H₁₇ClN₂ with respect to the peak area obtained in the chromatogram by the external standard method.

Category As described under Clotrimazole.

Strength (1) 1% (2) 3%

Storage Preserve in tightly closed containers, protected from light, stored at a cool and dry place.

Clotrimazole Oral Pellicles

Clotrimazole Oral Pellicles contain not less than 90.0% and not more than 110.0% of the labelled amount of clotrimazole (C₂₂H₁₇ClN₂).

Description White pellicles.

Identification (1) To a quantity of pellicles equivalent to about 20 mg of clotrimazole add 10 ml of 0.1 mol/L sulfuric acid, and filter. Add a few drops of trinitrophenol TS to the filtrate, a yellow precipitate is formed.

(2) To a quantity equivalent to about 20 mg of clotrimazole add 10 ml of acetone, warm on a water bath, cool, filter and evaporate the filtrate to dryness. Dissolve the residue with 1 ml of sulfuric acid, an orange-yellow colour is produced; the colour changes to opalescence on adding 3 ml of water and reappears on adding 3 ml of sulfuric acid.

Disintegration test Cut the pellicles to 6 pieces of one centimetre square, hold separately between two stainless steel sieve with pore 2.0 mm in diameter. Carry out the test

as described under Disintegration test for tablets (Appendix X A), the pellicles should completely melt and pass through the sieve in 15 minutes.

Other requirements Comply with the general requirements for pellicles (Appendix I M).

Assay Carry out the method for high performance liquid chromatography (Appendix V D), using a column packed with octadecylsilane bonded silica gel and a mixture of phosphate solution (Dissolve 4.35 g dipotassium hydrogen phosphate and dilute to 1000 ml with water, shake well) - methanol (25 : 75) as the mobile phase. Detection wavelength is 254 nm and the number of theoretical plates of the column is not less than 2500. The resolution factor between the peaks of clotrimazole and adjacent impurity should agree with the requirement.

Procedure Shear crush 20 sheets, accurately weighed. Dissolve proper quantities equivalent 12.5 mg clotrimazole, with proper quantity of methanol into a 25 ml volumetric flask, ultrasonic for 10 minutes until clotrimazole is dissolved, cool to room temperature, dilute with methanol to the volume, shake well and filter, take the successive filtrate as the test solution. Inject 20 μ l into the column and record the chromatogram. Dissolve a quantity of clotrimazole CRS, accurately weighed, and dilute with methanol to produce a solution of about 0.5 mg per ml, repeat the operation of the test solution, calculate the content of $C_{22}H_{17}ClN_2$ with respect to the peak area obtained in the chromatogram by the external standard method.

Category As described under Clotrimazole.

Strength 4 mg

Storage Preserve in tightly closed containers, protected from light, stored at a cool and dry place.

Clotrimazole Pellicles

Clotrimazole Pellicles contain not less than 90.0% and not more than 110.0% of the labelled amount of clotrimazole ($C_{22}H_{17}ClN_2$).

Description, Identification, Disintegration test, Other requirements As described under Clotrimazole Oral Pellicles.

Assay Shear crush accurately weighed 2 sheets. Weigh accurately a quantity of the mass equivalent to about 50 mg of clotrimazole to a stoppered conical flask. Dissolve in 20 ml of chloroform, add 20 ml of water, 5 ml of dilute sulfuric acid and 0.4 ml of dimethyl yellow-solvent blue 19 IS, titrate with sodium dioctylsulfosuccinate TS. Shake vigorously towards the end of titration and continue to titrate until the chloroform layer changes from green to reddish-grey. Perform another titration in the same manner, using 50 mg of clotrimazole CRS, accurately weighed. Calculate the content of $C_{22}H_{17}ClN_2$.

Category As described under Clotrimazole.

Strength 50 mg

Storage Preserve in tightly closed containers, protected from light, stored at a cool and dry place.

Clotrimazole Solution

Clotrimazole Solution contains not less than 90.0%

and not more than 110.0% of the labelled amount of clotrimazole ($C_{22}H_{17}ClN_2$).

Description A clear, colourless to faintly yellow liquid.

Identification Evaporate a quantity on a water bath to dryness. To the residue add chloroform to produce a solution of 2 mg per ml (solution 1). Dissolve a quantity of clotrimazole CRS in chloroform to produce a solution of 2 mg per ml (solution 2). Carry out the method for thin-layer chromatography (Appendix V B), using silica gel G as the coating substance and isopropyl ether as the mobile phase, the chromatographic chamber is saturated with ammonia vapour. Apply separately to the plate 10 μ l each of the two solutions. After developing and removal of the plate, dry it in air, and visualize in iodine vapour. The principal spot in the chromatogram obtained with solution (1) corresponds in position and colour to that obtained with solution (2).

Minimum fill Complies with the requirement (Appendix X F).

Assay Carry out the method for high performance liquid chromatography (Appendix V D), using a column packed with octadecylsilane bonded silica gel and a mixture of phosphate solution (Dissolve 4.35 g dipotassium hydrogen phosphate and dilute to 1000 ml with water, shake well) - methanol (25 : 75) as the mobile phase. Detection wavelength is 254 nm and the number of theoretical plates of the column is not less than 2500. The resolution factor between the peaks of clotrimazole and adjacent impurity should agree with the requirement.

Procedure Measure accurately 2 ml of the substance being examined into a 25 ml volumetric flask and dilute with methanol to the volume, shake well as the test solution. Inject 20 μ l into the column and record the chromatogram. Dissolve a quantity of clotrimazole CRS, accurately weighed, and dilute with methanol to produce a solution of about 0.6 mg per ml, repeat the operation of the test solution, calculate the content of $C_{22}H_{17}ClN_2$ with respect to the peak area obtained in the chromatogram by the external standard method.

Category As described under Clotrimazole.

Strength 1.5%

Storage Preserve in well closed containers.

Clotrimazole Suppositories

Clotrimazole Suppositories contain not less than 90.0% and not more than 110.0% of the labelled amount of clotrimazole ($C_{22}H_{17}ClN_2$).

Description Creamy white to faintly yellow conical suppositories.

Identification Dissolve the fatty base of 2 suppositories in 10 ml of petroleum ether by warming on a water bath, cool, discard the petroleum ether layer. The residue, washed with two portions of petroleum ether and dried on a water bath, complies with the tests for Identification described under Clotrimazole Solution.

Other requirements Comply with the general requirements for suppositories (Appendix I D).

Assay Melt 10 suppositories, accurately weighed, in an evaporating dish by warming on a water bath, cool and stir. Weigh accurately a quantity of the mass equivalent to about 50 mg of clotrimazole to a stoppered conical flask. Dissolve in

20 ml of chloroform, add 20 ml of water, 5 ml of dilute sulfuric acid and 0.4 ml of dimethyl yellow-solvent blue 19 IS, titrate with sodium dioctylsulfosuccinate TS. Shake vigorously towards the end of titration and continue to titrate until the chloroform layer changes from green to reddish-grey. Perform another titration in the same manner, using 50 mg of clotrimazole CRS, accurately weighed. Calculate the content of $C_{22}H_{17}ClN_2$.

Category As described under Clotrimazole.

Strength 0.15 g

Storage Preserve in tightly closed containers, stored at a temperature below 30°C.

Compound Clotrimazole Cream

Compound Clotrimazole cream contains not less than 90.0% and not more than 110.0% of the labelled amount of clotrimazole ($C_{22}H_{17}ClN_2$).

Formula	Clotrimazole	15.0 g
	Urea	150 g
	Base	a quantity
	To make	1000 g

Description White to slightly yellow cream.

Identification (1) To a quantity of cream equivalent to about 20 mg of clotrimazole add 10 ml of 0.5 mol/L sulfuric acid; warm on a water bath and stir to dissolve clotrimazole; cool and filter. Add a few drops of trinitrophenol TS to 2 ml of the filtrate, a slightly yellow precipitate is formed.

(2) To 1 ml of the above mentioned filtrate add 1 ml of sulfuric acid and shake, an orange-yellow colour is produced; the colour disappears on adding 3 ml of water, and reappears on adding 3 ml of sulfuric acid.

(3) Transfer a quantity of cream equivalent to about 0.2 g of urea to a test tube and heat. The urea is decomposed to produce ammonia gas which turns a wet litmus TP from red to blue.

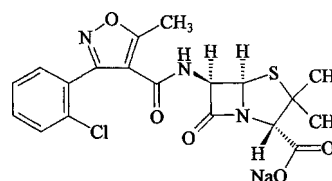
Other requirements Complies with the general requirements for cream (Appendix I F).

Assay Dissolve a quantity of the cream, accurately weighed, equivalent to about 50 mg of clotrimazole in 50 ml of chloroform-acetone (7 : 3) solution in a stoppered conical flask and heat to dissolve clotrimazole on a water bath. Add 5 g of anhydrous sodium sulfate, stir for 1-2 minutes, cool in a ice bath for 40 minutes, filter. Wash the residue with 10 ml each of chloroform-acetone (7 : 3) solution for three times, combine the washings to the filtrate. Expel the solvent to get an oily liquid on water bath. Add 20 ml of water, 5 ml of dilute sulfuric acid and 0.6 ml of dimethyl yellow-solvent blue 19 IS, titrate with dioctyl sodium sulfosuccinate TS, shake vigorously towards the end of titration and continue to titrate until the chloroform layer changes from green to reddish grey. Perform another titration in the same manner, using 50 mg of clotrimazole CRS, previously dried to constant weight at 105°C and calculate the content of $C_{22}H_{17}ClN_2$.

Category Antifungal.

Storage Preserve in tightly closed containers, protected from light, stored at a cool place.

Cloxacillin Sodium



$C_{19}H_{17}ClN_3NaO_5S$ 457.87

[7081-44-9]

Cloxacillin Sodium is sodium (2*S*, 5*R*, 6*R*)-6- [3-(*o*-chlorophenyl)-5-methyl-4-isoxazolecarboxamido]-3,3-dimethyl-7-oxo-4-thia-1-azabicyclo [3.2.0] heptane-2-carboxylate. Monohydrate of cloxacillin sodium is used for oral administration. It contains not less than 90.0% of $C_{19}H_{18}ClN_3O_5S$, calculated on the anhydrous basis.

Description A white or crystalline powder; odour, slight; taste, bitter; hygroscopic.

Freely soluble in water; soluble in ethanol; practically insoluble in ethyl acetate.

Specific optical rotation +163° to +172°, in a solution of 10 mg per ml in water (Appendix VI E).

Identification (1) The retention time of principal peak of the substance being examined in the chromatogram obtained in the Assay is identical with that of cloxacillin sodium CRS in the chromatogram of the reference solution.

(2) Drop the solution of 30 mg in 0.1 ml of methanol on the evaporating dish. After evaporating methanol in air, dry it in vacuum for hours. The infrared absorption spectrum (Appendix IV C) is concordant with the spectrum of cloxacillin CRS treated in the same manner.

(3) Yields the flame reaction of sodium salts (Appendix III).

Acidity Dissolve 1 g in 10 ml of water, pH 5.0-7.0 (Appendix VI H).

Clarity and colour of solution To 5 portions each of 0.6 g add 4.5 ml of water respectively, the solutions are clear and colourless; any opalescence produced is not more pronounced than that of the reference suspension I (Appendix IX B); any colour produced is not more intense than that of the reference solution Y₄ or YG₄ (Appendix IX A, method 1) (for parenteral use).

Related substances Dissolve an accurately weighed quantity in the mobile phase to produce a test solution of 1 mg per ml. Dilute an accurately measured quantity with water to produce a reference solution of 0.01 mg per ml. Carry out the method described under Assay, inject 20 µl of the reference solution into the column, adjust the attenuation so that the principal peak height in the chromatogram is 20% of the full scale of the chart. Inject 20 µl of the test solution and the reference solution respectively, and record the chromatogram for 5 times the retention time of the principal peak. In the chromatogram obtained with the test solution, the area of any peak apart from the principal peak, is not greater than the area of the principal peak in the chromatogram obtained with the reference solution (1 percent), the sum of the areas of all the peaks, apart from the principal peak, is not greater than five times the area of the principal peak in the chromatogram obtained with the reference solution (5 percent).

Water Not more than 4.5% (Appendix VIII M, method 1 A).

Pyrogens Complies with the test for pyrogens (Appendix XI D), using 1 ml of a solution of 25 mg per ml in sterile Water for Injection per kg of the rabbit's weight (for parenteral use).

Sterility Complies with the test for sterility (Appendix XI H, membrane filtration method), dissolving a quantity in the suitable solvent and transferring the solution to not less than 500 ml of 0.9% sterile sodium chloride solution.

Assay Carry out the method for high performance liquid chromatography (Appendix V D), using a column packed with octadecylsilane bonded silica gel and a mixture of 0.02 mol/l potassium dihydrogen phosphate solution (adjust the pH with potassium hydroxide solution to 5.0) -acetonitrile (75 : 25) as the mobile phase. Detection wavelength is 225 nm. Dissolve separately a quantity of Cloxacillin CRS and Floxacillin CRS in the mobile phase to produce a reference solution of 0.1 mg per ml. Inject 20 μ l of the reference solution into the column and record the chromatogram. The resolution factor between the peaks of cloxacillin and floxacillin should be not less than 2.5. The number of the theoretical plates of the column is not less than 1000 calculated with reference to the peak of cloxacillin. The tailing factor is not more than 1.5.

procedure Dissolve an accurately weighed quantity of cloxacillin in the mobile phase to produce a solution of 0.1 mg per ml. Inject 20 μ l of the solution into the column and record the chromatogram. Repeat the operation, using cloxacillin CRS. Calculate the content of $C_{19}H_{18}ClN_3O_5S$ with respect to the peak area obtained in the chromatogram by the external standard method.

Category β -lactam antibiotic.

Storage Preserve in hermetically sealed containers, stored in a dry place.

Preparation (1) Cloxacillin Sodium Capsules
(2) Cloxacillin Sodium Granules
(3) Cloxacillin Sodium for Injection

Cloxacillin Sodium Capsules

Cloxacillin Sodium Capsules contain not less than 90.0% and not more than 110.0% of the labelled amount of cloxacillin ($C_{19}H_{18}ClN_3O_5S$).

Identification The contents of cloxacillin sodium capsules comply with the tests (1) and (3) for Identification described under Cloxacillin Sodium.

Water Not more than 6.0% (Appendix VIII M, method 1 A).

Dissolution Carry out the dissolution test (Appendix X C, Method 1), using 900 ml water as the dissolution medium, adjust the rotational speed of the basket to 100 rpm. Withdraw the solution after exactly 45 minutes and filter. Dilute a quantity of the successive filtrate with water to produce a solution of 20 μ g per ml. Measure the absorbance of resulting solution at 225 nm (Appendix IV A). Dissolve an accurately weighed quantity of the mixed contents obtained in the test for weight variation of contents, equivalent to about the average weight in each capsule, in water with ultrasonic treatment and dilute to produce a solution of 20 μ g per ml, calculated by the labelled amount. Repeat the operation. Calculate the dissolution of $C_{19}H_{18}ClN_3O_5S$ from each capsule. Not less than 80% is

dissolved.

Other requirements Comply with the general requirements for capsules (Appendix I E)

Assay Dissolve an accurately weighed quantity, equivalent to about 100 mg of cloxacillin, of the mixed contents in the test for weight variation of contents in mobile phase and dilute to volume in a 100 ml volumetric flask, mix well and filter. Transfer 5 ml of the successive filtrate, accurately measured, to a 50 ml volumetric flask, dilute to volume with mobile phase and mix well as the test solution. Carry out the Assay described under Cloxacillin Sodium.

Category As described under Cloxacillin Sodium.

Strength Calculated as $C_{19}H_{18}ClN_3O_5S$
(1) 0.125 g (2) 0.25 g (3) 0.5 g

Storage Preserve in tightly closed containers, stored in a dry place.

Cloxacillin Sodium for Injection

Cloxacillin Sodium for Injection is a sterile powder of Cloxacillin Sodium. It contains not less than 90.0% of $C_{19}H_{18}ClN_3O_5S$, calculated on the anhydrous basis; not less than 95.0% and not more than 105.0% of the labelled amount of cloxacillin ($C_{19}H_{18}ClN_3O_5S$), calculated with reference to the average weight of contents.

Description A white or crystalline powder.

Identification Complies with the tests for Identification described under Cloxacillin Sodium.

Clarity and colour of solution Add 5 ml of water to each of 5 containers, the solutions are clear and colourless; any opalescence produced is not more pronounced than that of reference suspension 1 (Appendix IX B); any colour produced is not more intense than that of reference solution Y₄ or YG₄ (Appendix IX A, method 1).

Water Not more than 5.0% (Appendix VIII M, method 1 A).

Related substances Carry out the Related substances described under Cloxacillin Sodium, using an accurately weighed quantity of the mixed contents obtained in the test for weight variation of contents. In the chromatogram obtained with the test solution; the area of any peak, apart from the principal peak, is not greater than the area of the principal peak in the chromatogram obtained with the reference solution (1 percent); the sum of the areas of all the peaks, apart from the principal peak, is not greater than five times the area of the principal peak in the chromatogram obtained with the reference solution (5 percent).

Acidity, Pyrogens and sterility Comply with the corresponding tests described under Cloxacillin Sodium.

Other requirements Complies with the general requirements for injections (Appendix I B).

Assay Carry out the Assay described under Cloxacillin Sodium, using an accurately weighed quantity of the mixed contents obtained in the test for weight variation of contents.

Category As described under Cloxacillin Sodium.

Strength 0.5 g (calculated as $C_{19}H_{18}ClN_3O_5S$)

Storage Preserve in well closed containers, stored in a dry place.

Cloxacillin Sodium Granules

Cloxacillin Sodium Granules contain not less than 90.0% and not more than 110.0% of the labelled amount of cloxacillin ($C_{19}H_{18}ClN_3O_5S$).

Description Soluble granules; odour, fragrant; taste, sweet.

Identification Comply with the tests (1) and (3) for Identification described under Cloxacillin Sodium.

Acidity and alkalinity Dissolve a quantity in water to produce a solution of 25 mg per ml, pH 5.0-7.5 (Appendix VI H).

Loss on drying When dried to constant weight at 105°C, loses not more than 2.0% of its weight (Appendix VIII L).

Other requirements Comply with requirements for granules (Appendix I N).

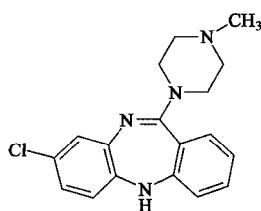
Assay Carry out the Assay described under Cloxacillin Sodium. Dissolve an accurately weighed quantity, equivalent to about 100 mg of cloxacillin, of the mixed contents obtained in the test for weight variation of contents in mobile phase and dilute to volume in a 100 ml volumetric flask, mix well and filter. Transfer 5 ml of the successive filtrate, accurately measured, to a 50 ml volumetric flask, dilute to volume with mobile phase and mix well as the test solution.

Category As described under Cloxacillin Sodium.

Strength 50 mg (calculated as $C_{19}H_{18}ClN_3O_5S$)

Storage Preserve in tightly closed containers, stored in a dry place.

Clozapine



$C_{18}H_{19}ClN_4$ 326.84

[5786-21-0]

Clozapine is 8-chloro-11-(4-methyl-1-piperazinyl)-5H-dibenzo[*b,e*][1,4]diazepine. It contains not less than 98.5% of $C_{18}H_{19}ClN_4$, calculated on the dried basis.

Description A pale yellow crystalline powder; odourless; tasteless.

Freely soluble in chloroform; soluble in ethanol; practically insoluble in water.

Melting range 181-185 °C (Appendix VI C).

Specific absorbance Measure the absorbances of a solution of 10 µg per ml in a mixture of 0.5 mol/L sulfuric acid solution-ethanol (1 : 99) at 242 nm and 296 nm (Appendix IV A), the values of *A* (1%, 1cm) are 710-770 and 293-320, respectively.

Identification (1) To about 100 mg add an equal amount of sodium carbonate in a dry test tube, mix well. Ignite, fumes are evolved which turn a filter paper moistened with 1% of sodium 1,2-naphthoquinone-4-sulfonate solution to

purplish-blue colour.

(2) The infrared absorption spectrum (Appendix IV C) is concordant with the reference spectrum of clozapine (Appendix XVI).

Loss on drying When dried to constant weight at 105°C, loses not more than 1.0% of its weight (Appendix VIII L).

Residue on ignition Not more than 0.1% (Appendix VIII N).

Assay Dissolve about 0.1 g, accurately weighted, in 20 ml of glacial acetic acid, add 1 drop of crystal violet IS, titrate with perchloric acid (0.1 mol/L) VS until the colour changes to bright green. Perform a blank determination and make any necessary correction. Each ml of perchloric acid (0.1 mol/L) VS is equivalent to 16.34 mg of $C_{18}H_{19}ClN_4$.

Category Antianxiety and anticonvulsant agent.

Storage Preserve in tightly closed containers, protected from light.

Preparation Clozapine Tablets

Clozapine Tablets

Clozapine Tablets contain not less than 90.0% and not more than 110.0% of the labelled amount of clozapine ($C_{18}H_{19}ClN_4$).

Description Pale yellow tablets.

Identification (1) To a quantity of powdered tablets equivalent to about 100 mg of clozapine, add an equal amount of sodium carbonate in a dry test tube, mix well. Ignite, fumes are evolved which turn a filter paper moistened with 1% of sodium 1,2-naphthoquinone-4-sulfonate solution to purplish-blue colour.

(2) To a quantity of powdered tablets equivalent to about 50 mg of clozapine, add 10 ml of chloroform, shake and filter, evaporate the filtrate to dryness. The infrared absorption spectrum (Appendix IV C) of the residue is concordant with the reference spectrum of clozapine (Appendix XVI).

Dissolution Carry out the dissolution test (Appendix X C, method 1), using 1000 ml of hydrochloric acid solution (9→1000) as the dissolution medium, adjust the rotatory speed of the basket to 100 rpm. Withdraw 10 ml of the solution after exactly 30 minutes and filter. Dilute an accurately weighed quantity of the successive filtrate with dissolution medium to produce a solution of 5 µg per ml, and mix well. Dissolve an accurately weighed quantity of clozapine CRS in dissolution medium to produce a solution of 5 µg per ml. Measure the absorbance of the resulting solution at 240 nm (Appendix IV A). Calculate the dissolution of $C_{18}H_{19}ClN_4$ from each tablet. Not less than 80% of the labelled amount is dissolved.

Other requirements Comply with the general requirements for tablets (Appendix I A).

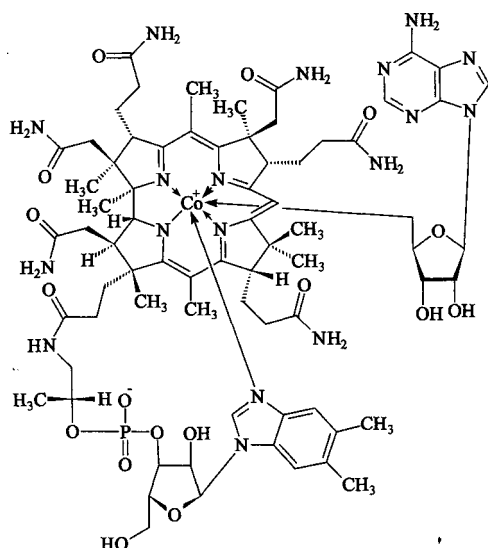
Assay Weigh accurately and powder 20 tablets. Transfer an accurately weighed quantity of the powder, equivalent to about 25 mg of clozapine, to a 100 ml volumetric flask. Add about 60 ml of a mixture of 0.5 mol/L sulfuric acid solution-ethanol (1 : 99), shake thoroughly to dissolve clozapine, dilute with the same solvent to volume and mix well. Filter, measure accurately 10 ml of the successive filtrate to a 250 ml volumetric flask, dilute to volume with the same solvent and mix well. Measure the absorbance of the resulting solution at 243 nm (Appendix IV A), calculate the content of $C_{18}H_{19}ClN_4$, taking 740 as the value of *A* (1%, 1 cm).

Category As described under Clozapine.

Strength (1) 25 mg (2) 50 mg

Storage Preserve in tightly closed containers, protected from light.

Cobamamide



$C_{72}H_{100}CoN_{18}O_{17}P$ 1579.60

[3870-90-1]

Cobamamide is 5,6-dimethylbenzimidazolyl-5'-deoxyadenosyl cobalamin. It contains not less than 95.0% of $C_{72}H_{100}CoN_{18}O_{17}P$, calculated on the dried basis.

Description Dark red crystals or a amorphous powder; hygroscopic; decomposed easily on exposure to light. Sparingly soluble in water; practically insoluble in ethanol, insoluble in acetone, ether or chloroform.

Identification Protect from light in the procedure.

(1) The light absorption of a solution of 50 µg per ml in potassium chloride solution [mix 125 ml of 0.2 mol/L potassium chloride solution with 53 ml of 0.2 mol/L hydrochloric acid solution, add water to 1000 ml] (Appendix IV A), exhibits four maxima at 264 nm, 285 nm, 305 nm and 460 nm.

(2) The light absorption of a solution of 50 µg per ml in phosphate BS (pH 7.0) (Appendix IV A), exhibits two maxima at 261 nm and 525 nm.

(3) The infrared absorption spectrum (Appendix IV C) is concordant with the reference spectrum of cobamamide (Appendix XVI).

Hydroxycobamine Protect from light in the procedure. The ratio of the absorption of the solution measured in the test (1) for Identification at 460 nm to that at 352 nm (Appendix IV A) is not less than 0.90.

Related substances Protect from light in the procedure. Carry out the method for high performance liquid chromatography (Appendix V D), using a column packed an octadecylsilane bonded silica gel and a mixture of acetonitrile-0.05 mol/L potassium dihydrogen phosphate TS (17 : 83), adjusted pH to 3.2 with 85% phosphoric acid as the mobile phase. Detection wavelength is 260 nm and the number of theoretical plates of the column is not less than 800, calculated with reference to the peak of cobamamide.

Dissolve a quantity of the substance being examined in water

to produce two solutions containing (1) 1.0 mg per ml and (2) 20 µg per ml, inject 10 µl of solution (2) into the column and adjust the attenuation of the detector so that the height of principle peak is about 20% of the full scale of the chart. Inject 10 µl each of solution (1) and (2), record the chromatogram for twice the retention time of the principle peak. The sum of the areas of the peaks other than principal peak in the chromatogram obtained with solution (1) is not greater than the area of the principal peak in the chromatogram obtained with solution (2).

Loss on drying When dried in vacuum over phosphorous pentoxide to constant weight at 60°C (under 0.66 kPa), loses not more than 12.0% of its weight (Appendix VIII L).

Assay Protect from light in the procedure. Dissolve an accurately weighed quantity in water to produce a solution of 500 µg per ml. Transfer 5 ml of the solution, accurately measured, to each of two 50 ml volumetric flasks, dilute with the above mentioned potassium chloride solution or the phosphate BS (pH 7.0) to volume respectively. Measure the absorbances of the resulting solutions at maximum wavelength in vicinity of 304.5 nm at an interval of 0.2 nm with dilute potassium chloride solution, using respectively above mentioned diluent solution as each blank. Calculate the content of $C_{72}H_{100}CoN_{18}O_{17}P$ by using the difference between the two of absorbances, taking 58.0 as the value of ΔA (1%, 1 cm).

Category Vitamin.

Storage Preserve in tightly closed container, protected from light.

Preparation Cobamamide Tablets

Cobamamide Tablets

Cobamamide Tablets contains not less than 90.0% and not more than 110.0% of the labelled amount of cobamamide ($C_{72}H_{100}CoN_{18}O_{17}P$).

Description Sugar coated tablets with pink cores.

Identification Protect from light in the procedure. Dissolve a quantity of finely pulverized tablets with coating removed in phosphate BS (pH 7.0) to produce a solution of 50 µg per ml, filter with membrane (0.45 µm). The filtrate complies with the test (2) for Identification described under Cobamamide.

Hydroxycobamamide Protect from light in the procedure.

Powder 10 tablets with coating removed and titurate with potassium chloride solution [mix 250 ml of 0.2 mol/L potassium chloride solution with 53 ml of 0.2 mol/L hydrochloric acid solution, add water to 1000 ml] in portions and transfer to a 50 ml volumetric flask, shake thoroughly to dissolve cobamamide and add potassium chloride solution to volume, mix well, filter with membrane (0.45 µm). Measure the absorbance of the filtrate (Appendix IV A), the ratio of the absorbance at 460 nm to that at 352 nm is not more than 0.80.

Content uniformity Protect from light in the procedure.

Carry out the test for content uniformity (Appendix X E). Shake 1 tablet with coating removed in a 10 ml volumetric flask with phosphate BS (pH 7.0) and dilute to volume with phosphate BS (pH 7.0), and dilute to volume, mix well, filter with membrane (0.45 µm). Measure the absorbance of the successive filtrate at 261 nm (Appendix IV A). The limit is not greater than 20%.

Other requirements Comply with the general requirements for tablets (Appendix I A).

Assay *Reference preparation* Dissolve about 20 mg of vitamin B₁₂ CRS, accurately weighed, in a 500 ml volumetric flask with water and dilute to volume, mix well.

Test preparation Powder 100 tablets with coating removed, triturate with water for several times and transfer to a 500 ml volumetric flask, shake thoroughly, filter with membrane (0.45 µm), collect the successive filtrate.

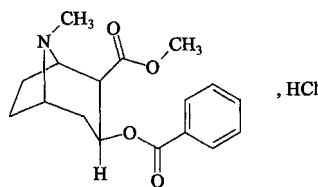
Procedure Transfer 10 ml of each of the reference and preparations, accurately measured, to 25 ml test tube with stopper respectively, add 15 ml of 0.65% potassium cyanide solution respectively, accurately measured, tightly close stopper, mix well, exposure under two 100 W lamp at a distance of 200 mm from both sides of the tubes for 1 hr. Measure the absorbances of the resulting solutions at 368 nm (Appendix IV A). Calculated the content of cobamamide by multiplying 1.1654.

Category As described under Cobamamide.

Strength 0.25 mg

Storage Preserve in tightly closed containers, protected from light.

Cocaine Hydrochloride



C₁₇H₂₁NO₄ · HCl 339.82 [53-21-4]

Cocaine Hydrochloride is [1R-(exo, exo)]-3-(benzoyloxy)-8-methyl-8-azabicyclo[3.2.1]octane-2-carboxylic acid methylester hydrochloride. It contains not less than 98.5% of C₁₇H₂₁NO₄ · HCl, calculated on the dried basis.

Description White crystals or a crystalline powder; odourless.

Very soluble in water; freely soluble in ethanol; soluble in chloroform; insoluble in ether.

Specific optical rotation -71° to -73°, in a solution of 20 mg per ml in water (Appendix VI E).

Identification (1) Heat about 0.1 g in a test tube with 1 ml of sulfuric acid in a water bath for 5 minutes and add carefully along the test tube wall 2 ml of water; the odour of methyl benzoate is perceptible. Benzoic acid crystallizes out gradually on cooling.

(2) To 5 ml of a water solution (1→50) add 5 drops of chromium trioxide solution (1→20), a yellow precipitate is produced which is redissolved on shaking; a persistent orangish-yellow precipitate is produced on further addition of 1 ml of hydrochloric acid.

(3) The infrared absorption spectrum (Appendix IV C) is concordant with the reference spectrum of cocaine hydrochloride (Appendix XVI).

(4) The aqueous solution yields the reactions characteristic of chlorides (Appendix III).

Acidity Dissolve 0.50 g in 10 ml of water, add 1 drop of methyl red IS. If the solution becomes pink, it changes to yellow on the addition of 0.50 ml of sodium hydroxide (0.02 mol/L) VS.

Cinnamylcocaine and other oxidizable substances Dissolve 0.10 g in 5 ml of water, add 0.3 ml of 5% sulfuric acid solution and 0.10 ml of potassium permanganate (0.02 mol/L) VS. Stopper the flask and allow to stand at 15-20°C in a dark place for 30 minutes, the purple colour is not completely discharged.

Loss on drying When dried to constant weight at 105°C, loses not more than 0.5% of its weight (Appendix VIII L).

Assay Dissolve about 0.3 g, accurately weighed, in 10 ml of glacial acetic acid, add 5 ml of mercuric acetate TS and 1 drop of crystal violet IS. Titrate with perchloric acid (0.1 mol/L) VS until the solution becomes pure blue. Perform a blank determination and make any necessary correction. Each ml of perchloric acid (0.1 mol/L) VS is equivalent to 33.98 mg of C₁₇H₂₁NO₄ · HCl.

Category Local anesthetic agent.

Storage Preserve in tightly closed containers, protected from light.

Cod Liver Oil

Cod Liver Oil is a fatty oil obtained from the liver of non-toxic marine fish. It is processed by partial destearinating at about 0°C and adjusting the vitamin content as required by addition of refined vegetable oil, concentrated cod liver oil or vitamin A and vitamin D₃. A suitable stabilizer may be added. Cod Liver Oil contains not less than 90.0% of the labelled amount of vitamin A; not less than 85.0% of the labelled amount of vitamin D.

Description A yellow to orange-red clear liquid; odour, slight and fishy, but not rancid.

Identification (1) Dilute a quantity with chloroform to produce a solution containing 10-20 Units of Vitamin A per ml. To 1 ml of the solution add 2 ml of a solution of antimony trichloride in chloroform (1→4), a blue to bluish-violet colour is produced immediately, and disappears gradually on standing.

(2) Carry out the method for high performance liquid chromatography (Appendix V D), using a column packed with octadecylsilane bonded silica gel and a mixture of methanol-acetonitrile (3 : 97) as the mobile phase. Detection wavelength is 254 nm. Inject a mixture of equal fraction of vitamin D₂ and D₃ equivalent to 5-10 Units each into the column, adjust the composition of mobile phase to that the resolution factor is greater than 1.0. Dry the test solution B described under the Assay of Vitamin D (Appendix VII K) with a stream of oxygen free nitrogen, add a few quantity of mobile phase to dissolve the residue, and inject this solution into the column, the retention time of principal peak of the substance being examined in the chromatogram is identical with that the principal peak of vitamin D₂ or D₃ in the chromatogram of the reference solution.

Acid value Transfer 15 ml each of ethanol and ether to a conical flask, add 5 drops of phenolphthalein IS and sodium hydroxide (0.1 mol/L) VS dropwise until a pink colour is produced. Add 2.0 g of the oil and boil under a reflux condenser for 10 minutes. Cool and titrate with sodium

hydroxide (0.1 mol/L) VS. The acid value (Appendix VII H) is not greater than 2.8.

Assay Vitamin A Carry out the method for Assay of Vitamin A (Appendix VII J).

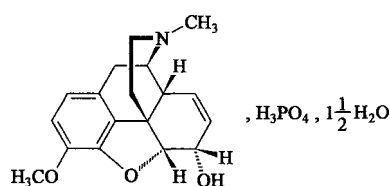
Vitamin D Carry out the method for Assay of Vitamin D (Appendix VII K).

Category Vitamin.

Strength (1) 1500 Units of vitamin A and 150 Units of vitamin D in each g.
(2) 3000 Units of vitamin A and 300 Units of vitamin D in each g.

Storage Preserve in tightly closed containers, fully filled and protected from light, stored in a cool and dry place.

Codeine Phosphate



$C_{18}H_{21}NO_3 \cdot H_3PO_4 \cdot 1\frac{1}{2}H_2O$ 424.39 [41444-62-6]

Codeine Phosphate is 7,8-didehydro-4,5 α -epoxy-3-methoxy-17-methylmorphinan-6 α -ol phosphate (1 : 1) (salt) sesquihydrate. It contains not less than 98.5% of $C_{18}H_{21}NO_3 \cdot H_3PO_4$, calculated on the dried basis.

Description A fine, white, needle-shaped crystalline powder; odourless; efflorescent. The aqueous solution exhibits acid reaction.

Freely solution in water; slightly soluble in ethanol; very slightly soluble in chloroform or ether.

Identification (1) Dissolve 0.2 g in 4 ml of water, add with constant stirring 20% sodium hydroxide solution dropwise until a white precipitate is produced. Scratch the inner walls of the vessel with a glass rod to complete the precipitation and filter. Wash the precipitate with water and dry at 105°C for 1 hour. The residue melts at 154-158°C (Appendix VI C).

(2) Dissolve about 0.1 g in 5 ml of water and alkalinify the solution with ammonia TS dropwise; no precipitate is formed.

(3) To about 1 mg on a porcelain plate, add 0.5 ml of sulfuric acid containing 2.5 mg of selenous acid; a green colour is immediately produced and then turns to blue.

(4) The infrared absorption spectrum (Appendix IV C) is concordant with the reference spectrum of Codeine Phosphate (Appendix XVI).

(5) Yields the reactions characteristic of phosphates (Appendix III).

Acidity Dissolve 0.4 g in 10 ml of water, pH 4.0-5.0 (Appendix VI H).

Clarity and Colour of solution A solution of 0.4 g in 10 ml of cold water is clear and colourless; any opalescence produced is not more pronounced than that of the reference suspension 1 (Appendix IX B), and its colour is not more intense than that of the reference solution Y₂ (Appendix IX A, method 1).

Chloride Carry out the limit test for chlorides (Appendix VIII A), using 0.10 g. Any opalescence produced is not more pronounced than that of a reference using 5.0 ml of sodium chloride standard solution (0.05%).

Sulfate Carry out the limit test for sulfates (Appendix VIII B), using 0.20 g. Any opalescence produced is not more pronounced than that of a reference using 2.0 ml of potassium sulfate standard solution (0.1%).

Morphine Dissolve 0.10 g in sufficient hydrochloric acid solution (9→1000) to produce 5 ml, add 2 ml of sodium nitrite TS, allow to stand for 15 minutes and add 3 ml of ammonia TS. Any colour produced is not more intense than that of a reference using 5.0 ml of morphine standard solution [dissolve 2.0 mg of anhydrous morphine in hydrochloric acid solution (9→1000) to produce 100 ml] (0.1%).

Loss on drying When dried to constant weight at 105°C, loses 5.0%-7.5% of its weight (Appendix VIII L).

Assay Dissolve about 0.25 g, accurately weighed, in 10 ml of glacial acetic acid, add 1 drop of crystal violet IS, titrate with perchloric acid (0.1 mol/L) VS until the colour changes to green. Perform a blank determination and make any necessary correction. Each ml of perchloric acid (0.1 mol/L) VS is equivalent to 39.74 mg of $C_{18}H_{21}NO_3 \cdot H_3PO_4$.

Category Analgesic and antitussive.

Storage Preserve in tightly closed containers, protected from light.

Preparation (1) Codeine Phosphate Injection
(2) Codeine Phosphate Syrup
(3) Codeine Phosphate Tablets

Codeine Phosphate Injection

Codeine Phosphate Injection is a sterile solution of Codeine Phosphate in Water for Injection. It contains not less than 95.0% and not more than 105.0% of the labelled amount of codeine phosphate ($C_{18}H_{21}NO_3 \cdot H_3PO_4 \cdot 1\frac{1}{2}H_2O$).

Description A clear, colourless liquid.

Identification Evaporate 10 ml to dryness on a water bath. The residue complies with the tests (1), (2), (3), (5) for Identification described under Codeine Phosphate.

pH value 4.0-5.5 (Appendix VI H).

Other requirements Complies with the general requirements for injections (Appendix I B).

Assay Measure accurately a volume equivalent to 0.3 g of codeine phosphate, evaporate to dryness on a water bath and dry at 105°C for 1 hour. Cool, dissolve the residue in 10 ml of glacial acetic acid, add 1 drop of crystal violet IS, titrate with perchloric acid (0.1 mol/L) VS until the colour changes to green. Perform a blank determination and make any necessary correction. Each ml of perchloric acid (0.1 mol/L) VS is equivalent to 42.44 mg of $C_{18}H_{21}NO_3 \cdot H_3PO_4 \cdot 1\frac{1}{2}H_2O$.

Category As described under Codeine Phosphate.

Strength (1) 1 ml : 15 mg (2) 1 ml : 30 mg

Storage Preserve in well closed containers, protected from light.

Codeine Phosphate Syrup

Codeine Phosphate Syrup contains not less than 0.47% and not more than 0.54% (g/ml) of the labelled amount of Codeine Phosphate ($C_{18}H_{21}NO_3 \cdot H_3PO_4 \cdot 1\frac{1}{2}H_2O$).

Formula	Codeine Phosphate	5 g
	Sucrose	650 g
	Preservative	a quantity
	Water	a quantity
	To make	1000 ml

Description A colourless to pale yellow viscous liquid; taste, sweet then bitter.

Identification Alkalize 1 ml with sodium hydroxide TS, add 1 ml of chloroform, shake vigorously, allow to stand. Transfer a few drops of chloroform extract to a porcelain plate, add 0.5 ml of sulfuric acid containing 2.5 mg of selenous acid, a green colour is produced immediately and then changes to blue.

Relative density Not lower than 1.200 (Appendix VI A).

Other requirements complies with the general requirements for syrup (Appendix I K).

Assay Measure accurately 10 ml with a "to contain" pipet to a separator. Wash the inner wall of the pipet with a quantity of water. Carry out the Assay as described under Codeine Phosphate Tablets beginning at the words "make alkaline with ammonia TS...". Each ml of sulfuric acid (0.01 mol/L) VS is equivalent to 8.488 mg of $C_{18}H_{21}NO_3 \cdot H_3PO_4 \cdot 1\frac{1}{2}H_2O$.

Category As described under Codeine Phosphate.

Strength (1) 10 ml (2) 100 ml

Storage Preserve in tightly closed containers, protected from light and stored in a cool place.

Codeine Phosphate Tablets

Codeine Phosphate Tablets contain not less than 93.0% and not more than 107.0% of the labelled amount of codeine phosphate ($C_{18}H_{21}NO_3 \cdot H_3PO_4 \cdot 1\frac{1}{2}H_2O$).

Description White tablets or coated tablets.

Identification (1) Dissolve a quantity of the powdered tablets equivalent to 0.2 g of codeine phosphate, in 5 ml of water filter, add 20% sodium hydroxide solution dropwise with frequently stirring until a white precipitate is produced then complete the precipitation by rubbing the vessel wall with a glass rod. Filter, wash the precipitate with water. Dry a portion of the residue at 105°C for 1 hour. It melts at 154-158°C (Appendix VI C). The residue complies with test (3) for Identification described under Codeine Phosphate. (2) Shake the powdered tablets with water and filter; the filtrate yields the reaction characteristic of phosphates (Appendix III).

Content uniformity Comply with the requirements

(Appendix X E). To 1 tablet in 200 ml volumetric flask add a quantity of water, shake 1 hour to dissolve codeine phosphate, dilute with water to volume, mix well and filter. Measure the absorbance of the successive filtrate at 280 nm (Appendix IV A).

Dissolution Comply with the dissolution test (Appendix X C, method 1), using 900 ml of water as the dissolution medium, adjust the rotational speed of the basket to 100 rpm. Withdraw 10 ml of the solution after exactly 20 minutes and filter. Dilute a quantity of the successive filtrate with water to produce a solution of 10 µg per ml. Measure the absorbance of the resulting solution at 212 nm (Appendix IV A). Calculate the dissolution of $C_{18}H_{21}NO_3 \cdot H_3PO_4 \cdot 1\frac{1}{2}H_2O$ from each tablet, taking 601 as the value of A (1%, 1 cm); not less than 80% of the labelled amount is dissolved.

Other requirements Comply with the general requirements for tablets (Appendix I A).

Assay Weigh accurately and powder 15 tablets (30 mg) or 25 tablets (15 mg). Weigh accurately a quantity of the powder equivalent to 0.15 g of codeine phosphate into a 100 ml volumetric flask, add water to make a suspension and add 20 ml of 0.25 mol/L sulfuric acid solution, shake for about 30 minutes until codeine phosphate is dissolved. Dilute with water to volume, shake thoroughly, filter. Measure accurately 50 ml of the successive filtrate to a separator, make alkaline with ammonia TS and extract with successive quantities of chloroform (25 ml, 15 ml, 15 ml, 15 ml) until extraction of the alkaloid is complete. Wash each chloroform extract with the same 10 ml portion of water and shake the aqueous layer with 5 ml of chloroform. Combine the chloroform extracts, evaporate to dryness on a water bath. To the residue add accurately 25 ml of sulfuric acid (0.01 mol/L) VS, heat to dissolve. Cool, add 2 drops of methyl red IS and titrate with sodium hydroxide (0.02 mol/L) VS. Each ml of sulfuric acid (0.01 mol/L) VS is equivalent to 8.488 mg of $C_{18}H_{21}NO_3 \cdot H_3PO_4 \cdot 1\frac{1}{2}H_2O$.

Category As described under Codeine Phosphate.

Strength (1) 15 mg (2) 30 mg

Storage Preserve in tightly closed containers, protected from light.

Codeine Phosphate and Platycodon Tablets

Codeine Phosphate and Platycodon Tablets contain not less than 10.8 mg and not more than 13.2 mg of codeine phosphate ($C_{18}H_{21}NO_3 \cdot H_3PO_4 \cdot 1\frac{1}{2}H_2O$), and not less than 9 mg of total platycodon saponins in each tablet.

Formula	Liquid Extract of Platycodon Root	50 g
	Codeine Phosphate	
	$(C_{18}H_{21}NO_3 \cdot H_3PO_4 \cdot 1\frac{1}{2}H_2O)$	12 g
	Excipient	a quantity
	to make	1000 tablets

Description Pale brown tablets or film coated tablets with pale brown core.

Identification Dissolve about 1 g of the powdered tablets in 10 ml of water and filter, the filtrate is used in test (1) and (2) for identification.

(1) Dilute 1 ml of the filtrate with water to 10 ml and shake, a persistent tiny foam is produced.

(2) Add 5 drops of the filtrate into 2 ml of glacial acetic acid and add slowly 0.5 ml of sulfuric acid, the interface shows a red to reddish-brown colour.

(3) To about 0.5 g of the powdered tablets, add 5 ml of water, shake thoroughly, add 1 ml of ammonia TS, extract with 10 ml of chloroform, wash the chloroform layer with 2 ml of water, evaporate the chloroform layer on a water bath to dryness. To the residue add 0.5 ml of sulfuric acid solution containing 2.5 mg of selenic acid, a green colour is produced immediately and changes to blue gradually.

(4) Dissolve about 1 g of the powdered tablets in 10 ml water, shake thoroughly and filter, transfer the filtrate to a separator. Extract with two 20 ml portions of ethyl acetate, evaporate the combined ethyl acetate layers to dryness, dissolve the residue in 2 ml dehydrate ethanol as the test solution. To 2 g of reference crude drug of radix platycodi add 10 ml of ethanol, soak for 24 hours and filter. Repeat the operation, using filtrate to produce the reference solution. Carry out the method for thin-layer chromatography (Appendix V B), using silica gel G as the coating substance and a mixture of ethyl acetate-methanol-water (14 : 3 : 3) as the mobile phase. Apply separately to the plate 2 μ l of each of the above two solutions. After developing and removal of the plate, dry it in air and examine under ultraviolet light (365 nm). The fluorescence spots in the chromatogram obtained with the test solution correspond in position and colour to the fluorescence spots obtained with the reference drug solution.

Content uniformity Codeine Phosphate Comply with the requirements for content uniformity (Appendix X E). To 1 tablet, carry out the method in the Assay. Calculate the content of $C_{18}H_{21}NO_3 \cdot H_3PO_4 \cdot 1\frac{1}{2}H_2O$.

Dissolution Carry out the dissolution test (Appendix X C, method 2), using 500 ml of water as the dissolution medium, adjust the rotational speed of the paddle to 100 rpm. Withdraw 5 ml of the solution after exactly 30 minutes and filter through a membrane filter. The successive filtrate is used as the test solution. Measure accurately the reference solution as described under the Assay of Codeine Phosphate, dilute with water to produce a solution of 0.03 mg of codeine phosphate per ml as the reference solution. Measure accurately 10 μ l each of the test solution and the reference solution, carry out the method in the Assay of Codeine Phosphate. Calculate the dissolution of $C_{18}H_{21}NO_3 \cdot H_3PO_4 \cdot 1\frac{1}{2}H_2O$ from each tablet. Not less than 80% of the labelled amount is dissolved.

Other requirements Comply with the general requirements for tablets (Appendix I A).

Assay Codeine Phosphate Carry out the method for high performance liquid chromatography (Appendix V D), using a column packed with octadecylsilane bonded silica gel and a mixture of 0.05 mol/L potassium dihydrogen phosphate solution (adjust to pH 3.0 with phosphoric acid) - acetonitrile (3.5 : 1) as the mobile phase. Detection wavelength is 220 nm and the number of the theoretical plates of the column is not less than 1000, calculated with reference to the peak of codeine phosphate.

Procedure Weigh accurately and powder 20 tablets. Weigh accurately a quantity of the powdered tablets, be equivalent to about 12 mg of codeine phosphate, into a 50 ml volumetric flask, add 2.5 ml of water and sonicate to make

disintegrated. Add a quantity of methanol, ultrasonic for 10 minutes to dissolve codeine phosphate, cool, dilute with methanol to volume, shake thoroughly and filter through a membrane filter. Measure accurately 2 ml of the successive filtrate into a 10 ml volumetric flask, dilute with the mobile phase to volume and mix well as the test solution. Inject 10 μ l of the test solution into the column, record the chromatogram. Dissolve an accurately weighed quantity of codeine phosphate CRS with the mobile phase to produce a solution of about 48 μ g per ml as the reference solution. Repeat the operation, using the reference solution instead of the test solution. Calculate the content of $C_{18}H_{21}NO_3 \cdot$

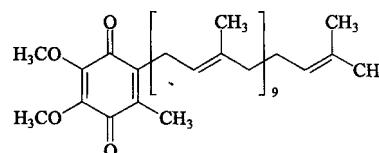
$H_3PO_4 \cdot 1\frac{1}{2}H_2O$ with respect to the peak area obtained in the chromatogram by the external standard method. The coefficient 1.068 is used in the calculation of the content of codeine phosphate.

Total Platycodon saponins Weigh accurately and powder 20 tablets. Dissolve an accurately weighed quantity of the powdered tablets, be equivalent to about 10 tablets, in a conical flask with stopper, add accurately 20 ml of water, tightly stoppered, ultrasonic for 15 minutes and filter. Transfer 4.0 ml of the successive filtrate into a separator, add 1 drop of concentrated ammonia solution, mix well, extract with two portions of chloroform, each of 15 ml. Discard the chloroform layer, extract the water layer with five portions of n-butanol saturated with water, each of 15 ml, combine the n-butanol layers and stand for 20 minutes. Filter the n-butanol layer into a stoppered conical flask, previously dried to constant weight, using a glass funnel with a wad of cotton wool. Evaporate the filtrate in vacuum to dryness in 90°C water bath, and dry in vacuum at 100°C for 2 hours, weigh and calculate the content of total platycodon saponins. It contains not less than 9 mg per tablet.

Category Antitussive expectorant.

Storage Preserve in tightly closed containers, stored in room temperature.

Coenzyme Q₁₀



$C_{59}H_{90}O_4$ 863.36

Coenzyme Q₁₀ is 2-(3,7,11,15,19,23,27,31,35,39-decamethyl-2,6,10,14,18,22,26,30,34,38-tetracontenyl)-5,6-dimethoxy-3-methyl-para-quinone. It contains not less than 98.0% of $C_{59}H_{90}O_4$, calculated on the anhydrous basis.

Description A yellow or orange-yellow crystalline powder; odourless; tasteless; decomposed easily on exposure to light.

Soluble in chloroform, benzene, acetone, ether and petroleum ether, very slightly soluble in ethanol, insoluble in water.

Melting range 48-52°C (Appendix VI C).

Identification (1) To the test solution obtained in the Assay, add 50 mg of sodium borohydride, the yellow colour of the solution disappears.

(2) The retention time of principal peak of the test solution in the chromatogram obtained in the Assay is identical with that of the principal peak of coenzyme Q₁₀ CRS in the chromatogram of the reference solution.

(3) The infrared absorption spectrum (Appendix IV C) is concordant with the reference spectrum of coenzyme Q₁₀ (Appendix XVI).

Related substances Protect from light throughout the procedure. Carry out the method as described under the Assay. Take the test solution obtained in the Assay as the test solution. Measure accurately 1.0 ml of the test solution obtained in the Assay to a 100 ml volumetric flask, dilute with dehydrated ethanol to volume as the reference solution. Inject 20 µl of the reference solution into the column. Adjust the attenuation so that the height of principal peak in the chromatogram is 25% full scale of the chart. Inject 20 µl each of the test solution and reference solution into the column, and record the chromatogram for twice the retention time of the principal peak. The sum of the areas of all peaks other than the principal peak are not greater than the area of the principal peak in the chromatogram obtained with the reference solution.

Water Not more than 0.2% (Appendix VIII M, method 1 A).

Residue on ignition Not more than 0.1% (Appendix VIII N), using 1.0 g.

Heavy metals Carry out the limit test for heavy metals (Appendix VIII H method 2), using the residue obtained in the test for Residue on ignition; not more than 0.002%.

Assay Carry out the method for high performance liquid chromatography (Appendix V D), using column packed with octadecylsilane bonded silica gel and a mixture of methanol-dehydrated ethanol (1 : 1) as the mobile phase. Column temperature is 35°C, detection wavelength is 275 nm and the number of the theoretical plates of the column is not less than 3000, calculated with reference to the peak of coenzyme Q₁₀.

Procedure Dissolve 20 mg, accurately weighed, in about 40 ml of dehydrated ethanol by shaking in a 50°C water bath, cool, transfer to a 100 ml volumetric flask, dilute with dehydrated ethanol to volume, mix well, as the test solution. Inject 20 µl into the column. Repeat the operation, using coenzyme Q₁₀ CRS instead of the substance being examined. Calculate the content of C₅₉H₉₀O₄ with reference to the peak area obtained in the chromatogram by the external standard method.

Category Coenzyme.

Storage Preserve in tightly closed containers, stored in a cool place and protected from light.

Preparation (1) Coenzyme Q₁₀ Capsules
(2) Coenzyme Q₁₀ Injection
(3) Coenzyme Q₁₀ Soft Capsules
(4) Coenzyme Q₁₀ Tablets

Coenzyme Q₁₀ Capsules

Coenzyme Q₁₀ Capsules contain not less than 90.0% and not more than 110.0% of the labelled amount of C₅₉H₉₀O₄.

Description Capsules containing yellow to orange-yellow powder or granules.

Identification Comply with the tests (1) and (2) for

Identification described under Coenzyme Q₁₀.

Content uniformity Protect from light throughout the procedure. Comply with the requirements for content uniformity except the limit is ±20% (Appendix X E). To the content of 1 capsule add a quantity of dehydrated ethanol, heat in a 50°C water bath with shaking to dissolve coenzyme Q₁₀, add dehydrated ethanol to produce a solution of about 0.2 mg of coenzyme Q₁₀ per ml. Transfer a quantity of the solution to a centrifuge tube with stopper, centrifuge at 300 rpm for 5 minutes. Carry out the method described under Assay using an accurately measured quantity of supernatant.

Related substances Comply with the test for related substance described under Coenzyme Q₁₀.

Other requirements Comply with the general requirements for capsules (Appendix I E).

Assay Protect from light throughout the procedure. To a quantity of the mixed contents in the test for weight variation of contents equivalent to about 20 mg of coenzyme Q₁₀ in a 100 ml volumetric flask, add a quantity of dehydrated ethanol, heat in a 50°C water bath with shaking to dissolve coenzyme Q₁₀, cool. Dilute with dehydrated ethanol to volume, mix well. Transfer a quantity of the solution to a centrifuge tube with stopper, centrifuge at 3000 rpm for 5 minutes. Measure accurately a quantity of supernatant and carry out the Assay described under coenzyme Q₁₀.

Category As described under Coenzyme Q₁₀.

Strength (1) 5 mg (2) 10 mg (3) 15 mg

Storage Preserve in tightly closed containers, stored in a dry place and protected from light.

Coenzyme Q₁₀ Injection

Coenzyme Q₁₀ Injection is a sterile aqueous solution of coenzyme Q₁₀. It contains not less than 90.0% and not more than 110.0% of the labelled amount of C₅₉H₉₀O₄.

Description A clear yellow liquid.

Identification Complies with the tests (1) and (2) for Identification described under Coenzyme Q₁₀.

pH value 3.2 to 5.5 (Appendix VI H).

Related substances Complies with the test for related substances described under Coenzyme Q₁₀.

Other requirements Complies with the general requirements for Injections (Appendix I B).

Assay Measure accurately 2 ml to a 25 ml volumetric flask, dilute with dehydrated ethanol to volume. Carry out the Assay described under Coenzyme Q₁₀.

Category As described under Coenzyme Q₁₀.

Strength 2 ml : 5 mg

Storage Preserve in well closed containers, stored in a cool place and protected from light.

Coenzyme Q₁₀ Soft Capsules

Coenzyme Q₁₀ soft capsules contain not less than 90.0% and not more than 110.0% of the labelled amount of C₅₉H₉₀O₄.

Description Soft capsules containing orange yellow oily liquid.

Identification Comply with the tests (1) and (2) for Identification described under coenzyme Q_{10} .

Related substances Carry out the test for Related substances described under coenzyme Q_{10} , using the solution prepared under the Assay as the test solution.

Other requirements Comply with the general requirements for Capsules (Appendix I E).

Assay Protect from light throughout the procedure. The quantity of the mixed contents obtained under the test for weight variation, add a quantity of anhydrous ethanol rapidly, heat in a 50°C water bath with shaking to dissolve coenzyme Q_{10} , cool, dilute with anhydrous ethanol to produce a solution of 0.2 mg per ml, mix well. Carry out the Assay as described under Coenzyme Q_{10} .

Category As described under Coenzyme Q_{10} .

Strength (1) 5 mg (2) 10 mg (3) 15 mg

Storage Preserve in tightly closed containers, stored in a dry place and protected from light.

Coenzyme Q_{10} Tablets

Coenzyme Q_{10} Tablets contain not less than 90.0% and not more than 110.0% of the labelled amount of $C_{59}H_{90}O_4$.

Description Yellow tablets.

Identification Comply with the tests (1) and (2) for Identification described under Coenzyme Q_{10} .

Content uniformity Protect from light throughout the procedure. Comply with the requirements for Content Uniformity except the limit is $\pm 20\%$ (Appendix X E). Triturate 1 tablet with dehydrated ethanol in a mortar and transfer with dehydrated ethanol in portions to a amber coloured volumetric flask, heat in a 50°C water bath with shaking to dissolve coenzyme Q_{10} , cool, add dehydrated to volume. Transfer a quantity of the solution to a centrifuge tube with stopper, centrifuge at 3000 rpm for 5 minutes. Measure accurately a quantity of the supernatant liquid and carry out the method described under Assay.

Related substances Carry out the test for Related substances described under Coenzyme Q_{10} , using the solution prepared under the Assay as the test solution.

Other requirements Comply with the general requirements for Tablets (Appendix I A).

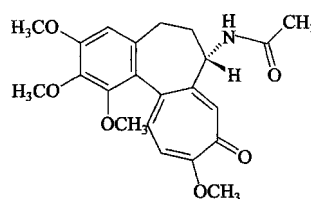
Assay Protect from light throughout the procedure. Weigh and powder 20 tablets. To an accurately weighed quantity equivalent to about 20 mg of coenzyme Q_{10} , in a 100 ml volumetric flask, add a quantity of dehydrated ethanol, heat in a 50°C water bath with shaking to dissolve coenzyme Q_{10} , cool, dilute with dehydrated ethanol to volume. Transfer a quantity of the solution to a centrifuge tube with stopper. Centrifuge at 3000 rpm for 5 minutes. Measure accurately a quantity of the supernatant and carry out the Assay described under Coenzyme Q_{10} .

Category As described under Coenzyme Q_{10} .

Strength (1) 5 mg (2) 10 mg (3) 15 mg

Storage Preserve in tightly closed containers, stored in a dry place and protected from light.

Colchicine



$C_{22}H_{25}NO_6$ 399.44

[64-86-8]

Colchicine is an alkaloid isolated from the corm of *Iphigenia indica* Kunth et Benth. (Liliaceae). It contains not less than 97.0% and not more than 103.0% of $C_{22}H_{25}NO_6$, calculated on the dried, solvent-free basis.

Description A pale yellow crystalline powder; odourless; darkens on exposure to light.

Freely soluble in ethanol or chloroform; soluble in water, but moderately concentrated solutions may deposit crystals of a hemihydrate; very slightly soluble in ether.

Melting range 148-153°C, with decomposition (Appendix VI C).

Specific optical rotation -425° to -450° , in a solution of 10 mg per ml in water (Appendix VI E), calculated on the dried, solvent-free basis.

Identification (1) Measure the light absorptions of the solution obtained in the Assay at 243 nm and 350 nm (Appendix IV A), the ratio of the absorbance at 243 nm to that at 350 nm is 1.70-2.00.

(2) The infrared absorption spectrum (Appendix IV C) is concordant with the reference spectrum of colchicine (Appendix XVI).

Chloroform and ethyl acetate Reference preparation To 1 ml, accurately measured, of ethanol-free chloroform in a 1000 ml volumetric flask, add 20 ml of internal standard solution (1.0% ethanol); to 1 ml, accurately measured, of ethanol-free ethyl acetate in another 1000 ml volumetric flask, add 100 ml of the internal standard solution. Dilute each with water to volume and mix well.

Test preparation Weigh accurately 3 separate portions of about 0.25 g each, in three 10 ml volumetric flasks, add accurately 0 ml, 0.2 ml or 1 ml of internal standard solution, dilute with water to volume, mix well.

Procedure Carry out the method for gas chromatography (Appendix V E), using a 2 m long column packed with 10% (g/g) polyethylene glycol 1000. Maintain the column temperature at 75°C. The sum of the contents of chloroform, ethyl acetate and the percentage loss on drying determined in the test below is not more than 10.0%.

Loss on drying When dried in vacuum over phosphorus pentoxide for 24 hours, loses not more than 3.0% of its weight (Appendix VIII L).

Residue on ignition Not more than 0.1% (Appendix VIII N).

Assay Dissolve a quantity, accurately weighed, in water to produce a solution of 10 μ g per ml, measure the absorbance at 350 nm (Appendix IV A). Calculate the content of $C_{22}H_{25}NO_6$, taking 425 as the value of A (1%, 1 cm).

Category Anti-gout and antineoplastic.

Storage Preserve in tightly closed containers, protected from light.

Preparation Colchicine Tablets

Colchicine Tablets

Colchicine Tablets contain not less than 90.0% and not more than 110.0% of the labelled amount of colchicine ($C_{22}H_{25}NO_6$).

Description White tablets.

Identification Mix a quantity of the powdered tablets containing 1 mg of colchicine with 0.2 ml of sulphuric acid in a white dish; a lemon colour is produced. Add 0.05 ml of nitric acid; the colour changes to greenish blue and then rapidly becomes reddish and finally yellow or almost colourless. Add an excess of 5 mol/L sodium hydroxide, the colour changes to red.

Content uniformity Comply with the requirements for content uniformity (Appendix X E). Triturate 1 tablet with water and transfer to a 50 ml (for strength 0.5 mg) or 100 ml (for strength 1 mg) volumetric flask, add 40 ml or 80 ml of water, dilute with water to volume, shake thoroughly and filter. Measure the absorbance of the filtrate at 350 nm (Appendix IV A), calculate the content of $C_{22}H_{25}NO_6$, taking 425 as the value of A (1%, 1 cm).

Other requirements Comply with the general requirements for tablets (Appendix I A).

Assay Weigh accurately and finely powder 20 tablets. Weigh accurately a quantity of the powder equivalent to about 1.0 mg of colchicine to a 100 ml volumetric flask, add about 50 ml of water, shake for 1 hour to dissolve colchicine, add water to volume and mix well. Filter and measure the absorbance of the successive filtrate at 350 nm (Appendix IV A). Calculate the content of $C_{22}H_{25}NO_6$, taking 425 as the value of A (1%, 1 cm).

Category As described under Colchicine.

Strength (1) 0.5 mg (2) 1 mg

Storage Preserve in tightly closed containers, protected from light.

Colistin Sulfate

[1264-72-8]

Colistin Sulfate is an antibiotic mixture of polymyxins. It has a potency of not less than 17000 Colistin Units per mg, calculated on the dried basis.

Description A white to pale-yellow powder; odourless or almost odourless; hygroscopic. Freely soluble in water; slightly soluble in ethanol; practically insoluble in acetone, chloroform or ether.

Identification (1) To about 20 mg add 2 ml of phosphate buffer solution (pH 7.0), 0.2 ml of 0.5% ninhydrin solution and heat to boil; a violet colour is produced.

(2) Dissolve about 2 mg in 5 ml of water, add 5 ml of 10% sodium hydroxide solution and 5 drops of 1% copper sulfate solution and shake thoroughly after each drop; a reddish-violet colour is produced.

(3) The aqueous solution yields the reactions characteristic

of sulfates (Appendix III).

Acidity An aqueous solution of 10 mg per ml, pH 4.0-6.5 (Appendix VI H).

Loss on drying When dried to constant weight at 105°C, loses not more than 6.0% of its weight (Appendix VIII L), using 0.2-0.3 g.

Assay Weigh accurately a quantity and add sterile water to produce a solution of about 10000 units per ml, carry out the microbiological assay of antibiotics (Appendix XI A).

Category Antifungal.

Storage Preserve in tightly closed containers, protected from light and stored in a dry place.

Preparation Colistin Sulfate Tablets

Colistin Sulfate Tablets

Colistin Sulfate Tablets contain not less than 90.0% and not more than 110.0% of the labelled amount of colistin.

Description White to pale yellow tablets.

Identification Triturate 1 tablet with a quantity of water to dissolve colistin sulfate and filter, the filtrate complies with the tests for Identification described under Colistin Sulfate.

Other requirements Comply with the general requirements for tablets (Appendix I A).

Assay Weigh accurately and powder 10 tablets. Weigh accurately a quantity of the powder equivalent to about 250000 colistin units, carry out the Assay described under Colistin Sulfate.

Category As described under Colistin Sulfate.

Strength (1) 500000 units (2) 1000000 units
(3) 3000000 units

Storage Preserve in tightly closed containers, protected from light and stored in a dry place.

Colloidal Bismuth Pectin

Colloidal Bismuth Pectin is a complex of uncertain composition of pectin and Bismuth. It contains not less than 14.0% and not more than 16.0% of bismuth pectin, calculated on the bismuth.

Description Yellow powder; odourless; flavourless. Practically insoluble in ethanol or organic solvents; agglomerate in water, uniformly disperse in water when shaking.

Identification (1) To 5 mg add 10 ml of water, stir, acidify with dilute sulfuric acid, add drops of 10% thiourea solution, a dark yellow colour is produced.

(2) To 10 mg add 25 ml of water, stir, acidify with dilute sulfuric acid, add drops of potassium iodate TS, a brownish-red or brownish-black precipitate is produced; separate the precipitate and dissolve in an excess of potassium iodate TS to produce an orange yellow solution, dilute with water to produce an orange precipitate.

(3) To 0.1 g add 10 ml of hot water, stir, cool, add 10 ml of ethanol to produce a gelatification.

Alkalinity Dissolve 50 mg of the dried substance in 50 ml of

water, shake well, pH 8.5-10.5 (Appendix VI H).

Colloid stability To 0.25 g in a 100 ml measuring cylinder with stopper add water to volume, shake thoroughly for 1 minute to a gelatinoid solution, allow to stand for 1 hour, the colloid is not less than 97 ml.

Sulfate Wet 2.0 g with 6 ml of hydrochloric acid, add water to 100 ml and filter. Dispart 50 ml of the successive filtrate into two portions. To the portion add 5 ml of 25% barium chloride solution, allow to stand for 10 minutes, filter again and again until the filtrate is clear; add 4.0 ml of potassium sulfate standard solution, shake well, allow to stand for 10 minutes as the reference solution. To another portion add 5 ml of 25% barium chloride solution, allow to stand for 10 minutes. Carry out the limit test for sulfates (Appendix VIII B), any opalescence produced is not more pronounced than that of the reference solution (0.08%).

Nitrate To 50 mg add 100 ml of water, stir and filter. To 20 ml of the successive filtrate add 2 ml of sulfanilic acid- α -naphthylamine TS and 10 mg of zinc powder, allow to stand for 15 minutes. Any colour produced is not more intense than that of the potassium nitrate standard solution, using 0.6 ml produced by same method (dissolve 81.5 mg of potassium nitrate previously, measured accurately and dried to constant weight at 105°C, in a quantity of water in 50 ml volumetric flask, dilute with water to volume, shake well; measure accurately 5 ml to 100 ml volumetric flask, dilute with water to volume, shake well. Each ml of the solution is equivalent to 0.05 mg of NO_3^-) (0.3%).

Lead Ignite andante 1.0 g in a crucible until the carbonization is complete, cool; add 0.5-1 ml of sulfuric acid, evaporate by heating until the vapor of sulfuric acid is removed; ignite the residue in a crucible at 600°C until the incineration is complete, cool; add 0.5 ml of nitric acid dropwise to dissolve the residue, heat on a water bath to dryness, cool, add 5 ml of potassium hydroxide solution (1→6), stir, heat to boil for 2 minutes, supply a quantity of water to the former volume and filter. Wash the residue with water, combine the filtrate and washings, adjust to pH7 with acetic acid, add 2 ml of acetate BS, dilute with water to 25 ml, add 2 ml of thioacetamide TS, shake well and allow to stand for 2 minutes. Any colour produced is not more intense than that of a reference lead standard solution operated in the same manner using 2.0 ml (0.002%).

Arsenic Dissolve 1.0 g in 5 ml of hydrochloric acid, add 23 ml of water. Carry out the limit test for arsenic (Appendix VIII J, method 1); not more than 0.0002%.

Assay Dissolve about 0.5 g, accurately weighed, in 5 ml of nitric acid solution (1→2) by heating, add 150 ml of water and two drops of xylenol orange IS, titrate with disodium edetate (0.05 mol/L) VS to yellow colour. Each ml of disodium edetate (0.05 mol/L) VS is equivalent to 10.45 mg of Bi.

Category Anti-ulcerative.

Storage Preserve in tightly closed containers, protected from light.

Preparation Colloidal Bismuth Pectin Capsules

Colloidal Bismuth Pectin Capsules

Colloidal Bismuth Pectin Capsules contain not less than 90.0% and not more than 110.0% of the labelled amount of Bi.

Description Hard capsules with yellow powders or

granules.

Identification The contents of capsules comply with the tests for Identification described under Colloidal Bismuth Pectin.

Other requirements Comply with the general requirements for capsules (Appendix I E).

Assay Mix a quantity of the contents in the test for weight variation, Weigh accurately a quantity equivalent to about 75 mg of Bi. Carry out the test for Assay described under Colloidal Bismuth Pectin.

Category As described under Colloidal Bismuth Pectin.

Strength (1) 40 mg (2) 50 mg (calculated on Bi)

Storage Preserve in tightly closed containers and protected from light.

Colloidal Chromium Phosphate [^{32}P] Injection

Colloidal Chromium Phosphate [^{32}P] Injection is a sterile colloidal dispersion of chromium phosphate [^{32}P]. It contains not less than 90.0% and not more than 110.0% of the labelled amount of radioactive concentration of phosphorus [-32] at the date and hour stated on the label.

Description A green colloidal liquid.

Identification (1) Complies with the test (1) for Identification described under Sodium Phosphate [^{32}P] Oral Solution.

(2) The principal spot obtained in the determination of Radiochemical purity has a prominent radioactive peak with R_f value of 0-0.1.

pH value 6.0-8.0 (Appendix VI H).

Colloidal particles size When viewed under an electron microscope, not less than 60% of the colloidal particles are 20-50 nm in diameter.

Bacterial endotoxin Dilute a quantity with Water BET for at least 15 times of its original volume; less than 15 EU/ml (Appendix XI E).

Sterility Carry out the test for sterility (Appendix XI H), the result complies with the requirements.

Radiochemical purity Carry out the determination of radiochemical activity (purity) (Appendix XIII, method 1), using acetic acid-water (0.5 : 100) as the mobile phase. Not less than 98% of the total radioactivity is found in the spot corresponding to chromium phosphate [^{32}P].

Radioactive concentration Not less than 37 MBq per ml (Appendix XIII).

Category Radiopharmaceutical.

Strength (1) 185 MBq (2) 370 MBq

Storage Preserve in well closed lead containers, stored in a cool place. The intensity of radiation on the surface of the container complies with relevant regulation.

Compound Almitrine Tablets

Compound almitrine tablets contain not less than

90.0% and not more than 110.0% of the labelled amount of almitrine bismesylate ($C_{26}H_{29}F_2N_7 \cdot 2CH_3SO_3H$) and raubasine ($C_{21}H_{24}N_2O_3$) respectively.

Formula	Almitrine bismesylate	30 g
	Raubasine	10 g

To make 1000 tablets

Description Film coated tablets with white or almost white core.

Identification The retention time of principal peaks of almitrine bismesylate and raubasine in the substance being examined in the chromatogram obtained in the Assay are identical with that of the principal peaks of almitrine bismesylate CRS and raubasine CRS in the chromatogram of the reference solution correspondingly.

Related substance Remove the film coating of tablets, the core contains bilayer, separate the external layer containing raubasine from the internal layer containing almitrine bismesylate. Dissolve a quantity of finely powdered external layer in chloroform to produce a solution of 10 mg of raubasine per ml, filter and use the successive filtrate as the test solution. Measure accurately a quantity of the test solution to produce three solutions in chloroform containing (1) 0.05 mg per ml, (2) 0.10 mg per ml, (3) 0.20 mg per ml. Carry out the method for thin-layer chromatography (Appendix V B). Using silica gel GF₂₅₄ and a mixture of chloroform-methanol (40 : 0.1) as the mobile phase. Apply separately to the plate 10 μ l each of above four solutions, after developing and removal of the plate, dry it in air, examine under ultraviolet light at 254 nm. The intensity of any secondary spot in the chromatogram obtained with the test solution, is compared with that of the principal spots obtained with solution (1), (2), (3), the total impurity is not more than 4%.

Dissolve a quantity of finely powdered internal layer in methanol to produce a solution of 20 mg of almitrine bismesylate per ml, filter, use the successive filtrate as the test solution. Measure accurately a quantity of the test solution to produce three solutions in methanol containing (1) 0.10 mg per ml, (2) 0.20 mg per ml (3) 0.40 mg per ml. Carry out the method for thin-layer chromatography (Appendix V B). Using silica gel GF₂₅₄ and the supernatant liquid of n-hexane-dichloromethane-ether-concentrated ammonia water (38 : 25 : 12 : 1.0) as the mobile phase. Apply separately to the plate 5 μ l each of above four solutions, after developing and removal of the plate, dry it in air, expose the plate to iodine vapor until the colour of spot changes and examine immediately. The intensity of any secondary spot, in the chromatogram obtained with the test solution, is compared with that of the principal spots obtained with Solution (1), (2), (3), the total impurity is not more than 2.5%.

Content uniformity Comply with the requirements for content uniformity (Appendix X E). Transfer 1 tablet to a 100 ml volumetric flask, add a quantity of the mobile phase in the Assay, ultrasonicate for 30 minutes, cool and dilute with the mobile phase to the volume, mix well, filter, use the successive filtrate as the test solution. Carry out the method described under the Assay and calculate the content.

Dissolution Carry out the dissolution test (Appendix X C, method 2). Using hydrochloride acid solution (0.5→1000) 1000 ml as dissolution medium, adjust the rotational speed of the paddle to 100 rpm. Withdraw a quantity of the solution as test solution after exactly 45 minutes and filter. Dilute a portion of the successive filtrate with 20 volumes of

the mobile phase described under the Assay as the test solution. Weigh accurately a quantity of almitrine bismesylate CRS and raubasine CRS to the same volumetric flask, add the dissolution medium to produce a solution of 30 μ g of almitrine bismesylate CRS per ml and 10 μ g of raubasine CRS per ml, then dilute a portion of the solution with 20 volumes of the mobile phase as reference solution. Inject separately 20 μ l each of the two solutions into the column, carry out the method described under the Assay, calculate the dissolutions of $C_{26}H_{29}F_2N_7 \cdot 2CH_3SO_3H$ and $C_{21}H_{24}N_2O_3$ form each tablet, not less than 70% of the labelled amount is dissolved respectively.

Other requirements Comply with the general requirements for tablets (Appendix I A).

Assay Carry out the method for high performance liquid chromatography (Appendix V D). Using a column packed with octadecylsilate bonded silica gel and a mixture of methanol-water (85 : 15) (add 5 μ l of diethylamine in 1000 ml) as the mobile phase. Detection wavelength is 222 nm. The number of theoretical plates of the column is not less than 900, calculated with reference to the peaks of almitrine bismesylate and raubasine respectively. The resolution factor between the peaks of almitrine bismesylate and raubasine complies with the related requirements.

Procedure weigh accurately and powder finely 10 tablets, dissolve a quantity of the powdered tablets equivalent to about 30 mg of almitrine bismesylate and 10 mg of raubasine in a quantity of the mobile phase in a 100 ml volumetric flask, ultrasonicate for 30 minutes, cool and dilute with the mobile phase to volume, mix well, filter. Inject 20 μ l of the successive filtrate into the column and record the chromatogram. Weigh accurately a quantity of almitrine bismesylate CRS and raubasine CRS respectively, dilute with the mobile phase to produce two solutions of 0.3 mg of almitrine bismesylate CRS per ml and 0.1 mg of raubasine CRS per ml. Measure in the same manner. Calculate the contents of $C_{26}H_{29}F_2N_7 \cdot 2CH_3SO_3H$ and $C_{21}H_{24}N_2O_3$ respectively.

Category Nootropic.

Storage Preserve in tightly closed containers, stored in a cool place and protected from light.

Compound Aspartate, Vitamin B₆ and Dipotassium Glycyrhetate Eye Drops

Compound Aspartate, Vitamin B₆ and Dipotassium Glycyrhetate Eye Drops contain not less than 90.0% and not more than 110.0% of the labelled amount of Naphazoline Hydrochloride ($C_{14}H_{14}N_2 \cdot HCl$), Aspartic Acid ($C_4H_7NO_4$), Vitamin B₆ ($C_8H_{11}NO_3 \cdot HCl$), Dipotassium Glycyrhetate ($C_{42}H_{60}K_2O_{16}$) and Neostigmine Methylsulfate ($C_{13}H_{22}N_2O_6S$) respectively; not less than 85.0% and not more than 115.0% of the labelled amount of Chlorphenamine Maleate ($C_{16}H_{19}ClN_2 \cdot C_4H_4O_4$).

Formula	Aspartic Acid	7.8 g
	Vitamin B ₆	0.5 g
	Dipotassium Glycyrhetate	1.0 g
	Naphazoline Hydrochloride	0.03 g
	Neostigmine Methylsulfate	0.05 g
	Chlorphenamine Maleate	0.1 g
	Excipient	a sufficient quantity

Water for Injection a sufficient quantity

To make 1000 ml

Description A clear, faintly yellow liquid.

Identification The retention time of the principal peaks of the substances being examined in the chromatogram of the Assay corresponds to those of the reference substances.

pH value 4.5-6.5 (Appendix VI H).

Colour The absorbance at 430 nm is not more than 0.06 (Appendix IV A).

Osmolality 0.9-1.1 (Appendix IX G).

Other requirements Comply with the general requirements for eye preparations (Appendix I G).

Assay *Vitamin B₆, neostigmine methylsulfate, naphazoline hydrochloride, chlorphenamine maleate, and dipotassium glycyrrhetate* Carry out the method for high performance liquid chromatography (Appendix V D), using a column packed with octadecylsilane bonded silica gel and a solution of sodium heptanesulphonate (dissolve 4.04 g of sodium heptanesulphonate and 2.72 g of potassium dihydrogen phosphate in 1000 ml of water, adjust pH to 3.0 with phosphoric acid) as mobile phase A, acetonitrile as mobile phase B, perform a gradient elution program as following table. The flow rate is 1.0 ml/min and detection wavelength is 260 nm, changed to 220 nm in 10 minutes. The retention time of the principal peaks of the substance being examined in the chromatogram is as follows; vitamin B₆: 6-9 minutes; neostigmine methylsulfate: 16-18 minutes; naphazoline hydrochloride: 23-26 minutes; chlorphenamine maleate: 27-30 minutes; dipotassium glycyrrhetate: 31-34 minutes. The number of the theoretical plates of the column is not less than 5000, calculated with reference to the peak of vitamin B₆. The resolution factor among the peaks of each component complies with the related requirements.

Time(min)	Mobile phase A(%)	Mobile phase B(%)
0	85	15
6	85	15
15	73	27
25	65	35
35	55	45
40	55	45
42	85	15
45	85	15

Procedure Measure accurately 10 ml of the eye drops to a 25 ml volumetric flask, dilute with water to volume, mix well. Inject 20 μ l of the resulting solution into the column, record the peak area correspondingly obtained in the chromatogram. Dissolve an accurately weighed quantity of vitamin B₆ CRS, neostigmine methylsulfate CRS, naphazoline hydrochloride CRS, chlorphenamine maleate CRS and dipotassium glycyrrhetate CRS with water to produce a solution of 0.2 mg of vitamin B₆, 0.02 mg of neostigmine methylsulfate, 0.012 mg of naphazoline hydrochloride, 0.04 mg of chlorphenamine maleate, and 0.4 mg of dipotassium glycyrrhetate per ml. Inject 20 μ l of the resulting solution into the column, calculate the content of C₈H₁₁NO₃ · HCl, C₁₃H₂₂N₂O₆S, C₁₄H₁₄N₂ · HCl, C₁₆H₁₉ClN₂ · C₄H₄O₄, C₄₂H₆₀K₂O₁₆.

Aspartic acid Carry out the method for high performance liquid chromatography (Appendix V D), using a column

packed with aminosilane bonded silica gel and a mixture of solution of potassium dihydrogen phosphate (dissolve 5.44 g of potassium dihydrogen phosphate in water, dilute to 1000 ml)-acetonitrile (58 : 42) as mobile phase. Detection wavelength is 220 nm. Dissolve a quantity of aspartic acid CRS and dipotassium glycyrrhetate CRS with water to produce a solution of 1.56 mg of aspartic acid and 0.2 mg of dipotassium glycyrrhetate per ml. Inject 20 μ l of the resulting solution into the column and the number of the theoretical plates of the column is not less than 2000, calculated with reference to the peak of aspartic acid. The resolution factor between the peaks of dipotassium glycyrrhetate and aspartic acid complies with the related requirements.

Procedure Measure accurately 2 ml of the eye drops to a 10 ml volumetric flask, dilute with water to volume, mix well. Inject 20 μ l of the resulting solution into the column, record the peak area correspondingly obtained in the chromatogram. Accurately weigh about 78 mg of aspartic acid in 50 ml volumetric flask, dissolve with water and dilute to the volume, mix well. Inject 20 μ l of the resulting solution into the column, calculate the content of C₄H₇NO₄.

Category Ophthalmics.

Strength (1) 13 ml (2) 15 ml

Storage Preserve in well closed containers.

Compound Glycyrrhiza Oral Solution

Compound Glycyrrhiza Oral Solution contains not less than 0.0765 mg and not more than 0.104 mg of anhydrous morphine (C₁₇H₁₉NO₃) per ml; and contains not less than 4.50 mg and not more than 5.50 mg of guaifenesin (C₁₀H₁₄O₄) per ml.

Formula	Liquid Extract of Liquorice Root	120 ml
	Compound Camphor Tincture	180 ml
	Glycerin	120 ml
	Guaifenesin	5 g
	Concentrated Ammonia Solution	a quantity
	Water	a quantity
	To make	1000 ml

Production Mix well the liquid extract of liquorice root and glycerin, add water 500 ml to the mixture, add cautiously a quantity of concentrated ammonia solution and adjust to pH 8-9, add the solution of guaifenesin (dissolve the guaifenesin in a quantity of hot water) with constant stirring, add compound camphor tincture, add water to produce 1000 ml and mix well. A quantity of stabilizing agent must be added.

Description A brown or brown-black liquid; odour, fragrance; taste, sweet; a little of precipitate may be produced during the storage period.

Identification (1) Mix a quantity well, transfer 10 ml into a separator. Adjust to pH about 2 with hydrochloride acid and mix well, extract with two 20 ml portions of chloroform and combine the extracts. Wash the extracts with 10 ml of water and filter the chloroform layer through anhydrous sodium sulfate, evaporate the filtrate in vacuum to dryness. Add 2 drops of formaldehyde TS and 0.5 ml of sulfuric acid to the residue, intense purple-red colour is produced immediately.

(2) Adjust the acid aqueous solution obtained under the Identification test (1) to pH value 9-10 with ammonia TS. Extract with a mixture of chloroform-isopropanol (3 : 1)

two times, each of 20 ml, and combine the extracts. Filter the extracts through anhydrous sodium sulfate, evaporate the filtrate in vacuum to dryness. Dissolve the residue in 1 ml of methanol as the test solution. Dissolve a quantity of morphine CRS in methanol and dilute to produce a solution of 1.0 mg per ml as the reference solution. Carry out the thin-layer chromatography (Appendix V B), using silica gel G as the coating substance and a mixture of toluene-acetone-anhydrous ethanol-concentrated ammonia TS (20 : 20 : 5 : 0.6) as the mobile phase. Apply separately to the plate 10 μ l each of above two solutions, after developing and removal of the plate, dry it in air, spray with Potassium Iodobismuthate, Dilute TS. The colour and position of the principal spots in the chromatogram obtained with the test solution correspond to the principal spots in the chromatogram obtained with reference solution.

(3) Mix a quantity well, to 3 ml add 5 ml of hydrochloride acid and 30 ml of chloroform, heat under reflux for 1.5 hours at 85°C, cool and filter the chloroform layer through anhydrous sodium sulfate, evaporate the filtrate to dryness. Dissolve the residue in 1 ml of methanol as the test solution. Dissolve a quantity of glycyrrhetic acid CRS in methanol and dilute to produce a solution of 0.5 mg per ml as the reference solution. Carry out the thin-layer chromatography (Appendix V B), using silica gel G as the coating substance and a mixture of petroleum ether (bp 60-90°C)-benzene-ethyl acetate-glacial acetic acid (10 : 20 : 7 : 1) as the mobile phase. Apply separately to the plate 10 μ l each of above two solutions, after developing and removal of the plate, dry it in air. Then spray with 10% phosphomolybdic acid solution of ethanol, heat at 105°C till the spots appear clearly. The colour and position of the principal spots in the chromatogram obtained with the test solution correspond to the principal spots in the chromatogram obtained with reference solution.

pH value 6.0-9.0 (Appendix VI H).

Other requirements Except clarity, complies with the general requirements for oral solution (Appendix I O).

Assay Morphine Carry out the method for high performance liquid chromatography (Appendix V D), using a column packed with octasilane bonded silica gel and a mixture of 0.05 mol/L potassium dihydrogen phosphate solution-0.0025 mol/L sodium heptanesulfonate solution-acetomitrile (5 : 5 : 2) as the mobile phase. Detection wavelength is 220 nm. The number of the theoretical plates of the column is not less than 1000, calculated with reference to the peak of morphine.

System suitability test for solid phase extraction column Using a column packed with octadecylsilane bonded silica gel, carry out the test as described under the Procedure. Transfer 0.5 ml of a 5% acetic acid solution containing 0.1 mg morphine CRS per ml, accurately measured, to the column pretreated. Collect the eluate into a 5 ml of volumetric flask to volume and mix well. Inject 10 μ l of the eluate and the reference solution as described under the Procedure into the column respectively, record the peak areas correspondingly obtained in the chromatogram. The ratio of the peak areas of morphine obtained in the chromatogram of the eluate to the peak areas of morphine obtained in the chromatogram of reference solution is not less than 0.97 and not more than 1.03.

Procedure Wash a solid phase extraction column with 15 ml of a mixture of methanol-water (3 : 1) and 5 ml of water in sequence, then wash the column with the ammonia solution of pH value about 9 (add drops of ammonia TS to a quantity of water until the pH value of the solution is about 9), until the pH value of the eluate is about 9. Sonicate a quantity for 10 minutes and mix well. Measure accurately 0.5 ml to the

above washed column, drop a quantity ammonia TS to adjust pH value of the solution in the column to about 9 (define the quantity of ammonia TS using another same volume of the successive filtrate previously), mix well, rinse with 20 ml of water after no solvent drips. Elute with 5% acetic acid solution, and collect the eluate into a 5 ml of volumetric flask to volume and mix well. Inject 20 μ l of the eluate into the column and record the chromatogram. Repeat the operation, using a 5% acetic acid solution containing morphine CRS 0.01 mg per ml instead of the eluate. Calculate the content of $C_{17}H_{19}NO_3$ with respect to the peak areas obtained in the chromatogram by the external standard method.

Guaifenesin Carry out the method for high performance liquid chromatography (Appendix V D), using a column packed with octasilane bonded silica gel and a mixture of 0.05 mol/L potassium dihydrogen phosphate solution-0.0025 mol/L sodium heptanesulfonate solution-acetomitrile (18 : 18 : 10) as the mobile phase. Detection wavelength is 220 nm. The number of the theoretical plates of the column is not less than 2000, calculated with reference to the peak of guaifenesin.

Procedure Wash a solid phase extraction column with 15 ml of a mixture of methanol-water (3 : 1) and 5 ml water in sequence, then wash the column with the ammonia solution of pH value about 9 until the pH value of the eluate is about 9. Sonicate a quantity for 10 minutes and mix well, measure accurately 1.0 ml into a 50 ml volumetric flask, dilute with water to volume and mix well. Measure accurately 0.5 ml to the above washed column, and collect the eluate to a 5 ml volumetric flask. Elute with 5% acetic acid solution containing 30% methanol after no solvent drips. Collect the eluate into the 5 ml of volumetric flask to volume and mix well. Inject 20 μ l of the eluate into the column and record the chromatogram. Dissolve a quantity of guaifenesin CRS, accurately weighed, in 5% acetic acid solution containing 30% methanol to produce a solution of 0.01 mg per ml as reference solution. Repeat the operation, using the reference solution instead of the eluate. Calculate the content of $C_{10}H_{14}O_4$ with respect to the peak areas obtained in chromatogram by the external standard method.

Category Antitussive expectorant

Strength (1) 10 ml (2) 100 ml (3) 120 ml
(4) 180 ml (5) 500 ml (6) 2000 ml
(7) 2500 ml

Storage Preserve in tightly closed containers, stored in a cool and dry place and protected from light.

Compound Liquorice Tablets

Compound Liquorice Tablets contain not less than 0.36 mg and not more than 0.44 mg of anhydrous morphine ($C_{17}H_{19}NO_3$) in each tablet.

Formula Extract of liquorice (medium powder) 112.5 g

Opium powder or powdered	
poppy capsule extractive	4 g
Camphor	2 g
Anise oil	2 g
Sodium benzoate (medium powder)	2 g

To make 1000 tablets

Processing Dry and pulverize the extract of liquorice, add sodium benzoate and opium powder, mix well and make granules. Add camphor, previously dissolved in a small

quantity of ethanol and anise oil, mix well and compress into tablets.

Description Brown or dark brown tablets; odour, characteristic; taste, sweet; hygroscopic.

Identification (1) Shake thoroughly 2 powdered tablets with 7 ml of water and adjust the mixture to about pH 9 with 10% anhydrous sodium carbonate solution. Extract twice with 20 ml each of a mixture of chloroform-isopropanol (3 : 1). Wash the combined extracts with a small quantity of ammonia TS and water in sequence, evaporate the extracts to dryness, dissolve the residue in 0.3 ml of methanol as the test solution; dissolve a quantity of morphine CRS in methanol to produce a solution of 2 mg per ml as the reference solution. Carry out the thin-layer chromatography (Appendix V B), using silica gel G as the coating substance and a mixture of ethyl acetate-methanol-concentrated ammonia solution (35 : 10 : 5) as the mobile phase. Apply separately to the same plate 10 µl each of the solutions, after developing and removal of the plate, dry it in air, spray with potassium iodobismuthate TS. The colour and position of the principal spot in the chromatogram obtained with the test solution correspond to the principal spot obtained with the reference solution.

(2) Dissolve a quantity of powdered tablets in water, filter. To a small quantity of the filtrate add 1-2 drops of diluted sulfuric acid, a faint brown precipitate is produced immediately, which is very soluble in concentrated ammonia solution.

Other requirements Comply with the general requirements for tablets except the disintegration test (Appendix I A).

Assay Carry out the method for high performance liquid chromatography (Appendix V D), using a column packed with octylsilane bonded silica gel and a mixture of 0.05 mol/L potassium dihydrogen phosphate solution-0.0025 mol/L Sodium heptanesulfonate solution-acetonitrile (5 : 5 : 2) as the mobile phase. The detection wavelength is 220 nm and the number of the theoretical plates of the column is not less than 1000, calculated with reference to the peak of morphine.

System suitability test for solid phase extraction column

Using a column packed with octadecylsilane bonded silica gel, carry out the test as described under the Procedure. Transfer 1 ml of a solution containing 0.05 mg morphine CRS per ml, accurately measured, to the column pretreated. Collect the eluate into a 5 ml of volumetric flask to volume and mix well. Inject 10 µl of the eluate and the reference solution described under the Procedure into the column respectively, record the peak areas correspondingly obtained in the chromatogram. The ratio of the peak areas of morphine obtained in the chromatogram of the eluate to the peak areas of morphine obtained in the chromatogram of reference solution is not less than 0.97 and not more than 1.03.

Procedure Wash a solid phase extraction column with 15 ml of a mixture of methanol-water (3 : 1) and 5 ml of water in sequence, then wash the column with the ammonia solution of pH about 9 (add drops ammonia TS to a quantity of water until the pH of the solution is about 9), until the pH of the eluate is about 9. Weigh accurately and powder 20 tablets. Triturate a quantity of the powder, accurately weighed, equivalent to about 10 tablets in a conical flask, accurately add 90 ml of water, treated by ultrasonic for 5 minutes, accurately add 10 ml of dilute hydrochloride solution (6 → 10), shake well, dissolve morphine by ultrasonic treatment, cool to room temperature and filter. Measure accurately 1.0 ml of successive filtrate to the above washed column, drop a quantity of ammonia TS to adjust pH of the solution in the

column to about 9 (define the quantity of ammonia TS using another same volume of the successive filtrate previously), mix well, rinse with 20 ml of water after no solvent drips. Elute with 5% acetic acid solution contains 2% methanol, and collect the eluate into a 5 ml of volumetric flask to volume and mix well. Inject 20 µl of the eluate into the column and record the chromatogram. Dissolve and dilute a quantity of morphine CRS with the 5% acetic acid solution contains 2% methanol to produce a solution of 0.01 mg per ml. Repeat the operation, calculate the content of $C_{17}H_{19}NO_3$ with respect to the peak areas obtained in the chromatogram by the external standard method.

Category Antitussive expectorant.

Storage Preserve in tightly closed containers, stored in a dry place.

Compound Miconazole Nitrate Cream

Compound miconazole nitrate cream contains not less than 90.0% and not more than 110.0% of the labelled amount of miconazole nitrate ($C_{18}H_{14}Cl_4N_2O \cdot HNO_3$) and clobetasol propionate ($C_{25}H_{32}ClFO_5$) respectively.

Formula	Miconazole Nitrate	20 g
	Clobetasol Propionate	0.5 g
	Creamy Base	a quantity
	To make	1000 g

Description A creamy white cream.

Identification (1) Dissolve about 2 g in 20 ml of anhydrous ethanol by gentle heating, evaporate filtrate to dryness on the water bath, cool and filter, drop a quantity of diphenylamine IS, a blue colour is produced.

(2) The retention time of principal peaks of clobetasol propionate and miconazole nitrate in the substance being examined in the chromatogram obtained in the Assay are identical with that of the principal peaks of clobetasol propionate CRS and miconazole nitrate CRS in the chromatogram obtained of the reference solution correspondingly.

Other requirements Complies with the general requirements for creams (Appendix I F).

Assay Carry out the method for high performance liquid chromatography (Appendix V D). Using a column packed with octadecylsilane bonded silica gel and a mixture of 0.5% ammonium acetate solution-acetonitrile-methanol (24 : 38 : 38) as the mobile phase. Detection wavelength is 240 nm, column temperature is 35°C. The number of theoretical plates of the column is not less than 2000, calculated with reference to the peak of miconazole nitrate. The resolution factor among the peaks of clobetasol propionate, miconazole nitrate and internal standard substance complies with the related requirements.

Internal standard solution Measure accurately 0.4 mg of dibutyl phthalate into a 100 ml volumetric flask, dilute with methanol to volume, mix well.

Procedure Weighed accurately about 2.5 g in a beaker, add accurately measured 1 ml of internal standard solution. Add 20 ml of methanol, heat in water bath at 80°C with intermittent stirring until the cream is completely dissolved, cool on ice-water bath until the base is completely freed, filter and repeat the extraction with 15 ml and 10 ml of methanol separately, combine the filtrate and washings to a 50 ml volumetric flask, add methanol to the volume, mix

well. Freezing for 2 hours and filter quickly. Inject 20 μ l of the successive filtrate into the column. Dissolve 12.5 mg of clobetasol propionate CRS, accurately weighed, in methanol in a 25 ml volumetric flask, dilute to volume, mix well. Weigh accurately 50 mg of miconazole nitrate CRS in a 50 ml volumetric flask, transfer 2 ml of the clobetasol propionate solution and 1 ml of the internal standard solution, both measured accurately, into the same volumetric flask, dilute with methanol to the volume, mix well. Measure in the same manner, Calculate the contents of $C_{18}H_{14}Cl_4N_2O \cdot HNO_3$ and $C_{25}H_{32}ClFO_5$ respectively.

Category Dermics.

Storage Preserve in tightly closed containers, stored in a cool place and protected from light.

Compound Platycodon Tablets

Compound Platycodon Tablets contain not less than 2.7 mg and not more than 3.3 mg of anhydrous morphine ($C_{17}H_{19}NO_3$) in each tablet.

Formula	Powdered Opium	30 g
	Powdered Platycodon Root	90 g
	Potassium Sulfate	180 g
	Excipient	a quantity
	To make	1000 tablets

Description Pale brown tablets.

Identification Comply with tests for Identification described under Opium, using a quantity of the powdered tablets equivalent to about 0.1 g of powdered opium.

Other requirements Comply with the general requirements for tablets (Appendix I A), but the disintegration time is 20 minutes.

Assay Carry out the method for high performance liquid chromatography (Appendix V D), using a column packed with octylsilane bonded silica gel and a mixture of 0.05 mol/L dihydrogen phosphate solution-0.0025 mol/L sodium heptanesulfonate solution-acetonitrile (2 : 2 : 1) as the mobile phase. The detection wavelength is 220 nm and the number of the theoretical plates of the column is not less than 1000, calculated with reference to the peak of morphine.

System suitability test for solid phase extraction column Using a column packed with octadecylsilane bonded silica gel, carry out the test as described under the Procedure. Transfer 1 ml of a solution of 0.3 mg morphine CRS per ml, accurately measured, to the column pretreated. Collect the eluate into a 5 ml of volumetric flask to volume and mix well. Inject 10 μ l of the eluate and the reference solution described under the Procedure into the column respectively, record the peak areas correspondingly obtained in the chromatogram. The ratio of the peak areas of morphine obtained in the chromatogram of the eluate to the peak areas of morphine obtained in the chromatogram of reference solution is not less than 0.97 and not more than 1.03.

Procedure Wash a solid phase extraction column with 15 ml of a mixture of methanol-water (3 : 1) and 5 ml of water in sequence, then wash the column with the ammonia solution of pH about 9 (add drops ammonia TS to a quantity of water until the pH of the solution is about 9), until the pH of the eluate is about 9. Weigh accurately and powder 20 tablets. Triturate a quantity of the powder, accurately weighed, equivalent to about 1 tablet in a conical flask, accurately add

10 ml of 5% acetic acid solution, dissolve morphine with ultrasonic treatment, cool to room temperature and filter. Measure accurately 1 ml of successive filtrate to the above washed column, drop a quantity of ammonia TS to adjust pH of the solution in the column to about 9 (define the quantity of ammonia TS using another same volume of the successive filtrate previously), mix well, rinse with 20 ml of water after no solvent drips. Elute with 5% acetic acid solution contains 2% methanol, and collect the eluate into a 5 ml of volumetric flask to volume and mix well. Inject 10 μ l of the eluate into the column and record the chromatogram. Dissolve and dilute a quantity of morphine CRS with the 5% acetic acid solution contains 2% methanol to produce a solution of 0.06 mg per ml. Repeat the operation, calculate the content of $C_{17}H_{19}NO_3$ with respect to the peak areas obtained in the chromatogram by the external standard method.

Category Antitussive expectorant.

Storage Preserve in tightly closed containers, and protected from light.

Compound Sodium Chloride Eye Drops

Compound sodium chloride eye drops contain 0.50%-0.61% (g/ml) of total chlorides (Cl).

Formula	Sodium chloride	9.0
	Potassium chloride	0.14 g
	Sodium bicarbonate	0.20 g
	Hydroxypropyl methyl cellulose	5.0 g
	Preservation	a quantity
	Water for injection	a quantity
	To make	1000 ml

Description A clear, colourless, slightly viscous liquid.

Identification (1) Yields the reactions characteristic of sodium, potassium, bicarbonate salts and chlorides (Appendix III).

(2) Heat 2 ml of eye drops, a white precipitate is produced immediately, which disappears after cooling.

pH Value 6.5-8.5 (Appendix VI H).

Viscosity Kinematic viscosity 4.5-8.5 mm²/s at 25°C (Appendix VI G, method 1, using a capillary tube; 0.8 mm in internal diameter).

Other requirements Comply with the general requirements for the eye drops (Appendix VI H).

Assay Measure accurately 10 ml with a "to contain" pipette into a conical flask, wash the interior of pipette with 50 ml of water in portions, combine the washings to the same conical flask, add 10 drops of potassium chromate IS, titrate with silver nitrate (0.1 mol/L) VS until the colour turns to light red, Each ml silver nitrate (0.1 mol/L) VS is equivalent to 3.545 mg of Cl.

Category Used for ophthalmic disorder.

Strength 0.55 g/ml (calculated as chloride)

Storage Preserve in tightly closed containers, stored in room temperature and protected from light.

Compound Zedoary Turmeric Oil

Suppositories

It contains not less than 90.0% and not more than 110.0% of the labelled amount of econazole nitrate ($C_{18}H_{15}Cl_3N_2O \cdot HNO_3$).

Formula	Econazole nitrate	50 g
	Z d y i i	21
	Excipients	a quantity

to make 1000 suppositories

Description Creamy yellow to pale yellowish-brown suppositories, special odour.

Identification To one suppository, add 30 ml of ethylene glycol, slightly warm on a water bath to dissolve zedoary turmeric, allow to cool until the matrix precipitate completely and filter. The filtrate complies with the follow tests;

- (1) To 1 ml, add a few drops of trinitrophenol TS, a yellowish-white precipitate is formed.
- (2) Vaporize the ethylene glycol of 2 ml of filtrate under the infrared light. To the residue add 2 drops of sulfuric acid and 1 drop of diphenylamine TS, a deep blue is produced.

Zedoary turmeric oil Transfer one suppository in a conical flask with stopper, accurately add 25 ml of anhydrous ethanol, slightly warm on a water bath to dissolve the matrix, allow to cool, place on an ice bath until the matrix precipitate, filter, taking the filtrate as test solution. Weigh accurately a quantity of Curcumenol CRS, dissolve in anhydrous ethanol to produce a solution of 1 mg per ml as reference solution. Carry out the method for thin-layer chromatography (Appendix V B). Apply 10 μ l each of above two solutions to the same high performance silica gel G plate separately, using the upper layer of a mixture of benzene-methanol-acetic acid (7.9 : 1.4 : 0.7) as the mobile phase, after developing and removal of the plate, dry it in air, stand in the iodine vapour. The position of the principal spot obtained with the test solution corresponds to the principal spot obtained with the reference solution, and the colour of the principal spot obtained with the test solution is equal to or more intense than that of the principal spot obtained with the reference solution.

Other requirements Comply with the general requirements for Suppositories (Appendix I D).

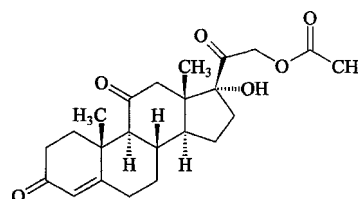
Assay Weigh accurately 10 suppositories, cut in chips, and mix well. Weigh accurately a quantity of the chips, equivalent to about 40 mg of econazole nitrate, in an iodine flask. Add 40 ml of trichloromethane with shaking, add 20 ml of water, 5 ml of dilute sulfuric acid and 1 ml of dimethyl yellow-solvent blue 19 IS, titrate with dioctyl sodium sulfosuccinate TS with continuously shaking until the colour of the layer of trichloromethane changes from green to reddish-grey. Repeat the operation, using about 40 mg of econazole nitrate CRS instead of the substance being examined, calculate the content with respect to the ratio of volume of dioctyl sodium sulfosuccinate TS consumed.

Category Medicine for gynecology.

Strength 50 mg

Storage Preserve in well closed containers, stored in a cool place.

Cortisone Acetate



$C_{23}H_{30}O_6$ 402.49

[50-04-4]

Cortisone Acetate is 17α , 21-dihydroxypregn-4-ene-3,11,20-trione-21-acetate. It contains not less than 97.0% and not more than 103.0% of $C_{23}H_{30}O_6$, calculated on the dried basis.

Description A white or almost white crystalline powder; odourless; tasteless at first but a bitter taste persists subsequently.

Freely soluble in chloroform; sparingly soluble in acetone or dioxane; slightly soluble in ethanol or ether; insoluble in water.

Specific optical rotation $+210^\circ$ to $+217^\circ$, in a solution of about 10 mg per ml in dioxane (Appendix VI E).

Specific absorbance Measure the absorbance of a solution of 10 μ g per ml, in dehydrated ethanol at 238 nm (Appendix IV A), the value of A (1%, 1 cm) is 375-405.

Identification (1) Dissolve 0.1 mg in 1 ml of methanol, add 8 ml of freshly prepared phenylhydrazine sulfate TS, heat at 70°C for 15 minutes; a yellow colour is produced.

(2) Dissolve about 2 mg in 2 ml of sulfuric acid, allow to stand for 5 minutes; a yellow or slightly orange colour is produced, which fades on diluting with 10 ml of water and the solution is clear.

(3) The retention time of principal peak in the chromatogram of the substance being examined, obtained in the Assay, is identical with that of principal peak in the chromatogram of the reference solution.

(4) The infrared absorption spectrum (Appendix IV C) is concordant with the reference spectrum of cortisone acetate (Appendix XVI).

Related substances Carry out the method as described under the Assay. Dissolve a quantity of the substance being examined in acetonitrile to produce a solution of about 1 mg per ml (1). Measure accurately 1 ml of solution (1) into a 100 ml volumetric flask and dilute with acetonitrile to the volume, shake well as solution (2). Inject 20 μ l of solution (2) into the column. Adjust the attenuation so that the principal peak height in the chromatogram is about 50% of full scale of the chart. Then inject separately 20 μ l of solution (1) and (2) into the column, and record the chromatogram for 2.5 times of the retention time of the principal peak. If there are any other peaks than the principal peak in the chromatogram of solution (1), the area of any one is not greater than 1/2 of area of the principal peak of solution (2), the sum of the areas of all peaks other than the principal peak is not greater than 1.5 times of area of the principal peak area of solution (2).

Loss on drying When dried to constant weight at 105°C , loses not more than 0.5% of its weight (Appendix VIII L).

Assay Carry out the method for high performance liquid chromatography (Appendix V D), using a column packed with octadecylsilane bonded silica gel and a mixture of

acetonitrile-water (36 : 64) as the mobile phase. Detective Wavelength is 254 nm. Dissolve a quantity of cortisone acetate CRS and hydrocortisone acetate CRS in acetonitrile to produce a solution including cortisone acetate and hydrocortisone acetate each 10 µg per ml and test. The resolution factor between the peaks of cortisone acetate and hydrocortisone acetate is not less than 4.0.

Procedure Dissolve a quantity of the substance being examined, accurately weighed, in acetonitrile to produce a solution of about 0.5 mg per ml, inject 10 µl into the column and record the chromatogram. Repeat the operations using cortisone acetate CRS instead of the substance being examined, calculate the content of $C_{22}H_{29}FO_6$ with respect to the peak area obtained in the chromatogram by the external standard method.

Category Corticosteroid.

Storage Preserve in tightly closed containers, protected from light.

Preparation (1) Cortisone Acetate Eye Ointment
(2) Cortisone Acetate Injection
(3) Cortisone Acetate Tablets

Cortisone Acetate Eye Ointment

Cortisone Acetate Eye Ointment contains not less than 90.0% and not more than 110.0% of the labelled amount of Cortisone Acetate ($C_{23}H_{30}O_6$).

Description A pale yellow eye ointment.

Identification To 1 g add 20 ml of petroleum ether in a conical flask with stopper, shake thoroughly to dissolve the ointment base and filter. Wash the residue with petroleum ether for several times. Dissolve the residue of cortisone acetate in 10 ml of dehydrated ethanol by heating and stirring. Allow to cool in ice bath, filter, evaporate the filtrate to dryness on water bath. Dissolve the residue in 2 ml of sulfuric acid, allow to stand for a few minutes; no fluorescence is produced under sun light, but yellow fluorescence is produced under ultraviolet light.

Other requirements Complies with the general requirements of Eye preparations (Appendix I G).

Assay Reference preparation Dissolve with 25 mg of Cortisone acetate CRS in a 100 ml volumetric flask with dehydrated ethanol and dilute to volume, mix well.

Test preparation Dissolve a quantity equivalent to 25 mg of cortisone acetate in a beaker with about 30 ml of dehydrated ethanol, heat in a water bath, shake thoroughly. Allow to cool in ice bath, and filter. Repeat the extraction for 3 times, combine the filtrates into a 100 ml volumetric flask, dilute to volume with dehydrated ethanol and mix well.

Procedure Measure accurately 1 ml each of the above two solutions into two separate test tubes with stopper, add 9 ml of dehydrated ethanol, 1 ml of triphenyltetrazolium chloride TS and 1 ml of tetramethylammonium hydroxide TS to each tube and mix well. Allow to stand at 25°C in the dark for 40 minutes, measure the absorbances (Appendix IV A) at 485 nm and calculate the content of $C_{23}H_{30}O_6$.

Category As described under cortisone acetate.

Strength (1) 0.25% (2) 0.5% (3) 1%

Storage Preserve in tightly closed containers, stored in dry and cool place.

Cortisone Acetate Injection

Cortisone Acetate Injection is a sterile aqueous suspension of cortisone acetate. It contains not less than 90.0% and not more than 110.0% of the labelled amount of Cortisone Acetate ($C_{23}H_{30}O_6$).

Description A suspension of minute granules which deposit on standing, a homogeneous creamy white suspension is obtained on shaking.

Identification (1) Extract 3 ml twice with 10 ml each of chloroform, separate the chloroform layer, filter, evaporate the filtrate to dryness on a water bath; the residue complies with the test (1), (2) for Identification described under Cortisone Acetate.

(2) The retention time of principal peak in the chromatogram of the substance being examined, obtained in the Assay, is identical with that of principal peak in the chromatogram of the reference solution.

pH value 4.5-7.0 (Appendix VI H).

Other requirements Complies with the requirements of injections (Appendix I B).

Assay Carry out the method described under the Assay of Cortisone Acetate. Measure accurately a quantity of the substance being examined which is equivalent to about 50 mg cortisone acetate, dilute with proper quantities of acetonitrile in a 50 ml volumetric flask, shake for 1 hour until cortisone is dissolved and dilute with acetonitrile to volume, mix well and filter. Measure accurately the succeeding filtrate 5 ml and put in a 50 ml volumetric flask, dilute with acetonitrile to volume, shake well. Inject accurately 20 µl into the column and record the chromatogram; Dissolve a quantity of cortisone acetate CRS in acetonitrile to produce a solution of 0.1 mg per ml. Repeat the above operations using cortisone acetate CRS instead of the substance being examined, calculate the content of $C_{22}H_{29}FO_6$ with respect to the peak area obtained in the chromatogram by the external standard method.

Category As described under Cortisone Acetate.

Strength (1) 2 ml : 50 mg (2) 5 ml : 125 mg
(3) 10 ml : 250 mg

Storage Preserve in well closed containers, protected from light.

Cortisone Acetate Tablets

Cortisone Acetate Tablets contain not less than 90.0% and not more than 110.0% of the labelled amount of cortisone acetate ($C_{23}H_{30}O_6$).

Description White tablets.

Identification To a quantity of powdered tablet equivalent to 60 mg of cortisone acetate add 25 ml of chloroform and allow to stand for 15 minutes with stirring. Filter and evaporate the filtrate to dryness on a water bath, the residue complies with tests (1) and (2) for Identification described under Cortisone Acetate.

Other requirements Comply with the general requirements for tablets (Appendix I A).

Assay Weigh accurately and powder 20 tablets. Transfer a quantity of the powder equivalent to 20 mg of cortisone acetate into a 100 ml volumetric flask, add 75 ml of

dehydrated ethanol, shake constantly for 1 hour until cortisone acetate is dissolved, dilute with dehydrated ethanol to volume and mix well. Filter, transfer 5 ml of the successive filtrate, accurately measured, into another 100 ml volumetric flask, add dehydrated ethanol to volume and mix well, measure the absorbance of the resulting solution at 238 nm (Appendix IV A). Calculate the content of $C_{23}H_{30}O_6$, taking 390 as the value of A (1%, 1 cm).

Category As described under Cortisone Acetate.

Strength (1) 5 mg (2) 25 mg

Storage Preserve in tightly closed containers, protected from light.

Cresol

C_7H_8O 108.14

[1319-77-3]

Cresol is a mixture of isomeric cresols obtained by fractional distillation from coal tar.

Description An almost colourless or faintly violetish-red or pale brownish-yellow clear liquid; odour, resembling that of phenol but more tarry. Darken with age or on exposure to light. Saturated water solution exhibits neutral or slightly acid reaction.

Miscible with ethanol, chloroform, ether, glycerin, fatty oils or volatile oils; sparingly soluble in water usually forming a cloudy solution; soluble in alkali hydroxide.

Relative density 1.030-1.050 (Appendix VI A).

Boiling range Carry out the method for determination of boiling range (Appendix VI B); Not less than 85% (ml/ml) distils between 190-205°C.

Identification (1) To the saturated aqueous solution add ferric chloride TS; a transient bluish-violet colour is produced.

(2) To the saturated aqueous solution add bromine TS, a pale yellow flocculent precipitate is formed.

Hydrocarbons Dissolve 1.0 ml in 60 ml of water. Any opalescence produced is not more pronounced than that of a reference suspension [mix 57 ml of water with 1.5 ml of sulfuric acid (0.01 mol/L) VS and 2 ml of barium chloride TS, allow to stand for 5 minutes].

Non-volatile substances Evaporate on a water bath to dryness, then dry to constant weight at 105°C, the residue is not more than 0.1%.

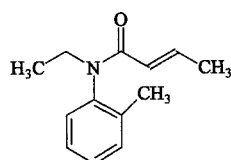
Water Not more than 0.8% (Appendix VIII M, method 2 A).

Category Antiseptic, Disinfectant.

Storage Preserve in tightly closed containers, protected from light.

Preparation Saponated Cresol Solution

Crotamiton



$C_{13}H_{17}NO$ 203.28

[483-63-6]

Crotamiton is a mixture of Z and E isomers of N-ethyl-o-crotonotoluidide. It contains not less than 97.0% of $C_{13}H_{17}NO$.

Description A colourless to pale yellow oily liquid; almost odourless; partly or completely solidifies at low temperatures.

Very soluble in ethanol or ether; slightly soluble in water.

Relative density 1.008-1.011 (Appendix VI A).

Refractive index 1.540-1.542 (Appendix IV F).

Identification (1) To about 10 ml of a saturated solution in water add a few drops of potassium permanganate TS; a brown colour is produced and a brown precipitate is formed on standing.

(2) The light absorption of a solution of 10 µg per ml in cyclohexane exhibits a maximum at 242 nm (Appendix IV A).

Z-isomer Dissolve a quantity of crotamiton in chloroform to produce a solution of 1 mg per ml as the test solution and a solution of 50 µg per ml as the reference solution. Carry out the method for gas chromatography (Appendix V E), using a capillary column 30 m long coated with a 0.25 µm film of polyethylene glycol 20 M (PEG-20M) as the stationary phase and maintain the column temperature at 180°C. Inject 2 µl of the reference solution into the column, adjust the sensitivity of the system so that the height of the E-isomer peak obtained in the chromatogram is 5% of the full scale of the recorder. Inject accurately measured 2 ml each of the test solution and the reference solution into the column and record the chromatogram. The elution order is Z-and E-isomer. The area of Z-isomer is not more than 15% of the sum of peak areas of Z-and E-isomer.

Chloride To 1.0 g add 25 ml of ethanol and 5 ml of 20% sodium hydroxide solution, heat under a reflux condenser for 1 hour. Cool, transfer to a separator, shake with 25 ml of ether and 10 ml of water. Allow to stand. Separate the aqueous layer and transfer to a 50 ml Nessler cylinder. Dilute to 25 ml with water, add 5 ml of nitric acid and a quantity of water to produce 50 ml. Add 1.0 ml of silver nitrate TS, mix well. Prepare the reference solution in the same manner using 10 ml of sodium chloride standard solution, adding 5 ml of 20% sodium hydroxide and diluting to 25 ml with water, add 5 ml of nitric acid and a quantity of water to produce 50 ml, add 1.0 ml of silver nitrate TS, mix well. Carry out the limit test for chlorides (Appendix VIII A). Any opalescence produced is not more pronounced than that of a reference solution (0.010%).

Free amines Dissolve 5.0 g in 70 ml of ether, shake and extract with two 10 ml portions of dilute hydrochloride acid. Wash the combined extracts with two 50 ml portions of ether. Evaporate acid extracts on a water bath to dryness and dry the residue at 105°C. The residue weighs not more than 2.5 mg.

Residue on ignition Not more than 0.1% (Appendix VIII N).

Assay Carry out the determination of nitrogen (Appendix VII D, method 1), using about 0.4 g, accurately weighed. Each ml of sulfuric acid (0.05 mol/L) VS is equivalent to 20.33 mg of $C_{13}H_{17}NO$.

Category antiscabietic.

Storage Preserve in tightly closed containers, protected from light.

Preparation Crotamiton Cream

Crotamiton Cream

Crotamiton cream contains not less than 90.0% and not more than 110.0% of the labelled amount of $C_{13}H_{17}NO$.

Description A white creamy.

Identification (1) Shake vigorously 0.2 g with 10 ml of hot water to dissolve crotamiton and filter. To the filtrate add a few drops of potassium permanganate TS; a brown colour is produced and a brown precipitate is formed on standing.

(2) To a quantity of the cream equivalent to about 50 mg of crotamiton, add 50 ml of cyclohexane and shake to disperse as test solution (heat on a water bath if necessary). Prepare a reference solution of 1 mg of crotamiton CRS per ml. Carry out the thin-layer chromatography (Appendix V B), using silica gel GF₂₅₄ as the coating substance and methanol as the mobile phase. Apply separately to the plate 10 μ l each of above two solutions, after developing and removal of the plate, dry it in air and examine under ultra-violet light at 254 nm. The position of the principal spot in the chromatogram obtained with the test solution corresponds to the principal spot obtained with reference solution.

(3) The light absorption of the solution obtained in Assay exhibits a maximum at 242 nm (Appendix IV A).

Other requirements Complies with the general requirements for creams (Appendix I F).

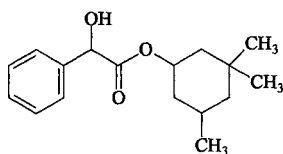
Assay Transfer an accurately weighed quantity equivalent to about 25 mg of crotamiton to a 50 ml volumetric flask, add a quantity of cyclohexane, heat in a hot water bath, shake to dissolve crotamiton. Allow it to cool to room temperature, dilute with cyclohexane to volume, mix well and allow to stand for 1 hour. Measure accurately 2 ml of the supernatant liquid into a 50 ml volumetric flask, dilute with cyclohexane to volume and mix well. Measure the absorbance of the resulting solution at 242 nm (Appendix IV A). Dissolve an accurately weighed quantity of crotamiton CRS in cyclohexane to produce a solution of 20 μ g per ml, measure the absorbance in the same manner. Calculate the content of $C_{13}H_{17}NO$.

Category As described under Crotamiton.

Strength (1) 10 g : 1 g (2) 30 g : 3 g

Storage Preserve in tightly closed containers, stored in a cool place.

Cyclandelate



$C_{17}H_{24}O_3$ 276.37

[456-59-7]

Cyclandelate is 3,3,5-trimethylcyclohexanol α -phenyl- α -hydroxyacetate. It contains not less than 99.0% of $C_{17}H_{24}O_3$, calculated on the dried basis.

Description A white or almost white amorphous powder; odour, characteristic; taste, bitter. Very soluble in ethanol or acetone; practically insoluble in

water.

Melting range 50-62°C, the melting range is within 7°C (Appendix VI C).

Identification (1) Dissolve about 0.5 g in 5 ml of sodium hydroxide TS and boil for 2 minutes, a camphor-like odour is produced, cool and filter. To 2 ml of filtrate, adjust the pH value with dilute sulfuric acid to pH 4, add 1 ml of potassium permanganate TS and shake, a benzaldehyde odour is produced.

(2) Add 1 drop of cupric sulfate TS to the filtrate obtained in test (1) for Identification and shake, the solution changes to blue colour, gradually turns to deep blue colour on standing.

(3) The light absorption of a solution of 0.5 mg per ml in ethanol, exhibits maxima at 252 nm, 258 nm and 264 nm (Appendix IV A).

(4) The infrared absorption spectrum (Appendix IV C) is concordant with the reference spectrum of cyclandelate (Appendix XVI).

Acidity Dissolve 1.0 g in 20 ml of neutralized ethanol (neutral to phenolphthalein IS), add a few drops of phenolphthalein IS; not more than 0.35 ml of sodium hydroxide (0.1 mol/L) VS is consumed to change the colour of the solution.

Clarity in ethanol A solution of 1.0 g in 10 ml of ethanol is clear and colourless; any opalescence produced is not more pronounced than that of reference suspension I (Appendix IX B).

Ketone ester Measure the absorbances of the solution obtained in the test (3) for Identification at 254 nm and 264 nm. The ratio of the two absorbances is 1.00-1.17.

Loss on drying When dried in vacuum over phosphorous pentoxide to constant weight, loses not more than 0.5% of its weight (Appendix VIII L).

Assay To about 1.5 g, accurately weighed, in a conical flask add an accurately measured 25 ml of ethanolic potassium hydroxide (0.5 mol/L) VS, heat on water bath to reflux for 30 minutes. Cool, rinse the reflux condenser with freshly boiled and cooled water, combine the washings into the conical flask. Add a few drops of phenolphthalein IS, titrate with sulfuric acid (0.25 mol/L) VS. Perform a blank determination and make any necessary correction. Each ml of ethanolic potassium hydroxide (0.5 mol/L) VS is equivalent to 138.2 mg of $C_{17}H_{24}O_3$.

Category Peripheral vasodilator.

Storage Preserve in tightly closed containers, protected from light.

Preparation Cyclandelate Capsules

Cyclandelate Capsules

Cyclandelate Capsules contain not less than 90.0% and not more than 110.0% of the labelled amount of cyclandelate ($C_{17}H_{24}O_3$).

Identification (1) To a quantity of the contents equivalent to about 0.1 g of cyclandelate add 10 ml of ether, stir to dissolve the cyclandelate and filter. Evaporate the filtrate on water bath to dryness, add 1 ml of sodium hydroxide TS, a camphor-like odour is produced. Cool, add 3 ml of dilute sulfuric acid and 1 ml of 3% potassium permanganate solution, heat to boil, a benzaldehyde odour is produced.

(2) To a quantity of the content equivalent to about 25 mg of

cyclandelate add ethanol to produce a solution of 0.5 mg per ml. filter. The light absorption of the filtrate exhibits three maxima at 252 nm, 258 nm and 264 nm (Appendix IV A).

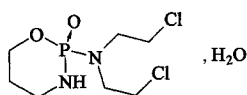
Other requirements Comply with the general requirements for capsules (Appendix I E).

Assay Stir thoroughly an accurately weighed quantity of the mixed contents obtained in the test for Weight variation equivalent to about 1 g of cyclandelate with ether. Filter, wash the residue with ether in portions, filter, evaporate the combined filtrate and washings on a water bath to dryness. Add an accurately measured 20 ml of ethanolic potassium hydroxide (0.5 mol/L) VS, reflux on a water bath for 1 hour. Cool and rinse the reflux condenser with freshly boiled and cooled water, add a few drops of phenolphthalein IS, titrate with sulfuric acid (0.25 mol/L) VS. Perform a blank determination and make any necessary correction. Each ml of ethanolic potassium hydroxide (0.5 mol/L) VS is equivalent to 138.2 mg of $C_{17}H_{24}O_3$.

Category, Storage As described under Cyclandelate.

Strength 0.1 g

Cyclophosphamide



$C_7H_{15}Cl_2N_2O_2P \cdot H_2O$ 279.10 [6055-19-2]
Cyclophosphamide is *N, N*-Bis (2-chloroethyl) tetrahydro-2*H*-1,3,2-oxaza-phosphorin-2-amine-2-oxide, monohydrate. It contains not less than 98.0% of $C_7H_{15}Cl_2N_2O_2P$, calculated on the anhydrous basis.

Description White crystals or a crystalline powder. It liquifies upon loss of its water of crystallization. Freely soluble in ethanol; soluble in water or acetone.

Melting point 48.5-52°C, determined without previous drying (Appendix VI C).

Identification (1) Mix about 0.1 g with 1 g of anhydrous sodium carbonate in a crucible, heat until melted, cool, add 20 ml of water to dissolve, filter. The filtrate, after acidified with nitric acid, yields the reactions characteristic of chlorides and phosphates (Appendix III).

(2) The retention time of principal peak of the substance being examined in the chromatogram obtained in the Assay is identical with that of cyclophosphamide CRS.

(3) The infrared absorption spectrum (Appendix IV C) is concordant with the reference spectrum of cyclophosphamide (Appendix XVI).

Acidity Dissolve 0.20 g in 10 ml of water, pH 4.5-6.5 (Appendix VI H).

Chloride Carry out the limit test for chlorides (Appendix VIII A), using 0.40 g. Any opalescence produced is not more pronounced than that of a reference using 7.2 ml of sodium chloride standard solution (0.018%), perform the comparison immediately.

Water 6.0%-7.0% (Appendix VIII M, method 1 A).

Sterility Dissolve each portion in 10 ml of sterile water, the resulting solutions comply with the test for sterility (Appendix XI H).

Assay Carry out the method for high performance liquid chromatography (Appendix V D), using a column packed with octadecylsilane bonded silica gel and a mixture of acetonitrile-water (36 : 65) as the mobile phase. Detection wavelength is 195 nm and the number of theoretical plates of the column is not less than 2000, calculate with reference to the peak area of cyclophosphamide. The resolution factor between the peaks of cyclophosphamide and internal standard complies with the related requirements.

Internal standard solution Dissolve 36 mg of ethyl parahydroxybenzoate in 2 ml of ethanol in a 200 ml volumetric flask, dilute with the mobile phase to volume, mix well.

Procedure Weigh accurately about 25 mg into a 50 ml volumetric flask, add 5 ml of the internal standard solution and dilute with the mobile phase to volume, shake well. Inject 20 μ l of the test solution into the column; Repeat the operation using cyclophosphamide CRS instead of the substance being examined, calculate the content of $C_7H_{15}Cl_2N_2O_2P$.

Category Antineoplastic.

Storage Preserve in tightly closed containers (for oral use) or in hermetically sealed containers (for injection), stored at a temperature below 30°C and protected from light.

Preparation (1) Cyclophosphamide for Injection
(2) Cyclophosphamide Tablets

Cyclophosphamide for Injection

Cyclophosphamide for Injection is a sterile preparation of crystalline cyclophosphamide. It contains not less than 95.0% and not more than 105.0% of the labelled amount of cyclophosphamide ($C_7H_{15}Cl_2N_2O_2P \cdot H_2O$), calculated on the basis of the average content.

Description White crystals or a crystalline powder.

Identification Complies with the tests for Identification described under Cyclophosphamide.

Chloride Dissolve the contents of one container in water to produce 10 ml, shake immediately with 10 ml of dilute nitric acid and 1 ml of silver nitrate TS. Perform the comparison immediately, any opalescence produced is not more pronounced than that of a reference using 1.8 ml (for strength 0.1 g) or 3.6 ml (for strength 0.2 g) for sodium chloride standard solution (dilute with water to produce 10 ml, add 10 ml of dilute nitric acid and 1 ml of silver nitrate TS, mix well, allow to stand in dark place for 5 minutes) (0.018%).

Acidity, Water Complies with the corresponding tests described under Cyclophosphamide.

Sterility Dissolve each portion in sterile water separately to produce solutions of 20 mg per ml. The solutions comply with the test for sterility (Appendix XI H).

Other requirements Complies with the general requirements for injections (Appendix I B).

Assay Carry out the Assay described under Cyclophosphamide, using the mixed contents obtained in the test for Weight variation of contents.

Category As described under Cyclophosphamide.

Strength (1) 0.1 g (2) 0.2 g

Storage Preserve in well closed containers, protected from

light and stored at a temperature below 30°C.

Cyclophosphamide Tablets

Cyclophosphamide Tablets contain not less than 90.0% and not more than 110.0% of the labelled amount of cyclophosphamide ($C_7H_{15}Cl_2N_2O_2P \cdot H_2O$).

Description Sugar-coated tablets with white core.

Identification Powder some tablets, with sugar coating removed. Extract a quantity of the powdered tablets equivalent to about 0.2 g of cyclophosphamide with ether, filter, evaporate the filtrate to dryness. The residue complies with the test (1) and (3) for Identification described under Cyclophosphamide.

(2) The retention time of principal peak of the substance being examined in the chromatogram obtained in the Assay is identical with that of cyclophosphamide CRS.

Acidity Shake a quantity of the powdered tablets equivalent to about 0.25 g of cyclophosphamide, with 20 ml of freshly boiled and cooled water, filter. To the filtrate add a few drops of phenolphthalein IS, titrate with sodium hydroxide (0.1 mol/L) VS, not more than 0.25 ml of sodium hydroxide (0.1 mol/L) VS is required.

Other requirements Comply with the general requirements for tablets (Appendix I A).

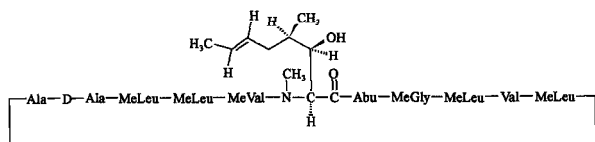
Assay Weigh accurately and powder 20 tablets, with sugar coating removed. To an accurately weighed quantity of the powder equivalent to about 0.1 g of cyclophosphamide in a 100 ml volumetric flask add 50 ml of water with ultrasonic treatment for 10 minutes, dilute with water to volume, shake well and filter. Transfer 25 ml of the successive filtrate into a 50 ml volumetric flask, add 5 ml of the internal standard solution, dilute with the mobile phase to volume, mix well. Carry out the Assay as described under Cyclophosphamide.

Category As described under Cyclophosphamide.

Strength 50 mg

Storage Preserve in tightly closed containers, protected from light and stored at a temperature below 30°C.

Cyclosporin



$C_{62}H_{111}N_{11}O_{12}$ 1202.63

[59865-13-3]

Cyclosporin is *cyclo* [[(E)-(2S,3R,4R)-3-hydroxy-4-methyl-2-(methylamino)oct-6-enoyl]-L-2-amino-butyl-L-N-methylglycyl-L-N-methyl-L-leucyl-L-valyl-L-N-methyl-L-leucyl-L-alanyl-D-alanyl-L-N-methyl-L-leucyl-L-N-methyl-L-leucyl-L-N-methyl-L-valyl]. It contains not less than 98.5% of $C_{62}H_{111}N_{11}O_{12}$, calculated on the dried basis.

Description A white or almost white powder; odourless.

Very soluble in methanol, ethanol or acetonitrile; freely soluble in ethyl acetate; soluble in acetone or ether; practically insoluble in water.

Specific optical rotation -182° to -192° , in a solution of 10 mg per ml in methanol (Appendix V E).

Identification (1) Dissolve about 5 mg in 5 ml of methanol, add a drop of potassium permanganate TS, the purplish-red colour disappears gradually on standing.

(2) The retention time of principal peak of cyclosporin in the substance being examined in the chromatogram obtained in the Assay is identical with that of principal peak of cyclosporin CRS in the chromatogram of the reference solution.

(3) The infrared absorption spectrum (Appendix IV C) is concordant with the reference spectrum of cyclosporin (Appendix XVI).

Related substances Dissolve an accurately weighed quantity in a mixture of acetonitrile-water (1 : 1) to produce a test solution of about 1.25 mg per ml. Dissolve an accurately weighed quantity of cyclosporin CRS in above solvent to produce a reference solution of about 12.5 µg per ml. Carry out the method described under Assay. Inject 20 µl of the reference solution into the column, adjust the attenuation so that the principal peak height in the chromatogram is 20% of full scale of the chart. Inject separately 20 µl each of the test solution and the reference solution and record the chromatogram for two times of the retention time of principal peak. Calculate the content of each impurity with respect to the peak area obtained in the chromatogram by the external standard method. Any individual impurity is not more than 0.7% and the sum of all such impurities, disregarding the impurities less than 0.05%, is not greater than 1.5%.

Loss on drying When dried in vacuum over phosphorous pentoxide at 60°C for 3 hours, loses not more than 2.0% of its weight (Appendix VIII L), using 0.5 g.

Heavy metals Carry out the limit test for heavy metals (Appendix VIII H, method 2), using 0.5 g: not more than 0.002%.

Assay Carry out the method for high performance liquid chromatography (Appendix V D), using a column packed with octadecylsilane bonded silica gel (a 0.25 mm × 1000 mm stainless steel capillary tube is connected to the column head) and a mixture of acetonitrile-water-*tert*-butyl methyl ether-phosphoric acid (430 : 520 : 50 : 1) as the mobile phase. Detection wavelength is 210 nm. The stainless steel capillary tube and the column are maintained at 70°C. The number of the theoretical plates of the column is not less than 1500, calculated with reference to the peak of cyclosporin.

Procedure Dissolve an accurately weighed quantity in a mixture of acetonitrile-water (1 : 1) to produce a solution of 1.25 mg per ml. Inject 20 µl into the column, and record the chromatogram. Repeat the operation, using cyclosporin CRS instead of the substance being examined. Calculate the content of $C_{62}H_{111}N_{11}O_{12}$ with respect to the peak area obtained in the chromatogram by the external standard method.

Category Immunosuppressant.

Storage Preserve in tightly closed containers, protected from light.

Preparation Cyclosporin Oral Solution

Cyclosporin Oral Solution

Cyclosporin Oral Solution contains not less than 90.0% and not more than 110.0% of the labelled amount of cyclosporin ($C_{62}H_{111}N_{11}O_{12}$).

Description A clear, pale yellow or yellow oily liquid.

Identification (1) Carry out the thin-layer chromatography (Appendix V B), using silica gel G as the coating substance. Apply separately to the plate 10 μ l of each of two solutions containing (1) 1 mg of the substance being examined, (2) 1 mg of cyclosporin CRS per ml in a mixture of methanol-chloroform (4 : 1) respectively, develop with ether as the mobile phase first, remove the plate, dry it in air, transfer the plate to another developing chamber and develop with a mixture of ethyl acetate-butanone-water-methanol (60 : 40 : 2 : 1) as the mobile phase, dry it in air, spray with potassium iodobismuthate TS and then with hydrogen peroxide TS. The colour and position of the principal spot in the chromatogram obtained with solution (1) correspond to that of the principal spot obtained with solution (2).

(2) The retention time of principal peak of cyclosporin in the solution being examined in the chromatogram obtained in the Assay is identical with that of principal peak of cyclosporin CRS in the chromatogram of the reference solution.

Test (1) and (2) are alternative.

Alcohol content Not less than 10% and not more than 15% (Appendix VII E), using butyl alcohol as solvent for the preparation of reference solution and test solution.

Other requirements Complies with the general requirements for oral solution (Appendix I O).

Assay Carry out the method for high performance liquid chromatography (Appendix V D), using a column packed with octadecylsilane bonded silica gel and a mixture of acetonitrile-water-phosphoric acid (740 : 260 : 0.25) as the mobile phase. Detection wavelength is 210 nm, and the column is maintained at 70°C. The resolution between the peak of cyclosporin and neighboring peak complies with the requirements. The number of theoretical plates of the column is not less than 600, calculated with reference to the peak of cyclosporin.

Procedure Dissolve an accurately weighed quantity in a mixture of methanol-chloroform (4 : 1) to produce a solution of 1 mg per ml. Inject 20 μ l into the column and record the chromatogram. Repeat the operation, using cyclosporin CRS instead of the substance being examined. Calculate the content of $C_{62}H_{111}N_{11}O_{12}$ with respect to the peak area obtained in the chromatogram by the external standard method, converted by relative density.

Category As described under Cyclosporin.

Strength 50 ml : 5 g

Storage Preserve in tightly closed containers, store in a cool and dark place, protected from light.

Cydiodine Buccal Tablets

Cydiodine Buccal Tablets are tablets of iodine encapsulated with β -cyclodextrin. It contains not less than 85.0% and not more than 115.0% of the labelled amount of iodine (I).

Description Pale brown-yellow tablets.

Identification (1) Powder finely 2 tablets, in a conical flask. Dissolve iodine with 10 ml of water. Add 2 ml of starch IS, a blue colour is produced. The colour disappears when the solution is boiled and reappears on cooling, but does not reappear when boiled for a long time.

(2) Powder finely 2 tablets, in a test tube with stopper. Add 3 ml of ethanol, heat in warm water bath for about 5 minutes. Add 3 ml of water and 1 ml of chloroform. Close and shake, a purple colour is produced in chloroform layer.

Content uniformity Comply with the requirements for content uniformity (Appendix X E) except the limit is $\pm 20\%$. Place 1 tablet in a conical flask with stopper. Add 0.3 g of potassium iodide, 100 ml of water and 6 ml of 10% acetic acid solution. Carry out the procedure as described under the Assay beginning at the words "shake to dissolve I". Calculate the content of I.

Other requirements Comply with the general requirements for tablets (Appendix I A).

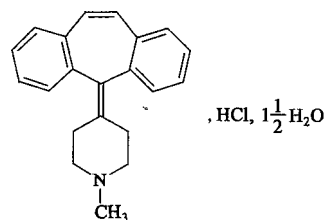
Assay Weigh accurately and powder 20 tablets. To an accurately weighed quantity of powder equivalent to about 10 mg of I, into a conical flask with stopper. Add 0.3 g of potassium iodide, 150 ml of water and 10 ml of 10% acetic acid solution, shake to dissolve I. Add accurately 10 ml of sodium thioacetamide (0.01 mol/L) VS, mix well. Stand for 10 minutes closely in dark. Adding 2 ml of starch IS, titrate with iodine (0.005 mol/L) VS until the colour changes to blue. Perform a blank determination and make any necessary correction. Each ml of sodium thioacetamide (0.01 mol/L) VS is equivalent to 1.269 mg of I.

Category Antiseptics.

Strength 1.5 mg

Storage Preserve in tightly closed containers, stored in a cool place and protected from light.

Cyproheptadine Hydrochloride



$C_{21}H_{21}N \cdot HCl \cdot 1\frac{1}{2}H_2O$ 350.89 [41354-29-4]

Cyproheptadine Hydrochloride is 4-(5H-dibenzo [a, d] cyclohept-5-ylidene)-1 methyl-piperidine hydrochloride sesquihydrate. It contains not less than 98.5% of $C_{21}H_{21}N \cdot HCl$, calculated on the dried basis.

Description A white to slightly yellow crystalline powder; almost odourless; taste, slightly bitter.

Freely soluble in methanol; soluble in chloroform; sparingly soluble in ethanol; slightly soluble in water; practically insoluble in ether.

Identification (1) The light absorption of a 16 μ g per ml solution in dehydrated ethanol exhibits a maximum at 286 nm and a minimum at 264 nm (Appendix IV A). The ratio of

the absorbance at 286 nm to that at 264 nm is 1.6-1.8.

(2) The infrared absorption spectrum (Appendix IV C) is concordant with the reference spectrum of cyproheptadine hydrochloride (Appendix XVI).

(3) The saturated aqueous solution yields the reactions characteristic of chlorides (Appendix III).

Acidity Shake thoroughly 1.0 g in 25 ml of water, add 1 drop of methyl red IS, titrate with sodium hydroxide (0.1 mol/L) VS, until the solution changes to yellow. The volume of sodium hydroxide (0.1 mol/L) VS consumed is not more than 0.15 ml.

Loss on drying When dried to constant weight at 100°C under a pressure not exceeding 0.7 kPa over phosphorous pentoxide, loses not less than 7.0% and not more than 9.0% of its weight (Appendix VIII L).

Residue on ignition Not more than 0.1% (Appendix VIII N), using 1.0 g.

Heavy metals Carry out the limit test for heavy metals (Appendix VIII H, method 2), using the residue obtained in the test for Residue on ignition; not more than 0.002%.

Assay Dissolve about 0.3 g, dried previously and accurately weighed, in 10 ml of glacial acetic acid by warming gently and cool. Add 5 ml of mercuric acetate TS and 1 drop of crystal violet IS, titrate with perchloric acid (0.1 mol/L) VS until the solution changes to blue. Perform a blank determination and make any necessary correction. Each ml of perchloric acid (0.1 mol/L) VS is equivalent to 32.39 mg of $C_{21}H_{21}N \cdot HCl$.

Category Antihistamine.

Storage Preserve in tightly closed containers, protected from light.

Preparation Cyproheptadine Hydrochloride Tablets

Cyproheptadine Hydrochloride Tablets

Cyproheptadine Hydrochloride Tablets contain not less than 93.0% and not more than 107.0% of the labelled amount of cyproheptadine hydrochloride ($C_{21}H_{21}N \cdot HCl$).

Description White tablets.

Identification (1) The solution obtained in the Assay complies with test (1) for Identification described under Cyproheptadine Hydrochloride.

(2) Dissolve a quantity of the powdered tablets equivalent to about 20 mg of anhydrous cyproheptadine hydrochloride in 7 ml of water, shake thoroughly and filter. The filtrate yields the reactions characteristic of chlorides (Appendix III).

Content uniformity Comply with the requirements for content uniformity (Appendix X E). Shake 1 tablet with 20 ml of hydrochloric acid solution (9 → 50) in a 100 ml volumetric flask and allow to disintegrate. Proceed as described under Assay, beginning at the words "add about 50 ml of dehydrated ethanol...".

Dissolution Carry out the dissolution test (Appendix X C, method 3), using 150 ml of 0.1 mol/L hydrochloric acid solution as the dissolution medium, adjust the rotational speed of the paddle to 75 rpm. Withdraw the solution after exactly 45 minutes and filter, take the successive filtrate as the test solution. Dissolve about 13 mg of cyproheptadine

hydrochloride CRS, accurately weighed, with ethanol in a 100 ml volumetric flask and shake until cyproheptadine hydrochloride CRS is dissolved, then dilute with ethanol to volume, mix well. Measure accurately 5 ml of the solution in a 50 ml volumetric flask, dilute with 0.1 mol/L hydrochloric acid solution to volume, mix well as the reference solution. Measure the absorbance of the test and the reference solution at 285 nm, calculate the dissolution of $C_{22}H_{29}FO_5$ from each tablet. Not less than 70% of the labelled amount is dissolved.

Other requirements Comply with the general requirements for tablets (Appendix I A).

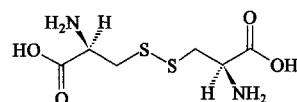
Assay Weigh accurately and powder 20 tablets. Transfer an accurately weighed quantity equivalent to about 1.5 mg of anhydrous cyproheptadine hydrochloride to a 100 ml volumetric flask. Add 2.0 ml of hydrochloric acid solution (9 → 50), shake for 2-3 minutes, then add about 50 ml of dehydrate ethanol and shake for 10 minutes to dissolve cyproheptadine hydrochloride. Dilute with dehydrated ethanol to volume, mix well and centrifuge. Measure the absorbance of the supernatant solution at 286 nm (Appendix IV A). Calculate the content of $C_{21}H_{21}N \cdot HCl$, taking 353 as the value of A (1%, 1 cm).

Category As described under Cyproheptadine Hydrochloride.

Strength 2 mg (calculated as $C_{21}H_{21}N \cdot HCl$)

Storage Preserve in tightly closed containers, protected from light.

Cystine



$C_6H_{12}N_2O_4S_2$ 240.30

Cystine is (R, R)-3,3'-dithiobis (2-amino-propanoic acid). It contains not less than 98.5% of $C_6H_{12}N_2O_4S_2$, calculated on the dried basis.

Description White crystals or crystalline powder.

Practically insoluble in water and in ethanol, soluble in dilute hydrochloric acid or in sodium hydroxide TS.

Specific optical rotation -215° to -230° , in a solution of 20 mg per ml in 1 mol/L hydrochloric acid solution (Appendix VI E).

Identification The infrared absorption spectrum (Appendix IV C) is concordant with the reference spectrum of cystine (Appendix XVI).

Acidity To 1.0 g add 100 ml of water, shake thoroughly, pH is 5.0-6.5 (Appendix VI H).

Transmittance of solution Dissolve 1.0 g in 20 ml of 1 mol/L hydrochloric acid solution, the transmittance at 430 nm is not less than 98.0% (Appendix IV A).

Chloride Dissolve 0.25 g in 5 ml of dilute nitric acid, add sufficient water to produce 25 ml. Carry out the limit test for chloride (Appendix VIII A). Any opalescence produced is not more pronounced than that of a reference solution using 5.0 ml of sodium chloride standard solution (0.02%).

Sulfate Dissolve 0.70 g in 5 ml of dilute hydrochloric acid by shaking, add sufficient water to produce 40 ml. Carry

out the limit test for sulfate (Appendix VIII B). Any opalescence produced is not more pronounced than that of a reference solution using 1.4 ml of potassium sulfate standard solution and 5 ml of dilute hydrochloric acid (0.02%).

Other amino acids Carry out the method for thin-layer chromatography (Appendix V B), using silica gel G as the coating substance and *n*-butanol-water-glacial acetic acid (5 : 2 : 1) as the mobile phase. Apply separately to the plate 2 μ l of a solution of 10 mg per ml in 1 mol/L hydrochloric acid solution. After developing and removal of the plate, dry it in air and spray with ninhydrin solution (dissolve 1 g ninhydrin in 50 ml of acetone) and heat at 80°C until the colour is produced and examine immediately. No spot other than the principal spot in the chromatogram is observed.

Loss on drying When dried at 105°C for 3 hours, loses not more than 0.2% of its weight (Appendix VIII L).

Residue on ignition Not more than 0.1% (Appendix VIII N), using 1.0 g.

Iron To the residue obtained in the test for Residue on ignition add 1 ml of nitric acid, evaporate to dryness on a water bath, add 4 ml of dilute hydrochloric acid, warm to effect dissolution, transfer the solution to a 50 ml of Nessler cylinders. Carry out the limit test for iron (Appendix VIII G). Any colour produced is not more intense than that of a reference solution using 1.0 ml of iron standard solution (0.001%).

Heavy metals Carry out the limit test for heavy metals (Appendix VIII H, method 2), using 1.0 g; not more than 0.001%.

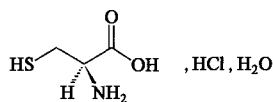
Arsenic Dissolve 2.0 g in 23 ml of water, add 5 ml of hydrochloric acid. Carry out the limit test for arsenic (Appendix VIII J, method 1); not more than 0.0001%.

Assay Weigh accurately about 15 mg. Carry out the method for determination of nitrogen (Appendix VII D, method 2). Each ml of sulfuric acid (0.005 mol/L) VS is equivalent to 1.2015 mg of $C_3H_7NO_2S$.

Category Amino acid.

Storage Preserve in tightly closed containers, protected from light.

Cysteine Hydrochloride



$C_3H_7NO_2S \cdot HCl \cdot H_2O$ 175.64

Cysteine Hydrochloride is (L)-2-amino-3-mercaptopropanoic acid hydrochloride monohydrate. It contains not less than 98.5% of $C_3H_7NO_2S \cdot HCl$, calculated on the dried basis.

Description White crystals or crystalline powder; odorous; taste, sour. Freely soluble in water; sparingly soluble in ethanol; practically insoluble in acetone.

Specific optical rotation +5.5° to +7.0°, in a solution of 80 mg per ml in 1 mol/L hydrochloric acid solution (Appendix VI E).

Identification The infrared absorption spectrum (Appendix IV C) is concordant with the reference spectrum of Cysteine hydrochloride (Appendix XVI).

Acidity Dissolve 0.20 g in 20 ml of water, pH 1.5-2.0 (Appendix VI H).

Transmittance of solution Dissolve 0.5 g in 10 ml of water, the transmittance at 430 nm is not less than 98.0% (Appendix IV A).

Chlorine content Dissolve about 0.25 g, accurately weighed, in 10 ml of water and 10 ml of nitric acid solution (1→2), add accurately 25 ml of silver nitrate VS (0.1 mol/L) and 50 ml of a 1% solution of potassium permanganate measured, heat in a water bath for 30 minutes, cool, add 30% solution of hydrogen peroxide until the colour of solution disappear. Add 8 ml of ammonium ferric sulfate IS and 1 ml of nitro-benzene, titrate with ammonium thiocyanate (0.1 mol/L) VS, perform a blank determination and make any necessary correction. Each ml of silver nitrate (0.1 mol/L) VS is equivalent to 3.545 mg of chlorine. It contains not less than 19.8% and not more than 20.8% of chlorine.

Sulfate Carry out the limit test for sulfate (Appendix VIII B), using 0.7 g. Any opalescence produced is not more pronounced than that of a reference solution using 1.4 ml of potassium sulfate standard solution (0.02%).

Other amino acids Dissolve an accurately weighed quantity of substance being examined in 2% *N*-ethylmaleimide solution to produce a solution of 4 mg per ml as a test solution. Dissolve 10 mg of cystine CRS, accurately weighed, in 3 ml of 0.1 mol/L hydrochloric acid solution, ultrasonicate, add a quantity of water to dissolve, and dilute with water to 100 ml, mix well. To an accurately measured 1.0 ml of the solution add 4 ml of 2% *N*-ethylmaleimide solution, mix well, as a reference solution. Carry out the method for thin-layer chromatography (Appendix V B), using silica gel G as the coating substance and *n*-butanol-glacial acetic acid-water (5 : 1 : 2) as the mobile phase. Apply separately to the plate 5 μ l of each of above two solutions. After developing and removal of the plate, dry it in air and spray with ninhydrin solution (dissolve 1 g ninhydrin in 50 ml of acetone) and heat at 80°C until the colour is produced and examine immediately. Any secondary spot in the chromatogram obtained with the test solution is not more intense than the principal spot obtained with the reference solution (0.5%).

Loss on drying When dried in vacuum over phosphorous pentoxide for 24 hours, loses not less than 8.0% and not more than 12.0% of its weight (Appendix VIII L).

Residue on ignition Not more than 0.1% (Appendix VIII N), using 1.0 g.

Iron Carry out the limit test for iron (Appendix VIII G), using 1.0 g. Any colour produced is not more intense than that of a reference solution using 1.0 ml of iron standard solution (0.001%).

Heavy metals Carry out the limit test for heavy metals (Appendix VIII H, method 1), using the residue obtained in the test for Residue on ignition; not more than 0.001%.

Arsenic Dissolve 2.0 g in 23 ml of water, add 5 ml of hydrochloric acid, carry out the limit test for arsenic (Appendix VIII J, method 1); not more than 0.0001%.

Pyrogens Complies with the test for pyrogens (Appendix XI D), using 10 ml of a solution of 15 mg per ml in Sodium Chloride Injection per kg of the rabbit's weight.

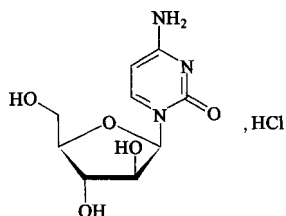
Assay Weigh accurately about 0.25 g in an iodine flask. Add 20 ml of water and 4 g of potassium iodide to dissolve by shaking, add 5 ml of dilute hydrochloric acid solution and 25.0 ml of iodine (0.05 mol/L) VS, allow to stand in the dark for 15 minutes, cool the solution in an ice bath for 5

minutes. Titrate with sodium thiosulfate (0.1 mol/L) VS, using 2 ml of starch IS added toward the end of titration until the blue colour disappears. Perform a blank determination and make any necessary correction. Each ml of iodine (0.05 mol/L) VS is equivalent to 15.76 mg of $C_9H_7NO_2S \cdot HCl$.

Category Amino acid.

Storage Preserve in tightly closed containers, stored in a cool and dry place and protected from light.

Cytarabine Hydrochloride



$C_9H_{13}N_3O_5 \cdot HCl$ 279.68

[69-74-9]

Cytarabine Hydrochloride is 4-amino-1- β -D-arabinofuranosyl-2 (1H)-pyrimidinone monohydrochloride. It contains not less than 97.0% and not more than 103.0% of $C_9H_{13}N_3O_5 \cdot HCl$, calculated on the dried basis.

Description White, fine needle crystals or crystalline powder.

Very soluble in water; sparingly soluble in ethanol; practically insoluble in ether.

Melting range 189-195°C, with decomposition (Appendix VI C).

Specific optical rotation +127° to +133°, in a solution of 10 mg per ml in water (Appendix VI E).

Identification (1) The light absorption of the solution obtained in the Assay exhibits a maximum at 280 nm and a minimum at 241 nm (Appendix IV A).

(2) The infrared absorption spectrum (Appendix IV C) is concordant with the reference spectrum of cytarabine hydrochloride (Appendix XVI).

(3) The aqueous solution yields the reaction characteristic of chlorides (Appendix III).

Loss on drying When dried in vacuum over phosphorous pentoxide to constant weight, loses not more than 0.5% of its weight (Appendix VIII L).

Assay Dissolve a quantity, accurately weighed, in hydrochloric acid solution (9→1000) to produce a solution of 10 μ g per ml, measure the absorbance at 280 nm (Appendix IV A). Calculate the content of $C_9H_{13}N_3O_5 \cdot HCl$, taking 484 as the value of A (1%, 1 cm).

Category Antineoplastic.

Storage Preserve in tightly closed containers, protected from light and stored in a cold place.

Preparation Cytarabine Hydrochloride for Injection

Cytarabine Hydrochloride for Injection

Cytarabine Hydrochloride for Injection is a

lyophilized sterile powder. It contains not less than 93.0% and not more than 107.0% of the labelled amount of cytarabine hydrochloride ($C_9H_{13}N_3O_5 \cdot HCl$).

Description A white, lyophilized mass or powder.

Identification Complies with the tests (1) and (3) for Identification described under Cytarabine Hydrochloride.

Acidity An aqueous solution of 10 mg per ml, pH 4.0-6.0 (Appendix VI H).

Loss on drying When dried to constant weight in vacuum over phosphorous pentoxide, loses not more than 3.0% of its weight (Appendix VIII L).

Other requirements Complies with the general requirements for injections (Appendix I B).

Assay Dissolve the contents of 10 vials, separately, in hydrochloric acid solution (9→1000) to produce a solution of 10 μ g per ml. Measure the absorbance of each solution at 280 nm (Appendix IV A). Calculate the content of $C_9H_{13}N_3O_5 \cdot HCl$ in each vial, taking 484 as the value of A (1%, 1 cm), and calculate the average content of 10 vials.

Category As described under Cytarabine Hydrochloride.

Strength (1) 50 mg (2) 100 mg

Storage Preserve in well closed containers, protected from light and stored in a cold place.

Cytochrome C for Injection

Cytochrome C for Injection is a sterile lyophilized product of cytochrome C with the addition of suitable excipient and antioxidant. It contains not less than 90.0% and not more than 115.0% of the labelled amount of cytochrome C.

Description A pink, lyophilized mass. Freely soluble in water.

Identification (1) Dissolve the contents of one container in 5 ml of water. Complies with test (1) for Identification described under Cytochrome C Solution, using 1 ml.

(2) Complies with test (2) for Identification described under Cytochrome C solution, using the remaining solution obtained in the Assay.

Acidity or Alkalinity Dissolve a quantity in Water for Injection to produce a solution of 3 mg per ml, pH 6.0-7.5 (Appendix VI H).

Sterility Complies with the test for sterility (Appendix XI H), using 2 containers. Dissolve the contents of each container in Sodium Chloride Injection to produce a solution of 1.5 mg per ml.

Bacterial endotoxin and allergen Complies with the tests for pyrogens and allergen described under Cytochrome C Solution.

Activity Carry out the Determination of Cytochrome C Activity (Appendix XIII B), not less than 90.0%.

Other requirements Complies with the general requirements for injections (Appendix I B) except the test for weight variation of contents.

Assay Dissolve the contents of three containers separately in a quantity of phosphate BS described under Cytochrome C Solution, transfer to three 100 ml volumetric flasks

respectively, and dilute to volume with the same solvent. Complete the Assay described under the Cytochrome C Solution beginning at the words "add 15 mg of sodium hydrosulfite". Repeat the assay if the content of one container fails to comply with the requirement.

Category As described under Cytochrome C Solution.

Strength 15 mg

Storage Preserve in well closed containers, stored in a cool place, protected from light.

Cytochrome C Injection

Cytochrome C Injection is a sterile solution of cytochrome C in Water for Injection. It contains not less than 90.0% and not more than 110.0% of the labelled amount of cytochrome C.

An equal quantity of glycyl glycine is added as stabilizer and a quantity of sodium bisulfite and sodium sulfite as antioxidant.

Description A clear, orange-red liquid.

Identification (1) Complies with test (1) for Identification described under Cytochrome C solution, using 1 ml.

(2) Complies with test (2) for Identification described under Cytochrome C solution, using the remaining solution obtained in the Assay.

pH value 6.0-7.5 (Appendix VI H).

Bacterial endotoxin and allergen Complies with the tests for pyrogens and allergen described under Cytochrome C solution.

Activity Carry out the Determination of Cytochrome C Activity (Appendix XIII B), not less than 90.0%

Other requirements Complies with the general requirements for injections (Appendix I B).

Assay Carry out the Assay described under Cytochrome C solution, beginning at the words "in a 50 ml volumetric flask...", using 1 ml, accurately measured.

Category As described under Cytochrome C solution.

Strength 2 ml : 15 mg

Storage Preserve in well closed containers, protected from light and stored in a cool place.

Cytochrome C Solution

Cytochrome C solution is the solution of cytochrome C extracted from pig or bovine hearts. It contains not less than 15 mg of cytochrome C per ml. A quantity of antimicrobial preservative may be added.

Description A clear, deep red liquid.

Identification (1) To 1 ml of the test preparation obtained under the test for iron content add dropwise 20% trichloroacetic acid solution, a brown or brownish-red flocculent precipitate is produced and the red colour of the solution disappears. The precipitate can be dissolved in water, and the solution exhibits a brownish-red colour.

(2) Dilute 1 ml of the test preparation obtained under the

test for iron content in a 50 ml volumetric flask with phosphate BS (Dissolve 1.38 g of sodium dihydrogen phosphate and 31.2 g of disodium hydrogen phosphate in water to produce 1000 ml, adjust the pH value to 7.3) to volume, add about 15 mg of sodium hydrosulfite, shake thoroughly. The light absorption of the solution exhibits maxima at 520 nm and 550 nm, and a minimum at 535 nm (Appendix IV A).

Iron content *Standard iron preparation* Dissolve 50 g of ammonium ferric sulfate in a mixture of 300 ml of water and 6 ml of sulfuric acid, add a quantity of water to produce 1000 ml, mix well. Measure accurately 25 ml to an iodine flask, add 5 ml of hydrochloric acid, mix well, add 12 ml of potassium iodide TS, stopper the flask, allow to stand for 10 minutes. Titrate the iodine with sodium thiosulfate (0.1 mol/L) VS, add 1 ml of starch IS towards the end of titration, continue the titration until the blue colour disappears. Each ml of sodium thiosulfate (0.1 mol/L) VS is equivalent to 5.585 mg of iron. Calculate the iron content (mg) per ml according to the consumed volume of sodium thiosulfate (0.1 mol/L) VS. Mix an accurately measured quantity with dilute sulfuric acid solution (dilute 2 ml of dilute sulfuric acid TS with water to produce 500 ml), to produce a solution of 23 µg of Fe per ml.

Test preparation Dilute a quantity, accurately measured, equivalent to about 100 mg of cytochrome C in a 10 ml volumetric flask to volume with water.

Procedure Evaporate 5 ml of test preparation, accurately measured, in a crucible previously ignited to constant weight, to dryness, dry to constant weight at 105°C and weigh accurately as W_1 . Ignited gently to carbonize completely, continue the ignition at 500 to 600°C until incineration is complete, weigh accurately as W_2 . Transfer 1 ml of test preparation, accurately measured, to a 25 ml volumetric flask, add 0.7 ml of 30% hydrogen peroxide solution and 0.5 ml of dilute sulfuric acid TS, heat in a water bath for 30 minutes, allow to cool. Add accurately 2 ml of 2,2'-dipyridyl TS, allow to stand in a cool water bath, add 5 ml of sodium sulfite TS slowly with shaking, then heat in a water bath at 60-70°C for 30 minutes, cool to room temperature, dilute with water to volume and mix well. Measure the absorbance of the resulting solution at 522 nm (Appendix IV A) as A_1 ; measure accurately 2 ml of standard iron solution to a 25 ml volumetric flask and proceed in the same manner beginning at the words "add 0.7 ml of 30% hydrogen peroxide solution", measure the absorbance as A_2 . It contains not less than 0.40% and not more than 0.46% of iron calculated with the following expression:

$$\text{Content of Iron} = \frac{A_1 \times 23}{A_2 (W_1 - W_2)} \%$$

Bacterial endotoxin Carry out the test for bacterial endotoxin (Appendix XI E): Less than 5 EU per mg of cytochrome C.

Allergen Dilute a quantity with sterile Water for Injection to produce a solution of 7.5 mg of cytochrome C per ml. Inject 0.5 ml of the diluted solution into abdominal cavity of each of 6 health guinea pigs weighing 250-350 g for 3 times successively, once every other day; and 1 ml of test preparation into femoral (auricular) vein after two weeks. None of the guinea pigs shows two or more than two types of allergic reactions within 15 minutes, such as hair pricking, short of breathing, sneezing, retching or continuous cough for three times; or one of the following allergic reactions: raleing, twitching, collapsing or dying.

Activity Carry out the Determination of Cytochrome C Activity (Appendix XIII B), not less than 95.0%.

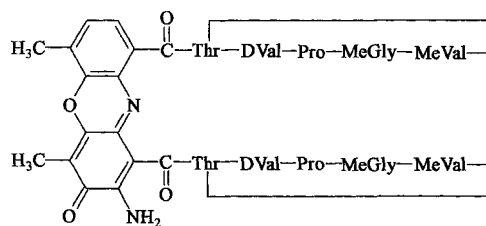
Assay Dilute 1 ml of the test preparation, accurately measured, obtained in the test for Iron content in a 50 ml volumetric flask to volume with phosphate BS described in Identification test (2), add 15 mg of sodium hydrosulfite, shake thoroughly. Measure the absorbance at the maximum wave length found at intervals of 10 nm in the vicinity of 550 nm (Appendix IV A), calculate the content of cytochrome C, taking 23.0 as the value of A (1%, 1 cm).

Category Cell respiration activator.

Storage Preserve in tightly closed containers, stored at a temperature below 4°C.

Preparation (1) Cytochrome C for Injection
(2) Cytochrome C Injection

Dactinomycin



$C_{62}H_{86}N_{12}O_{16}$ 1255.44

[50-76-0]

Dactinomycin contains not less than 95.0% of $C_{62}H_{86}N_{12}O_{16}$, calculated on the dried basis.

Description Bright red or deep red crystals, or an orang-red crystalline powder; odourless; hygroscopic; very unstable on exposure to light. The solution in ethanol is levorotatory. Freely soluble in acetone, chloroform or isopropanol; sparingly soluble in methanol; slightly soluble in ethanol; practically insoluble in water, but soluble in water at 10°C.

Specific optical rotation -292° to -317° , in a solution of 1 mg per ml in methanol.

Identification (1) The light absorption of the solution obtained in the Assay (Appendix IV A) exhibits two maxima at $241\text{ nm} \pm 2\text{ nm}$ and $442\text{ nm} \pm 2\text{ nm}$. The ratio of the absorbance at 241 nm to that at 442 nm is 1.3-1.5.

(2) The infrared absorption spectrum (Appendix IV C) is concordant with the reference spectrum of dactinomycin (Appendix XVI).

Crystallinity Complies with the test for crystallinity (Appendix IX D).

Loss on drying When dried in vacuum over phosphorous pentoxide to constant weight at 60°C, loses not more than 5.0% of its weight (Appendix VIII L).

Bacterial endotoxin Carry out the test for bacterial endotoxin (Appendix XI E). It contains less than 100 EU per mg.

Sterility Complies with the test for sterility (Appendix XI H, membrane filtration method), using no less than 500 ml of 0.9% sterile sodium chloride solution.

Assay Dissolve an accurately weighed quantity in methanol to produce a solution of 20 μg per ml, measure the absorbance at $442\text{ nm} \pm 2\text{ nm}$ (Appendix IV A). Calculate the content of $C_{62}H_{86}N_{12}O_{16}$, taking 202 as the value of A (1%, 1 cm).

Category Antineoplastic antibiotic.

Storage Preserve in hermetically sealed containers, protected from light and stored in a dry place.

Preparation Dactinomycin for Injection

Dactinomycin for Injection

Dactinomycin for Injection is a sterile mixture of dactinomycin and sucrose. It contains not less than 93.0% and not more than 107.0% of the labelled amount of dactinomycin ($C_{62}H_{86}N_{12}O_{16}$), calculated on the basis of the average content in each

container.

Description A pale orang-red crystalline powder; unstable on exposure to light.

Identification Complies with the test (1) for Identification described under Dactinomycin in a solution of 0.03 mg per ml in methanol.

Acidity or alkalinity Dissolve the contents of one container in 5 ml of water, pH 5.5-7.5 (Appendix VI H).

Loss on drying When dried in vacuum over phosphorous pentoxide to constant weight at 60°C, loses not more than 1.0% of its weight (Appendix VIII L).

Content uniformity Complies with the requirements for content uniformity, using the content of each container obtained under Assay (Appendix X E).

Bacterial endotoxin Complies with the requirements described under Dactinomycin.

Sterility Complies with the test for sterility described under Dactinomycin, using six containers.

Other requirements Complies with the general requirements for injections (Appendix I B), except the test for weight variation of contents.

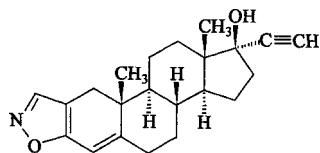
Assay Dissolve the contents of ten containers separately in methanol, transfer to 10 ml volumetric flasks and dilute with methanol to volume, shake thoroughly and allow to stand. Measure the absorbance of the supernatant liquid at $442\text{ nm} \pm 2\text{ nm}$ (Appendix IV A), calculate the content of $\text{C}_{62}\text{H}_{86}\text{N}_{12}\text{O}_{16}$ in each container, taking 202 as the value of A (1%, 1 cm), and calculate the average content of ten containers.

Category As described under Dactinomycin.

Strength 0.2 mg (calculated as $\text{C}_{62}\text{H}_{86}\text{N}_{12}\text{O}_{16}$)

Storage Preserve in well closed containers and protected from light.

Danazol



$\text{C}_{22}\text{H}_{27}\text{NO}_2$ 337.46

[17230-88-5]

Danazol is 17 α -pregna-2,4-dien-20-yno [2,3-*d*] isoxazol-17 β -ol. It contains not less than 97.0% and not more than 103.0% of $\text{C}_{22}\text{H}_{27}\text{NO}_2$, calculated on the dried basis.

Description White or almost white crystals or a crystalline powder.

Freely soluble in chloroform; soluble in acetone; sparingly soluble in ethanol; insoluble in water.

Melting range 223-230°C, with decomposition (Appendix VI C).

Specific optical rotation +21° to +27°, in a solution of about 10 mg per ml in chloroform (Appendix VI E).

Identification (1) Dissolve about 2 mg in 5 ml of ethanol, add 2 drops of silver nitrate TS, a white precipitate is produced.

(2) The retention time of principal peak in the chromatogram of the substance being examined, obtained in the Assay, is identical with that of principal peak in the chromatogram of the reference solution.

(3) The infrared absorption spectrum (Appendix IV C) is concordant with the reference spectrum of danazol (Appendix VI).

Loss on drying When dried to constant weight in vacuum at 60°C, loses not more than 1.0% of its weight (Appendix VIII L).

Related substances Carry out the method for thin-layer chromatography (Appendix V B), using silica gel G as the coating substance and a mixture of cyclohexane-ethyl acetate (7:3) as the mobile phase. Apply separately to the plate 5 μ l each of two solutions in chloroform-methanol (9:1) containing (1) 10 mg, (2) 0.20 mg of the substance being examined per ml. After developing and removal of the plate, dry it in air and examine under ultraviolet light at 254 nm. Any spot other than the principal spot in the chromatogram obtained with solution (1) is not more intense than the principal spot obtained with solution (2).

Assay Carry out the method for high performance liquid chromatography (Appendix V D), using a column packed with octadecylsiane bonded silica gel and a mixture of acetonitrile-methanol-water (4:4:3) as the mobile phase. Detection wavelength is 270 nm, and the number of theoretical plates of the column is not less than 2500, calculated with reference of the peak of danazol.

Procedure Dissolve a quantity, accurately weighed, in the mobile phase to produce a solution of 0.2 mg per ml, inject accurately 10 μ l of the solution into the column and record the chromatogram. Repeat the operation using the danazol CRS instead of the substance being examined, calculate the content of $\text{C}_{22}\text{H}_{27}\text{NO}_2$ with respect to the peak area obtained in the chromatogram by the external standard method.

Category Gonadotrophin inhibitor.

Storage Preserve in tightly closed containers, protected from light.

Preparation Danazol Capsules

Danazol Capsules

Danazol Capsules contain not less than 90.0% and not more than 110.0% of anhydrous danazol ($\text{C}_{22}\text{H}_{27}\text{NO}_2$).

Identification (1) Extract a quantity of the contents of the capsules with chloroform, filter and evaporate the filtrate to dryness. The residue complies with the tests for Identification described under Danazol.

(2) The light absorption of the solution of the substance being examined exhibits a maximum at 285 nm (Appendix IV A).

Dissolution Carry out the dissolution test (Appendix X C, method 2), using 1000 ml of hydrochloric acid (0.1 mol/L)-isopropanol (3:2) as the dissolution medium, the rotational speed of the paddle is adjusted to 80 rpm. Withdraw 25 ml of the solution after exactly 30 minutes and filter. Discard the initial filtrate, accurately measure a quantity of the successive filtrate, dilute with dissolution medium to produce a solution of 20 μ g per ml. Measure the absorbance at 286 nm (Appendix IV A), using a 20 μ g per ml solution of danazol CRS in the same solvent as reference. Calculate the dissolution of $\text{C}_{22}\text{H}_{27}\text{NO}_2$ from each capsule.

not less than 70% of the labelled amount is dissolved.

Other requirements Comply with the general requirements for capsules (Appendix I E).

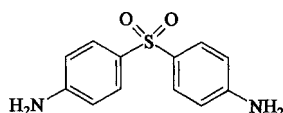
Assay Mix the contents obtained in the test for weight variation. Transfer an accurately weighed quantity equivalent to about 30 mg of danazol to a 100 ml volumetric flask, add 50 ml of dehydrated ethanol, heat in a warm water bath for 10 minutes with shaking. Cool to room temperature, dilute with dehydrated ethanol to volume and mix well. Filter, transfer 5 ml of the successive filtrate, accurately measured, to another 100 ml volumetric flask and dilute with dehydrated ethanol to volume, shake well as the test solution. Dissolve a quantity of danazol CRS, accurately weighed, in anhydrous ethanol to produce a solution of about 15 µg per ml as the reference solution. Measure the absorbance of the two solutions above at 285 nm (Appendix IV A) and calculate the content of $C_{22}H_{27}NO_2$.

Category As described under Danazol.

Strength (1) 0.1 g (2) 0.2 g

Storage Preserve in tightly closed containers, protected from light.

Dapsone



$C_{12}H_{12}N_2O_2S$ 248.31

[80-08-0]

Dapsone is 4,4'-sulfonylbisbenzenamine. It contains not less than 99.0% of $C_{12}H_{12}N_2O_2S$, calculated on the dried basis.

Description White or almost white crystals or a crystalline powder; odourless; taste, slightly bitter. Freely soluble in acetone; soluble in methanol; sparingly soluble in ethanol; practically insoluble in water; but soluble in dilute hydrochloric acid.

Melting range 176-181°C (Appendix VI C).

Identification (1) The light absorption of a solution of 5 µg per ml in methanol exhibits maxima at 261 nm and 296 nm; the absorbance is about 0.35-0.38 and 0.59-0.62, respectively (Appendix IV A).

(2) The infrared absorption spectrum (Appendix IV C) is concordant with the reference spectrum of dapsone (Appendix XVI).

(3) Yields the reactions characteristic of primary aromatic amines (Appendix III).

Related substances Carry out the method for thin-layer chromatography (Appendix V B), using silica gel G as the coating substance and a mixture of toluene-acetone (2:1) as the mobile phase. Apply separately to the plate 10 µl each of three solutions in methanol containing (1) 10 mg, (2) 100 µg and (3) 20 µg of the substance being examined per ml. After developing and removal of the plate, dry it in air and spray with 0.5% sodium nitrite in hydrochloric acid solution (0.1 mol/L), allow to stand for a few minutes, spray with 0.1% N-(1-naphthyl)-ethylenediamine dihydrochloride solution. No spots other than the principal spot in the chromatogram obtained with solution (1) are more intense than the principal spot obtained with solution (2), and not more than two of such spots are more intense than the

principal spot obtained with solution (3).

Loss on drying When dried to constant weight at 105°C, loses not more than 1.0% of its weight (Appendix VIII L).

Residue on ignition Not more than 0.1% (Appendix VIII N), using 1.0 g.

Heavy metals Carry out the limit test for heavy metals (Appendix VIII H, method 2), using the residue obtained in the test for Residue on ignition; not more than 0.001%.

Assay To about 0.25 g, accurately weighed, add 30 ml of water and 20 ml of hydrochloric acid solution (1→2). Carry out the method for dead-stop titration (Appendix VII A), titrate with sodium nitrite (0.1 mol/L) VS. Each ml of sodium nitrite (0.1 mol/L) VS is equivalent to 12.42 mg of $C_{12}H_{12}N_2O_2S$.

Category Antileprosy drug.

Storage Preserve in tightly closed containers.

Preparation Dapsone Tablets

Dapsone Tablets

Dapsone Tablets contain not less than 93.0% and not more than 107.0% of the labelled amount of dapsone ($C_{12}H_{12}N_2O_2S$).

Description White or almost white tablets.

Identification (1) Dissolve a quantity of the substance being examined in methanol to produce a solution of 5 µg per ml and filter. The succeeding filtrate complies with the test (1) for Identification described under Dapsone.

(2) Stir a quantity of powdered tablets equivalent to 0.1 g of dapsone with 20 ml of acetone, filter and evaporate the filtrate to dryness. The residue complies with test (3) for Identification described under Dapsone.

Dissolution Carry out the dissolution test (Appendix X C, method 1), using 20 ml of hydrochloric acid diluted with water to 1000 ml as the dissolution medium. Adjust the rotational speed of the basket to 100 rpm. Withdraw a quantity of the solution after exactly 60 minutes and filter, discard the initial filtrate, use the successive filtrate as the test preparation. Weigh accurately a quantity of dapsone CRS, previously dried to constant weight at 105°C, dissolve it in the dissolution medium to produce a solution of 50 µg per ml and use it as the reference preparation. Transfer accurately 2 ml each of the two preparations separately to two 25 ml volumetric flasks, to each add 5 ml of sodium hydroxide TS, dilute with water to volume and mix well. Measure the absorbances at 290 nm (Appendix IV A) and calculate the dissolution of $C_{12}H_{12}N_2O_2S$ from each tablet, not less than 75% of the labelled amount is dissolved.

Other requirements Comply with the general requirements for tablets (Appendix I A).

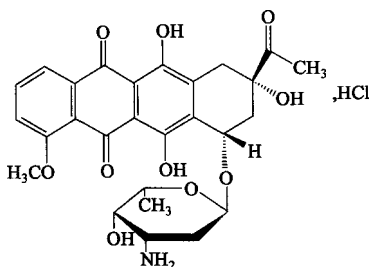
Assay Weigh accurately and powder 20 tablets. Weigh accurately a quantity of the powdered tablets equivalent to 0.25 g of dapsone. Carry out the Assay described under Dapsone. Each ml of sodium nitrite (0.1 mol/L) VS is equivalent to 12.42 mg of $C_{12}H_{12}N_2O_2S$.

Category As described under Dapsone.

Strength (1) 50 mg (2) 100 mg

Storage Preserve in tightly closed containers.

Daunorubicin Hydrochloride



$C_{27}H_{29}NO_{10} \cdot HCl$ 563.98

[23541-50-6]

Daunorubicin hydrochloride is (1*S*, 3*S*)-3-Acetyl-1,2,3,4,6,11-hexahydro-3,5,12-trihydroxy-10-methoxy-6,11-dioxo-1-naphthacenyl-3-amino-2,3,6-trideoxy- α -L-lyxo-hexopyranoside hydrochloride.

It contains not less than 88.9% of Daunorubicin ($C_{27}H_{29}NO_{10}$), calculated on the anhydrous and residual solvent-free basis.

Description An orange-red crystalline powder, hygroscopic. Freely soluble in water or methanol, slightly soluble in ethanol, practically insoluble in acetone.

Identification (1) The retention time of the principal peak of Daunorubicin in the substance being examined in the chromatogram obtained in the Assay is identical with that of the principal peak of Daunorubicin CRS in the chromatogram of the reference solution correspondingly.

(2) The infrared absorption spectrum (Appendix IV C) is concordant with the reference spectrum of Daunorubicin (Appendix VI).

(3) Dissolve about 10 mg in 0.5 ml of nitric acid, add 0.5 ml of water and heat over a flame for 2 minutes. Allow to cool and add silver nitrate solution TS. A white precipitate is formed.

Crystallinity Complies with the test for crystallinity (Appendix IX D).

Acidity An aqueous solution of 5 mg per ml, pH 4.5-6.5. (Appendix VI H).

Related substances Carry out the method and use the solution as described under Assay. Adjust the attenuation so that the principal peak height in the chromatogram is 20%-25% of full scale of chart. Dissolve a quantity of the substance being examined, accurately weighed, in mobile phase to produce a solution of 1.0 mg per ml as the test solution. Measure accurately 1 ml to a 100 ml volumetric flask, dilute with the mobile phase to volume and mix well as the reference solution. Inject separately 10 μ l each of the test solution and the reference solution into the column and record the chromatogram for four times the retention time of the principal peak. Each peak area and the sum of the areas of all peaks other than the principal peak in the chromatogram obtained with the test solution are not greater than 1.5 times and 3 times of the area of the principal peak in the chromatogram obtained with the reference solution.

Residual solvent *chloroform, acetone, methanol, ethanol and 1-butanol*

Dissolve about 0.2 g, accurately weighed, in 5 ml of water in a head-sampling bottle. Encapsulate the bottle. Used as the test solution. Weigh accurately, a quantity of

chloroform, methanol, acetone, ethanol and 1-butanol, separately, dissolve with Dimethyl Sulphoxide to produce stock solutions individually. Measure accurately a quantity of each stock solution, dilute with water to obtain a mixed solution containing 6 μ g of chloroform, 20 μ g of acetone, 10 μ g each of methanol and ethanol, 0.2 mg of 1-butanol per ml. Measure 5 ml accurately in a head-sampling bottle. Encapsulate the bottle. Used as the reference solution.

Carry out the method for Residual solvent (Appendix VIII P). The gas chromatograph is equipped with a flame-ionization detector and a fused-silica capillary column coated with a layer of 6% cyanopropylphenyl/94% dimethylsiloxane or equivalent phase column. Maintain the temperature of the column at 50°C. The injection port is maintained at a temperature of 140°C. The detector is maintained at a temperature of 250°C. Nitrogen or Helium is used as the carrier gas, the flow rate is 5.0 ml per minute. Head-sampling method is used. The head-sampling condition is 80°C for 45 minutes. The injection volume is 1.0 ml. Inject the reference solution into the column and record the chromatogram. The resolution factor between main peaks complies with the related requirements. Inject separately each of the test solution and the reference solution into the column and record the chromatogram. Calculate the content of chloroform, methanol, acetone, ethanol and 1-butanol with respect to the peak area of chloroform, methanol, acetone, ethanol and 1-butanol obtained in the chromatogram by the external standard method respectively. The content of methanol and ethanol are not more than 0.2% individual. The content of 1-butanol is not more than 1.0%. The content of chloroform and acetone comply with the related requirements.

Water Not more than 3.0% (Appendix VIII M, method 1 A).

Bacterial endotoxin Carry out the test for Bacterial endotoxin (Appendix XI E); less than 4.3 EU per mg.

Assay Carry out the method for high performance liquid chromatography (Appendix V D), using a column packed with octadecylsilane bonded silica gel and a mixture of water-acetonitrile (adjust the pH to 2.2 ± 0.2 with phosphoric acid) (62 : 38) as the mobile phase. The detection wavelength is 254 nm. Dissolve a quantity of daunorubicin CRS and doxorubicin hydrochloride CRS in mobile phase to produce a mixed solution containing 0.1 mg each of the two substances per ml. Inject 10 μ l of the solution into the column and record the chromatogram. The resolution factor between doxorubicin and daunorubicin is more than 2.0.

Procedure Dissolve a quantity of the substance being examined, accurately weighed, with mobile phase to produce a solution containing 0.1 mg per ml. Inject 10 μ l into the column and record the chromatogram. Repeat the operation, using daunorubicin CRS instead of the substance being examined, calculate the content of daunorubicin ($C_{27}H_{29}NO_{10}$) with respect to the peak area obtained in the chromatogram by the external standard method.

Category Antitumour.

Storage Preserve in tightly closed containers, stored in a cool place and protected from light.

Preparation Daunorubicin Hydrochloride for Injection

Daunorubicin Hydrochloride for Injection

Daunorubicin Hydrochloride for Injection is a

sterile mixture of Daunorubicin Hydrochloride and suitable amount of Mannitol or other excipient. It contains not less than 90.0% and not more than 115% of the labelled amount of Daunorubicin ($C_{27}H_{29}NO_{10}$).

Description A red loosen mass or powder.

Identification Complies with the tests (1) and (3) for Identification described under Daunorubicin Hydrochloride.

Related substances Carry out the method and use the solution as described under Daunorubicin Hydrochloride. Dissolve a quantity of the substance being examined, accurately weighed, in mobile phase to produce a solution of 1.0 mg per ml as the test solution. Measure accurately 1 ml to a 100 ml volumetric flask, dilute with the mobile phase to volume and mix well as the reference solution. Each peak area and the sum of the areas of all peaks other than the principal peak in the chromatogram obtained with the test solution are not greater than 2 times and 4 times of the area of the principal peak in the chromatogram obtained with the reference solution.

Content uniformity Complies with the test for content uniformity (Appendix X E), the content of daunorubicin in each bottle is calculated by Assay.

Acidity Carry out the method for Acidity described under Daunorubicin Hydrochloride.

Water Carry out the method for Water described under Daunorubicin Hydrochloride.

Bacterial endotoxin Carry out the method for Bacterial endotoxin described under Daunorubicin Hydrochloride.

Sterility Dissolve a quantity of the substance being examined in suitable amount of solvent, transfer to at least 500 ml of sterile 0.9% of sodium chloride solution. Complies with the test for sterility (Appendix XI H, membrane filtration method).

Other requirements Complies with the general requirements for injection (Appendix I B).

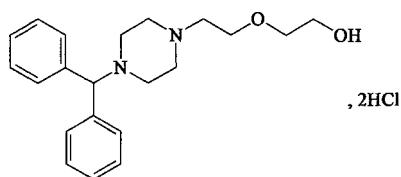
Assay Take 10 packages. Dissolve the substance being examined in each original bottle with mobile phase and dilute to produce a solution of 0.1 mg per ml. Carry out the Assay described under Daunorubicin Hydrochloride. Calculate the content of daunorubicin in each bottle. The average value of these 10 contents is the final result.

Category As described under Daunorubicin Hydrochloride.

Strength 20 mg (Calculated on $C_{27}H_{29}NO_{10}$)

Storage Preserve in well closed containers, stored in a cool place and protected from light.

Decloxizine Hydrochloride



$C_{21}H_{28}N_2O_2 \cdot 2HCl$ 413.39

[3733-63-9]

Decloxizine Hydrochloride is 2-[2-[4-(Diphenylmethyl)-1-piperazinyl] ethoxy] ethanol dihydro-

chloride. It contains not less than 98.5% of $C_{21}H_{28}N_2O_2 \cdot 2HCl$, calculated on the dried basis.

Description A white to pale yellowish white powder; odourless; taste, bitter; hygroscopic.

Very soluble in water; freely soluble in ethanol; sparingly soluble in chloroform; very slightly soluble in acetone; insoluble in ether.

Melting range 201-207°C, with decomposition (Appendix VI C).

Identification (1) Dissolve about 0.1 g in 15 ml of ethanol, add 15 ml of trinitrophenol TS, allow to stand for 15 minutes and filter. Wash the residue with ethanol in portions, dry in vacuum for 2 hours. It melts at about 200°C with decomposition (Appendix VI C).

(2) The light absorption of a solution of 10 µg per ml in 0.1 mol/L sulfuric acid solution exhibits a maximum at 225 nm (Appendix IV A).

(3) The infrared absorption spectrum (Appendix IV C) is concordant with the reference spectrum of Decloxizine Hydrochloride (Appendix XVI).

(4) The aqueous solution yields the reactions characteristic of chlorides (Appendix III).

Loss on drying When dried to constant weight at 105°C, loses not more than 3.0% of its weight (Appendix VIII L).

Residue on ignition Not more than 0.15% (Appendix VIII N).

Heavy metals Dissolve 0.5 g in a small quantity of water, add 2 ml of dilute acetic acid and sufficient water to produce 25 ml. Carry out the limit test for heavy metals (Appendix VIII H, method 1): not more than 0.002%.

Assay Dissolve about 0.15 g, accurately weighed, in 15 ml of glacial acetic acid, add 5 ml of mercuric acetate TS and 1 drop of crystal violet IS, titrate with perchloric acid (0.1 mol/L) VS until the colour changes to blue. Perform a blank determination and make any necessary correction. Each ml of perchloric acid (0.1 mol/L) VS is equivalent to 20.67 mg of $C_{21}H_{28}N_2O_2 \cdot 2HCl$.

Category Antihistaminic.

Storage Preserve in tightly closed containers, protected from light.

Preparation Decloxizine Hydrochloride Tablets

Decloxizine Hydrochloride Tablets

Decloxizine Hydrochloride Tablets contain not less than 90.0% and not more than 110.0% of the labelled amount of decloxizine hydrochloride ($C_{21}H_{28}N_2O_2 \cdot 2HCl$).

Description Sugar-coated tablets with white core; hygroscopic.

Identification (1) The light absorption of the solution obtained in the Assay exhibits a maximum at 224 nm (Appendix IV A).

(2) Shake a quantity of powdered tablets with water and filter, the filtrate yields the reactions characteristic of chlorides (Appendix III).

Other requirements Comply with the general requirements for tablets (Appendix I A).

Assay Weigh accurately and powder 20 tablets. To an accurately weighed quantity of the powder equivalent to about 0.1 g of decloxizine hydrochloride in a 100 ml volumetric

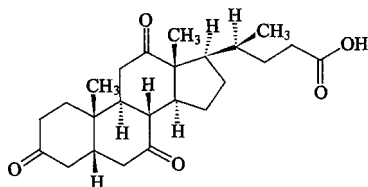
flask add 0.1 mol/L hydrochloric acid solution to dissolve decloxizine hydrochloride and dilute to volume, mix well and filter. Discard the initial filtrate, transfer 2 ml of the successive filtrate, accurately measured, to another 100 ml volumetric flask, dilute with 0.1 mol/L hydrochloric acid solution to volume and mix well. Measure the absorbance of the resulting solution at 224 nm (Appendix IV A). Repeat the operation using a solution containing 20 µg per ml of decloxizine hydrochloride CRS in 0.1 mol/L hydrochloric acid solution in the same manner. Calculate the content of decloxizine hydrochloride ($C_{21}H_{23}N_2O_2 \cdot 2HCl$).

Category As described under Decloxizine Hydrochloride.

Strength (1) 25 mg (2) 50 mg

Storage Preserve in tightly closed containers, protected from light.

Dehydrocholic Acid



$C_{24}H_{34}O_5$ 402.53

[81-23-2]

Dehydrocholic Acid is 3,7,12-trioxo-5β-cholan-24-oic acid. It contains not less than 98.5% of $C_{24}H_{34}O_5$, calculated on the dried basis.

Description A white friable powder; odourless; taste, bitter.

Sparingly soluble in chloroform; slightly soluble in ethanol; practically insoluble in water; soluble in sodium hydroxide TS.

Specific optical rotation +29.0° to +32.5°, in a solution of 20 mg per ml in dioxane (Appendix VI E).

Identification (1) Dissolve about 5 mg in 1 ml of sulfuric acid and 1 drop of formaldehyde solution, allow to stand for 5 minutes, add 5 ml of water, a yellow colour with bluish green fluorescence is produced.

(2) To about 20 mg add 1 ml of ethanol, shake thoroughly, add 5 drops of dinitrobenzene solution (dissolve 1 g of dinitrobenzene in 100 ml of ethanol; freshly prepared,) and 0.5 ml of sodium hydroxide solution (1→8), allow to stand, a purple or purplish red is produced, changing to dark brown on standing.

(3) The infrared absorption spectrum (Appendix IV C) is concordant with the reference spectrum of dehydrocholic acid (Appendix XVI).

Odours To 2.0 g add 100 ml of water, boil for 2 minutes, no odour is produced.

Clarity and colour of ethanol solution To 0.10 g add 30 ml of ethanol, shake thoroughly to dissolve dehydrocholic acid, the solution is clear and colourless.

Chloride To 1.0 g add 100 ml of water, shake for 5 minutes, filter. Carry out the limit test for chloride (Appendix VIII A), using 25 ml of successive filtrate. Any opalescence produced is not more pronounced than that of a reference solution using 5.0 ml of sodium chloride standard solution (0.02%).

Sulfate Carry out the limit test for sulfate (Appendix VIII

B), using 10 ml of the successive filtrate obtained in the test for chloride. Any opalescence produced is not more intense than that of a reference solution using 5.0 ml of potassium sulfate standard solution (0.05%).

Barium To 2.0 g add 100 ml of water and 2 ml of hydrochloric acid, boil for 2 minutes, allow to cool and filter, wash the filter paper with water, combine the washing and filtrate, dilute with water to 100 ml, mix well; to 10 ml of the solution add 1 ml of dilute sulfuric acid, no turbidity is produced.

Loss on drying When dried to constant weight at 105°C, loses not more than 1.0% of its weight (Appendix VIII L).

Residue on ignition Not more than 0.3% (Appendix VIII N), using 1.0 g.

Heavy metals Carry out the limit test for heavy metals (Appendix VIII H, method 2), using the residue obtained in the test for Residue on ignition; not more than 0.002%.

Microbial limit test Salmonella species is absent (Appendix XI J).

Assay Weigh accurately about 0.5 g, add 60 ml of neutralized ethanol (neutral to phenolphthalein IS), heating on water bath to dissolve dehydrocholic acid, cool, add a few drops of phenolphthalein IS and 20 ml of freshly boiled and cooled water, titrate with sodium hydroxide (0.1 mol/L) VS, add 100 ml of freshly boiled and cooled water toward the end of titration, continue the titration to end point. Each ml of sodium hydroxide (0.1 mol/L) VS is equivalent to 40.25 mg of $C_{24}H_{34}O_5$.

Category Cholecystagogue.

Storage Preserve in tightly closed containers, protected from light.

Preparation Dehydrocholic Acid Tablets

Dehydrocholic Acid Tablets

Dehydrocholic Acid Tablets contain not less than 93.0% and not more than 107.0% of the labelled amount of dehydrocholic acid ($C_{24}H_{34}O_5$).

Description White tablets.

Identification Triturate 1 tablet with 10 ml of sodium carbonate TS to dissolve dehydrocholic acid, add diazotized sulfanilic acid TS, a red colour is produced gradually.

Other requirements Comply with the general requirements for tablets (Appendix I A).

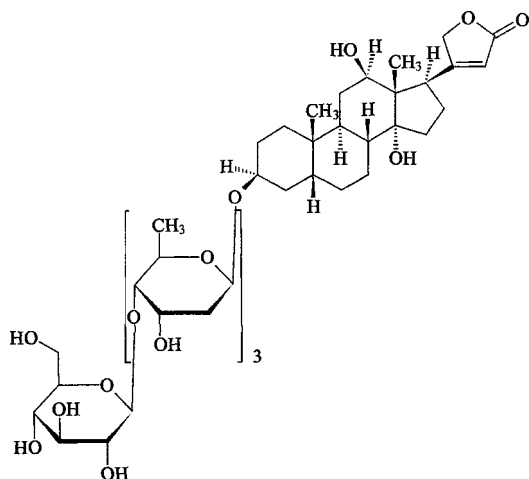
Assay Weigh accurately and powder 20 tablets. To a quantity equivalent to about 0.5 g of dehydrocholic acid, accurately weighed, add 40 ml of neutralized ethanol (neutral to phenolphthalein IS) and 20 ml of water, heating on water bath for 10 minutes, shake thoroughly to dissolve dehydrocholic acid. Add 3 drops of phenolphthalein IS, titrate with sodium hydroxide (0.1 mol/L) VS, add 100 ml of freshly boiled water toward the end of titration, continue the titration to end point. Each ml of sodium hydroxide (0.1 mol/L) VS is equivalent to 40.25 mg of $C_{24}H_{34}O_5$.

Category As described under Dehydrocholic Acid.

Strength 0.25 g

Storage Preserve in tightly closed containers, protected from light.

Deslanoside



$C_{47}H_{74}O_{19}$ 943.09

[17598-65-1]

Deslanoside is 3-[(*O*-β-*D*-glucopyranosyl)-(1→4)-*O*-2,6-dideoxy-β-*D*-ribo-hexopyranosyl)-(1→4)-*O*-2,6-dideoxy-β-*D*-ribo-hexopyranosyl)-(1→4)-*O*-2,6-dideoxy-β-*D*-ribo-hexopyranosyl)oxy]-12,14-dihydroxy-3β,5β,12β-card-20(22)-enolide. It contains not less than 96.0% and not more than 104.0% of $C_{47}H_{74}O_{19}$, calculated on the dried basis.

Description A white crystalline powder; odourless; taste, bitter; hygroscopic.

Slightly soluble in methanol; very slightly soluble in ethanol; practically insoluble in water or chloroform.

Specific optical rotation +7° to +9°, in a solution of 20 mg per ml in anhydrous pyridine (Appendix VI E).

Identification (1) Dissolve about 2 mg in 2 ml of glacial acetic acid in a test tube, add 1 drop of ferric chloride TS, mix, and add slowly, along the wall, 2 ml of sulfuric acid to form a sub-layer; a brown ring is formed at the junction of the liquids and a greenish-blue colour is produced in the glacial acetic acid layer.

(2) Dissolve 2 mg in 2 ml of ethanol, add 10 drops each of 3,5-dinitrobenzoic acid TS and ethanolic potassium hydroxide TS, and mix; a violet colour is produced.

(3) Carry out the method for thin-layer chromatography (Appendix V B), using kieselguhr G as the coating substance, and a mixture of chloroform-tetrahydrofuran-formamide (50:50:6) as the mobile phase, the plate being impregnated with a mixture of formamide-acetone (1:9). Apply separately to the plate 2 μl each of two solutions in a mixture of chloroform and methanol (1:1) containing (1) 10 mg per ml of the substance being examined and (2) 10 mg per ml of deslanoside CRS. After developing and removal of the plate, dry at 120°C for 15 minutes, spray with a mixture of sulfuric acid-ethanol (1:9) and heat at 120°C for 20 minutes. Examine under ultra-violet light (365 nm), the fluorescence and position of the principal spots in the chromatogram obtained with these solutions should be identical.

Related substances Carry out the method for thin-layer chromatography (Appendix V B), using silica gel G as the coating substance and a mixture of dichloromethane-methanol-water (75:23:2) as the mobile phase. Apply

separately to the plate 2 μl each of four solutions in a mixture of chloroform-methanol (1:1) containing (1) 10 mg, (2) 0.10 mg, (3) 0.20 mg and (4) 0.50 mg of the substance being examined per ml. After developing and removal of the plate, dry it in air and spray with sulfuric acid-ethanol (1:9), heat at 120°C for 2 minutes and examine under ultraviolet light (365 nm). Compare the intensity of each secondary spot in the chromatogram obtained with solution (1) with those of the principal spots obtained with the other solutions. The total amount of impurities assessed does not exceed 10%.

Loss on drying When dried to constant weight at 105°C, loses not more than 1.0% of its weight (Appendix VIII L).

Assay Transfer separately 10 mg of the substance being examined and deslanoside CRS into separate 50 ml volumetric flask, add a quantity of 70% ethanol to dissolve, dilute with 70% ethanol to volume and mix well. Measure accurately 5 ml to separate 25 ml volumetric flask, dilute with 70% ethanol to volume and mix well, as the test solution and the reference solution. Measure accurately 10 ml each of the two solutions. To each solution add 6 ml of alkaline trinitrophenol TS, accurately measured, mix well and allow to stand for 30 minutes at 20-25°C. Measure the absorbances (Appendix IV B) at 485 nm. Calculate the content of $C_{47}H_{74}O_{19}$.

Category Cardiac glycoside.

Storage Preserve in tightly closed containers, protected from light.

Preparation Deslanoside Injection

Deslanoside Injection

Deslanoside Injection is a sterile solution of deslanoside in 10% ethanol. It contains not less than 90.0% and not more than 110.0% of the labelled amount of deslanoside ($C_{47}H_{74}O_{19}$).

Description A colourless, clear liquid.

Identification Complies with the test (1) and (2) for Identification described under Deslanoside, using 4 ml of deslanoside injection.

pH value 5.0-7.0 (Appendix VI H).

Other requirements Complies with the general requirements for injections (Appendix I B).

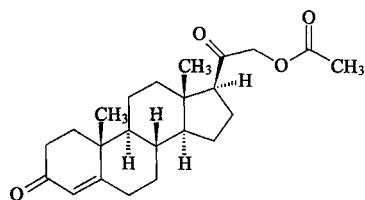
Assay Dilute 5 ml, accurately measured, with 70% ethanol and dilute to volume in a 25 ml volumetric flask, mix well, as the test solution. Dissolve an accurately weighed quantity of deslanoside CRS with 70% ethanol to produce a solution of 40 μg per ml as the reference solution. Carry out the Assay described under Deslanoside, beginning at the words "Measure accurately 10 ml each of the two solutions...". Calculate the content of $C_{47}H_{74}O_{19}$.

Category As described under Deslanoside.

Strength 2 ml:0.4 mg

Storage Preserve in well closed containers, protected from light.

Desoxycortone Acetate



$C_{23}H_{32}O_4$ 372.51

[152-58-9]

Desoxycortone Acetate is 21-(acetyloxy)-pregna-4-ene-3,20-dione. It contains not less than 96.0% and not more than 104.0% of $C_{23}H_{32}O_4$, calculate _____ r b _____.

Description A white or almost white crystalline powder; odourless.

Sparingly soluble in ethanol or acetone; slightly soluble in vegetable oil; practically insoluble in water.

Melting range 155-161°C (Appendix VI C).

Specific optical rotation +175° to +185°, in a solution of 10 mg per ml in dioxane (Appendix VI E).

Specific absorbance Measure the absorbance of a solution of 10 µg per ml in ethanol at 240 nm (Appendix IV A), the value of A (1%, 1cm) is 430-460.

Identification (1) Dissolve about 5 mg in 0.5 ml of ethanol, add 0.5 ml of ammoniated silver nitrate TS, a black precipitation is produced.

(2) To about 50 mg add 2 ml of ethanolic potassium hydroxide solution, heat on water bath for 5 minutes and cool, add 2 ml of sulfuric acid (1→2), boil for 1 minute, the odour of ethyl acetate is perceptible.

Related substance Carry out the method for thin-layer chromatography (Appendix V B), using silica gel GF₂₅₄ as the coating substance and a mixture of dichloromethane-ether-methanol-water (77 : 15 : 8 : 1.2) as the mobile phase. Apply separately to the plate 5 µl each of the solutions of substance being examined in chloroform-methanol (9 : 1) containing (1) 10 mg, (2) 0.1 mg and (3) 0.2 mg of the substance being examined per ml. After developing and removal of the plate, dry it in air, and examine under ultraviolet light at 254 nm. Any spot other than the principal spot in the chromatogram obtained with the solution (1) is not more intense than the principal spot in the chromatogram obtained with the solution (3). If one secondary spot in the chromatogram obtained with the solution (1) is more intense than the principal spot in the chromatogram obtained with the solution (2), it is not more intense than the principal spot in the chromatogram obtained with solution (3).

Loss on drying When dried to constant weight at 105°C, losses not more than 0.5% of its weight (Appendix VIII L).

Residue on ignition Not more than 0.1% (Appendix VIII N).

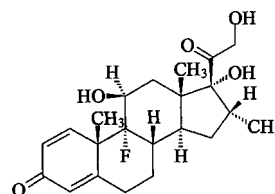
Assay Dissolve an accurately weighed quantity in aldehyde free ethanol to produce a solution of 35 µg per ml. To 10 ml, accurately measured, in 25 ml volumetric flask add 2 ml of vitastain TS rapidly under a current of nitrogen, stoppered, place in 30°C water bath for 1 hour, cool rapidly and dilute with aldehyde free ethanol to volume, shake well. Measure the absorbance (Appendix IV A) at 485 nm.

Repeat the operation using a quantity of Desoxycortone Acetate CRS and measure the absorbance correspondingly. Calculate the content of $C_{23}H_{32}O_4$.

Category Corticosteroids.

Storage Preserve in tightly close containers, protected from light.

Dexamethasone



$C_{22}H_{29}FO_5$ 392.47

Dexamethasone is 9-fluoro-11β,17,21-trihydroxy-16α-methyl-21-pregna-1,4-diene-3,20-dione. It contains not less than 97.0% and not more than 102.0% of $C_{22}H_{29}FO_5$, calculated on the dried basis.

Description A white or almost white crystalline powder; odourless.

Sparingly soluble in acetone, ethanol methanol and dioxane; slightly soluble in chloroform; very slightly soluble in ether; insoluble or practically insoluble in water.

Melting range 254-264°C (melting range is not more than 4°C), with decomposition (Appendix VI C).

Specific optical rotation +72° to +82°, in a solution of 10 mg per ml in dioxane (Appendix VI E).

Specific absorbance Measure the absorbance of a solution of about 10 µg per ml in ethanol at 240 nm (Appendix IV A), the value of A (1%, 1 cm) is 380-410.

Identification (1) Dissolve 2 mg in 2 ml of sulfuric acid by shaking, a reddish-brown colour is produced within 5 minutes; add 10 ml of water and mix well, the colour disappears.

(2) The infrared absorption spectrum (Appendix IV C) is concordant with the reference spectrum of dexamethasone (Appendix XVI).

(3) It yields the reaction characteristic of organic fluorine compounds (Appendix III).

Related substances Carry out the method for high performance liquid chromatography (Appendix V D), using a column (4.6 mm × 250 mm, 5 µm) packed with phenylsilane bonded silica gel and a mixture of 0.02 mol/L ammonium formate solution (Adjust the pH to 3.6 by aminic acid)-acetonitrile (78 : 22) as the mobile phase. Detection Wavelength is 254 nm. Dissolve a quantity of the substance being examined, accurately weighed, in mobile phase to produce the test solution (1) of about 0.5 mg per ml. Measure accurately 1 ml the test solution into a 100 ml volumetric flask and dilute to volume with mobile phase, mix well as the reference solution (2); Dissolve a quantity of Methylprednisolone CRS in the test solution (1) to make a pre-test solution (3) of each 5 µg per ml. Inject proper quantities of the solution (3) into the column. The resolution factor between the peaks of methylprednisolone and dexamethasone is not less than 5.7 and the peak of methylprednisolone followed by the peak of dexamethasone. Inject 10 µl of the solution (2) into the column. Adjust the

attenuation so that the principal peak height in the chromatogram is about 40% of full scale of the chart. Inject separately accurately 10 μ l each of the solution (1) and (2) into the column, and record the chromatogram for triple the retention time of the principal peak. If there are any other impurity peaks in the chromatogram of solution (1), any peak area is not greater than the principal peak area of solution (2) and the sum of the areas of all peaks other than the principal peak is not greater than twice of area of the principal peak of solution (2).

Loss on drying When dried at 105°C for 3 hours, loses not more than 0.5% of its weight (Appendix VIII L).

Residue on ignition Not more than 0.2% (Appendix VIII N).

Assay Carry out the method for high performance liquid chromatography (Appendix V D), using a column packed with octadecylsilane bonded silica gel and a mixture of acetonitrile-water (4 : 6) as the mobile phase. Detection wavelength is 240 nm, the number of theoretical plates of the column is not less than 3000, calculated with reference to the peak of dexamethasone. The resolution factor complies with related requirements.

Procedure Dissolve 15 mg of dexamethasone CRS, accurately weighed, in 2 ml of methanol in 50 ml volumetric flask, dilute with the mobile phase to volume, shake well. Inject 20 μ l of the resulting solution into the column. Repeat the operation using 15 mg of the substance being examined instead of dexamethasone CRS, calculate the content of $C_{22}H_{29}FO_5$.

Category Corticosteroid.

Storage Preserve in tightly closed containers and protected from light.

Preparation (1) Compound Dexamethasone Cream
(2) Dexamethasone Tablets

Compound Dexamethasone Acetate Cream

Compound dexamethasone acetate cream contains not less than 90.0% and not more than 110.0% of the labelled amount of dexamethasone acetate ($C_{24}H_{31}FO_6$).

Formula

Dexamethasone acetate	0.75 g
Camphor	10 g
Menthanol	10 g
Nipagin	1 g
Base	a quantity
Purified water	a quantity
To make	1000 g

Description A white cream; characteristic flavour of camphor.

Identification (1) Dissolve a quantity of camphor CRS and menthanol CRS in the anhydrous ethanol to produce a solution of 0.4 mg per ml respectively, use the solution as the reference solution. Carry out the method for gas chromatography (Appendix V E). Using a column packed with 10% polyglycol 20 M, maintain the column temperature at 150°C. The number of theoretical plates of the column is not less than 1000, calculated with reference to the peak of camphor. The resolution factor between the peaks of camphor and menthanol is more than 2.0. Inject separately 2

μ l each of above two solutions in the Assay into the column and record the chromatogram, the chromatogram obtained with the solution shows two peaks with the same retention time as the peaks of camphor CRS and menthanol CRS in the chromatogram obtained with the reference solution corresponding.

(2) The retention time of the principal peak of dexamethasone acetate in the substance being examined in the chromatogram obtained in the Assay is identical with that of the principal peak of dexamethasone acetate CRS in the chromatogram of the reference solution.

Other requirements Complies with the general requirements for creams (Appendix I F).

Assay Carry out the method for high performance liquid chromatography (Appendix V D). Using a column packed with octadecylsilane bonded silica gel and a mixture of methanol-water (70 : 30) as the mobile phase. Detection wavelength is 240 nm. The number of theoretical plates of the column is not less than 2000, calculated with reference to the peak of dexamethasone acetate. The resolution factor among the peaks of dexamethasone acetate, internal standard substance and neighbour impurities complies with the related requirements.

Internal standard solution Dissolve a quantity of methyltestosterone CRS in methanol to produce a solution of about 0.20 mg per ml.

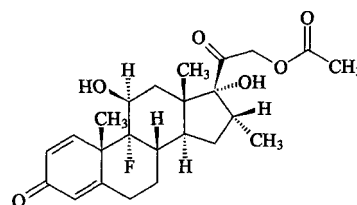
Procedure Weigh accurately a quantity of cream, equivalent to about 1.35 mg of dexamethasone acetate, into a beaker, add accurately measured 5 ml of internal standard solution, then add 20 ml of methanol, heat on water bath at 80°C with stirring, cool on ice bath until base freezes, filter, wash the base with two 10 ml portions of methanol, combine the filtrate and washings to a 50 ml volumetric flask, dilute with methanol to the volume, mix well, cool in ice bath for 2 hours, filter quickly and inject 20 μ l of the successive filtrate into the column and record the chromatogram. Dissolve about 13 mg of dexamethasone acetate CRS, weighed accurately, in a 50 ml volumetric flask, dilute with methanol to the volume, mix well. Measure accurately 5 ml of the solution and internal standard solution respectively in a 50 ml volumetric flask, dilute with methanol to the volume, mix well. Measure in the same manner, calculate the content of $C_{24}H_{31}FO_6$.

Category Corticosteroid.

Strength (1) 10 g : 7.5 mg (2) 20 g : 15 mg

Storage Preserve in tightly closed containers and stored in the cool place.

Dexamethasone Acetate



$C_{24}H_{31}FO_6$ 434.50

[1177-87-3]

Dexamethasone Acetate is 9 α -fluoro-11 β , 17 α , 21-trihydroxy - 16 α - methyl - pregna - 1,4 - diene - 3,20-dione-21-acetate. It contains not less than

97.0% and not more than 102.0% of $C_{24}H_{31}FO_6$, calculated on the dried basis.

Description White or almost white crystals or a crystalline powder; odourless; taste, slightly bitter. Freely soluble in acetone; soluble in methanol or dehydrated ethanol; sparingly soluble in ethanol or chloroform; very slightly soluble in ether; insoluble in water.

Melting range 223-233°C, with decomposition (Appendix VI C).

Specific optical rotation +82° to +88°, in a solution of about 10 mg per ml in dioxane (Appendix VI E).

Specific absorbance Measure the absorbance of a solution of 15 µg per ml in ethanol at 240 nm (Appendix IV A), the value of *A* (1%, 1 cm) is 343-371.

Identification (1) Dissolve about 10 mg in 1 ml of methanol by warming, add 1 ml of hot alkaline cupric tartrate TS; a red precipitate is produced.

(2) To 50 mg add 2 ml of ethanolic potassium hydroxide TS, heat in a water bath for 5 minutes, cool, add 2 ml of sulfuric acid solution (1→2) and boil gently for 1 minute; the odour of ethyl acetate is perceived.

(3) The infrared absorption spectrum (Appendix IV C) is concordant with the reference spectrum of dexamethasone acetate (Appendix XVI).

(4) It yields the reaction characteristic of organic fluorine compounds (Appendix III).

Related substances Carry out the method for high performance liquid chromatography (Appendix V D), using a column packed with octadecylsilane bonded silica gel and a mixture of methanol-tetrahydrofuran-sodium acetate solution (Dissolve 12.0 g of sodium acetate in water and dilute to 1000 ml, mix well, adjust the pH to 4.5 ± 0.05 by glacial acetic acid) (30 : 10 : 60) as the mobile phase. Detect wavelength is 242 nm. The resolution factor between the peaks of dexamethasone acetate and hydrocortisone acetate is not less than 11.0. Dissolve about 25 mg of the substance being examined with 17 ml methanol in 25 ml volumetric flask, dilute with sodium acetate solution (pH 4.5) to volume, mix well as the test solution (1). Dissolve about 10 mg of hydrocortisone acetate with 7 ml of methanol in a 10 ml volumetric flask and dilute with sodium acetate solution (pH 4.5) to volume, mix well as the solution (2). Measure accurately each 1 ml of solution (1) and solution (2) into a 100 ml volumetric flask, dilute with mobile phase to the volume, mix well as the reference solution (3). Inject 20 µl of the solution (3) into the column, adjust the attenuation so that the peak height of dexamethasone acetate in the chromatogram is 35%-40% of full scale of the chart. Inject separately accurately 20 µl each of the solution (1) and (3) into the column, and record the chromatogram for twice the retention time of the principal peak. If there are any impurity peaks in the chromatogram of solution (1), any peak area is not greater than half of the peak area of dexamethasone acetate in solution (3) and the sum of the area of all peaks other than the principal peak is not greater than the area of dexamethasone acetate in solution (3).

Loss on drying When dried to constant weight at 105°C, loses not more than 0.5% of its weight (Appendix VIII L).

Residue on ignition Not more than 0.1% (Appendix VIII N).

Selenium Carry out the limit test for selenium (Appendix VIII D), using 0.10 g of the substance being examined; not more than 0.0050%.

Assay Carry out the method for high performance liquid chromatography (Appendix V D), using a column packed

with octadecylsilane bonded silica gel and a mixture of methanol-water (70 : 30) as the mobile phase. Detection wavelength is 240 nm, and the number of the theoretical plates of the column is not less than 1500, calculated with reference to the peak of dexamethasone acetate. The resolution factor between the peaks of dexamethasone acetate and internal standard complies with the related requirements.

Internal standard solution Dissolve methyltestosterone in the mobile phase to produce a solution of about 0.2 mg per ml.

Procedure Dissolve about 13 mg of dexamethasone acetate CRS, accurately weighed, in methanol in a 50 ml volumetric flask, and dilute with water to volume, mix well, as the reference solution. Transfer 5 ml each of the reference solution and the internal standard solution, accurately measured, in a 25 ml volumetric flask, dilute with the mobile phase to volume, mix well, inject 20 µl of the resulting solution into the column. Repeat the operation, using the substance being examined instead of dexamethasone acetate CRS, calculate the content of $C_{24}H_{31}FO_6$.

Category Corticosteroid.

Storage Preserve in tightly closed containers, protected from light.

Preparation (1) Dexamethasone Acetate Cream
(2) Dexamethasone Acetate Injection
(3) Dexamethasone Acetate Tablets

Dexamethasone Acetate Cream

Dexamethasone Acetate cream contains not less than 90.0% and not more than 110.0% of the labelled amount of dexamethasone acetate ($C_{24}H_{31}FO_6$).

Description A white cream.

Identification (1) To about 14 g of the ointment in a beaker add 50 ml of dehydrated ethanol, warm by heating on a water bath, cool in an ice bath, filter and evaporate the filtrate to dryness. The residue complies with test (1) for Identification described under Dexamethasone Acetate.

(2) To about 5 g of the ointment, add 30 ml of dehydrated ethanol, warm on a water bath, cool in an ice bath for 30 minutes and filter. To the filtrate add dehydrated ethanol to 20 ml, used as the solution (1). Dissolve 12.5 mg of dexamethasone acetate CRS in dehydrated ethanol to make up to 100 ml, used as the solution (2). Carry out the method for thin layer chromatography (Appendix V B), using silica gel G as the coating substance and a mixture of chloroform-acetone (4:1) as the mobile phase. Apply separately to the plate 4 µl each of the two solutions. After developing and removal of the plate, dry it in air, spray with a mixture of sulfuric acid-dehydrated ethanol (4:1), heat at 105°C until the spot in the chromatogram obtained with the solution (2) is visualized. The principal spot in the chromatogram obtained with the solution (1) corresponds in colour and position to that in the chromatogram obtained with the solution (2).

(3) The retention time of principal peak in the chromatogram of the substance being examined, obtained in the Assay, is identical with that of principal peak in the chromatogram of the reference solution.

Tests (1), (3) and (1), (2) are alternative.

Other requirements Complies with the general requirements for creams (Appendix I F).

Assay Carry out the method for high performance liquid

chromatography (Appendix V D), using a column packed with octadecylsilane bonded silica gel and a mixture of methanol-water (66 : 34) as the mobile phase. Detection wavelength is 240 nm and the number of theoretical plates of the column, calculated with the peak of dexamethasone acetate, is not less than 3500.

Procedure Dissolve a quantity of the cream, be equivalent to about 0.5 mg dexamethasone acetate, accurately weighed, with accurately 50 ml methanol and stir 30 second at 9500 rpm by homogenizer, then put in the ice water bath for 1 hour, filter with organic membrane (0.45 μ m), drop the first 5 ml and take the succeeding filtrate as the test solution. Inject 20 μ l into the column and record the chromatogram. Dissolve a quantity of dexamethasone acetate CRS, accurately weighed, and dilute with methanol to produce a solution of about 10 μ g per ml, repeat the operation, calculate the content of $C_{24}H_{31}FO_6$ with respect to the peak area obtained in the chromatogram by the external standard method.

Category As described under Dexamethasone Acetate.

Strength (1) 4 g:2 mg (2) 5 g:2.5 mg
(3) 10 g:5 mg

Storage Preserve in tightly closed containers, stored at a cool place.

Dexamethasone Acetate Injection

Dexamethasone Acetate Injection is a sterile suspension of dexamethasone acetate. It contains not less than 90.0% and not more than 110.0% of the labelled amount of $C_{24}H_{31}FO_6$.

Description A suspension of minute granules which deposit on standing, a homogeneous creamy white suspension is obtained on shaking.

Identification (1) Evaporate 12 ml of suspension on water bath to dryness. The residue complies with the tests for Identification (1), (2) described under Dexamethasone Acetate.

(2) To 1 ml of suspension add 2 ml of sulfuric acid along with the tube wall, heat on water bath, a brownish-red ring is produced in the lower layer. Add carefully 5 ml of water and the brownish-red colour disappears.

Acidity pH 4.5-6.5 (Appendix VI H).

Other requirements Complies with the requirements for the injection (Appendix I B).

Assay *Reference preparation* Dissolve an accurately weighed quantity in dehydrated ethanol to produce a solution of 0.25 mg per ml.

Test preparation Measure accurately a quantity, shake well, equivalent to 20 mg of triamcinolon actonide acetate into a 100 ml volumetric flask, dilute with dehydrated ethanol to volume, and mix well. Filter with the dry filter paper, discard the initial filtrates and use the successive filtrate.

Procedure To 1 ml each of the two preparations, accurately measured, in separate dry test tube with stopper add 9 ml of dehydrated ethanol and 1 ml of triphenyl-tetrazolium chloride TS, accurately measured, and mix well, then add 1 ml of tetramethylammonium hydroxide TS, accurately measured, respectively. Allow to stand in a dark place at 25°C for 40-45 minutes. Carry out the method for spectrophotometry, measure the absorbance at 485 nm

(Appendix IV A). Calculate the content of $C_{24}H_{31}FO_6$.

Category As described under Dexamethasone Acetate.

Strength (1) 0.5 ml:2.5 mg (2) 1 ml:5 mg
(3) 5 ml:25 mg

Storage Preserve in well closed containers, protected from light.

Dexamethasone Acetate Tablets

Dexamethasone Acetate Tablets contain not less than 90.0% and not more than 110.0% of the labelled amount of dexamethasone acetate ($C_{24}H_{31}FO_6$).

Description White tablets.

Identification (1) The retention time of principal peak in the chromatogram of the substance being examined, obtained in the Assay, is identical with that of principal peak in the chromatogram of the reference solution.

(2) Macerate a quantity of powdered tablets equivalent to 7 mg of dexamethasone acetate in 25 ml of ethanol, shaking constantly for 15 minutes. Filter and evaporate the filtrate to dryness on a water bath, the residue yields the reaction characteristic of organic fluorine compounds (Appendix III).

Content uniformity Comply with the requirements (Appendix X E). Triturate 1 tablet with ethanol and transfer to a 50 ml volumetric flask with 40 ml of ethanol. Heat in a water bath at 50-60°C for 10 minutes with constant shaking to dissolve dexamethasone acetate. Cool to room temperature, add ethanol to volume and shake thoroughly. Filter and discard the initial filtrate, measure the absorbance of the successive filtrate at 240 nm (Appendix IV A), calculate the content of $C_{24}H_{31}FO_6$, taking 357 as the value of A (1%, 1 cm).

Other requirements Comply with the general requirements for tablets (Appendix I A).

Assay Carry out the method for high performance liquid chromatography (Appendix V D), using a column packed with octadecylsilane bonded silica gel and a mixture of methanol-water (70 : 30) as the mobile phase. Detection wavelength is 240 nm and the number of theoretical plates of the column, calculated with the peak of dexamethasone acetate, is not less than 4000.

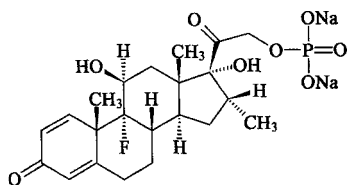
Procedure Weigh accurately and powder 20 tablets. To a quantity, weighed accurately, equivalent to about 2.5 mg of dexamethasone acetate in a 50 ml volumetric flask, add a quantity of mobile phase, for 30 minutes of ultrasonic treatment until dexamethasone acetate is dissolved. Dilute with mobile phase to the volume, shake well and filter, take the successive filtrate as the test solution. Inject 20 μ l into the column and record the chromatogram. Dissolve a quantity of dexamethasone acetate CRS, accurately weighed, and dilute with methanol to produce a solution of about 50 μ g per ml, repeat the operation, calculate the content of $C_{24}H_{31}FO_6$ with respect to the peak area obtained in the chromatogram by the external standard method.

Category As described under Dexamethasone Acetate.

Strength 0.75 mg

Storage Preserve in tightly closed containers, protected from light.

Dexamethasone Sodium Phosphate



$C_{22}H_{28}FNa_2O_8P$ 516.41

[2392-39-4]

Dexamethasone Sodium Phosphate is 9-fluoro-11 β ,17 α ,21-trihydroxy-16 α -methyl-21-pregna-1,4-diene-3,20-dione 21-(dihydrogen phosphate), disodium salt. It contains not less than 96.0% and not more than 102.0% of $C_{22}H_{28}FNa_2O_8P$, calculated on the dried basis.

Description A white to slightly yellow powder; odourless; taste, slightly bitter; hygroscopic.

Soluble in water or methanol; slightly soluble in acetone or ether.

Specific optical rotation $+72^\circ$ to $+80^\circ$, in a solution of about 10 mg per ml in water (Appendix VI E).

Identification (1) The retention time of principal peak in the chromatogram of the substance being examined, obtained in the Assay, is identical with that of principal peak in the chromatogram of the reference solution.

(2) The infrared absorption spectrum (Appendix IV C) is concordant with the reference spectrum of dexamethasone sodium phosphate (Appendix XVI).

(3) It yields the reaction characteristic of organic fluorine compounds (Appendix III).

(4) To 40 mg add 2 ml of sulfuric acid, heat gently until white fume evolves, add 0.5 ml of nitric acid dropwise, continue the heating until the vapor of nitrogen oxide is completely expelled, cool, add 2 ml of water dropwise, again heat gently until white fume evolves and the solution becomes slightly yellow, cool, add 10 ml of water dropwise, add ammonia TS until the solution is neutral to litmus paper, decolourize with a small amount of active carbon and filter, the filtrate yields the reactions characteristic of sodium salts and phosphates (Appendix III).

Alkalinity Dissolve 50 mg of the dried substance in 10 ml of water, pH 7.5-10.5 (Appendix VI H).

Clarity and colour of solution A solution of 0.20 g in 10 ml of water is clear. Any opalescence produced is not more pronounced than that of reference suspension I (Appendix IX B), and any colour produced is not more intense than that of reference solution Y₂ (Appendix IX A, method 1).

Free phosphoric acid Dissolve 20 mg, accurately weighed, in 15 ml of water in a 25 ml volumetric flask. Add 11 ml of water to 4.0 ml of a standard phosphate solution [place 0.35 g of potassium dihydrogen phosphate, previously dried at 105°C for 2 hours and accurately weighed, in a 1000 ml volumetric flask, dissolve it in water, add 10 ml of sulfuric acid solution (3→10) and dilute with water to volume, mix well, dilute with water to 1/10 of its original concentration immediately before use] in another 25 ml volumetric flask; to each flask add 2.5 ml of molybdo-sulfuric acid TS and 1 ml of 1-amino-2-naphthol-4-sulfonic acid solution (mix well 5 g of anhydrous sodium sulfite and 94.3 g of sodium bisulfite with 0.7 g of 1-amino-2-naphthol-4-sulfonic acid, dissolve

1.5 g of this mixture in 10 ml of water immediately before use, filter if necessary), add water to volume and mix well, allow to stand at 20°C for 30-50 minutes. The absorbance of the solution containing the substance being examined, measured at 740 nm (Appendix IV A), is not greater than that of the standard solution.

Related substances Carry out the method as described under Assay. Dissolve a quantity of the substance being examined in mobile phase to produce a solution of about 1 mg per ml as the test solution (1). Dissolve a quantity of dexamethasone CRS, accurately weighed, in methanol to produce a solution of about 1 mg per ml as the reference solution (2). Measure accurately 1 ml each of solution (1) and solution (2) into a 100 ml volumetric flask and dilute with mobile phase to the volume, shake well as the solution (3). Inject 20 μ l of solution (3) into the column. Adjust the attenuation so that the principal peak height of dexamethasone sodium phosphate in the chromatogram is 15%-20% of full scale of the chart. Then inject separately 20 μ l of solution (1) and (2) into the column and record the chromatogram for twice of the retention time of the principal peak. If there is any peak which retention time is identical with that of dexamethasone in the chromatogram of solution (1), its area is not greater than 0.5% of the principal peak area of solution (2); The area of any peak other than the principal peak is not greater than 1/2 of that of the peak of dexamethasone sodium phosphate in solution (3), the sum of the area of all peaks other than the principal peak is not greater than twice of area of the peak of dexamethasone sodium phosphate in solution (3).

Methanol and acetone Dissolve about 0.16 g, accurately weighed, in water in a 10 ml volumetric flask, add 2 ml of 0.1% (ml/ml) *n*-propanol as internal standard, dilute with water to volume and mix well as the test solution (1). Measure about 7.9 mg of methanol and 79 mg of acetone, accurately weighed, into a 10 ml volumetric flask, dilute with water to volume as solution (2). Measure accurately 1 ml of solution (2) into a 10 ml volumetric flask, add 2 ml of internal standard, dilute with water to volume and shake well as the reference solution (3). Carry out the method for residual solvent (Appendix VIII P), using a column packed with macromolecule multihole glomerule. The number of theoretical plates of the column, calculated with the peak of *n*-propanol, is not less than 700. The temperature of the column is 150°C. The result complies with the related requirements.

Loss on drying When dried under reduced pressure to constant weight at 100°C, loses not more than 16.0% of its weight (Appendix VIII L).

Assay Carry out the method for high performance liquid chromatography (Appendix V D), using a column packed with octadecylsilane bonded silica gel and a mixture of triethylamine solution (Dilute 7.5 ml of triethylamine with water to 1000 ml, adjust pH to 3.0 ± 0.05 with phosphoric acid)-methanol-acetonitrile (55:40:5) as the mobile phase. Detection wavelength is 242 nm and the number of theoretical plates of the column, calculated with the peak of dexamethasone sodium phosphate, is generally 7000. The resolution factor between the peaks of dexamethasone sodium phosphate and dexamethasone is not less than 4.4.

Procedure Dissolve a quantity of the substance being examined, accurately weighed, with water in a 50 ml volumetric flask, and dilute with water to volume, shake well. Measure accurately proper quantities, dilute with mobile phase to produce a solution of about 40 μ g per ml. inject 20 μ l into the column and record the chromatogram. Repeat the operation using dexamethasone sodium phosphate CRS instead of the substance being examined, calculate the

content of $C_{22}H_{28}FN_2O_8P$ with respect to the peak area obtained in the chromatogram by the external standard method.

Category Corticosteroid.

Storage Preserve in tightly closed containers, protected from light and stored in a dry place.

Preparation (1) Dexamethasone Sodium Phosphate Eye Drops
(2) Dexamethasone Sodium Phosphate Injection

Dexamethasone Sodium Phosphate Eye Drops

Dexamethasone Sodium Phosphate Eye Drops contain not less than 90.0% and not more than 110.0% of the labelled amount of Dexamethasone Sodium Phosphate ($C_{22}H_{28}FN_2O_8P$).

Description A colourless, clear liquid.

Identification The retention time of the principal peak in the chromatogram obtained with the test preparation is identical with that of the principal peak in the chromatogram of the reference solution.

pH value 7.0-8.5 (Appendix VI H).

Other requirements Comply with the general requirements for Eye preparations (Appendix I G).

Assay Carry out the Assay as described under Dexamethasone Sodium Phosphate. Measure accurately a quantity of the substance being examined, dilute with mobile phase to produce a solution of about 50 μ g per ml as the test solution (1). Dissolve about 12.5 mg of dexamethasone sodium phosphate CRS, accurately weighed, with water in a 50 ml volumetric flask and dilute with water to volume, shake well, then measure proper quantities and dilute with mobile phase to produce a solution of 50 μ g per ml as the reference solution (2). Inject separately 20 μ l of solution (1) and solution (2) into the column and record the chromatogram. Calculate the content of $C_{22}H_{28}FN_2O_8P$ with respect to the peak area obtained in the chromatogram by the external standard method.

Category As described under Dexamethasone Sodium Phosphate.

Strength 5 ml:1.25 mg

Storage Preserve in well closed containers, protected from light.

Dexamethasone Sodium Phosphate Injection

Dexamethasone Sodium Phosphate Injection is a sterile solution of dexamethasone sodium phosphate in Water for Injection. It contains not less than 90.0% and not more than 110.0% of the labelled amount of dexamethasone sodium phosphate ($C_{22}H_{28}FN_2O_8P$).

It may also contain a stabilizer and a solubilizer.

Description A colourless and clear liquid.

Identification The retention time of the principal peak in the chromatogram obtained with the test preparation is

identical with that of the principal peak in the chromatogram of the reference solution.

pH value 7.0-8.5 (Appendix VI H).

Other requirements Complies with the general requirements for injections (Appendix I B).

Assay Carry out the Assay as described under Dexamethasone Sodium Phosphate. Measure accurately a quantity of the substance being examined, dilute with mobile phase to produce a solution of about 50 μ g per ml as the test solution (1). Dissolve about 12.5 mg of dexamethasone sodium phosphate CRS, accurately weighed, with water in a 50 ml volumetric flask and dilute with water to volume, shake well, then measure proper quantities and dilute with mobile phase to produce a solution of 50 μ g per ml as the reference solution (2). Inject separately 20 μ l of solution (1) and solution (2) into the column and record the chromatogram. Calculate the content of $C_{22}H_{28}FN_2O_8P$ with respect to the peak area obtained in the chromatogram by the external standard method.

Category As described under Dexamethasone Sodium Phosphate.

Strength (1) 1 ml:1 mg (2) 1 ml:2 mg
(3) 1 ml:5 mg

Storage Preserve in well closed containers, protected from light.

Dexamethasone Tablets

Dexamethasone Tablets contain not less than 90.0% and not more than 110.0% of the labelled amount of dexamethasone ($C_{22}H_{29}FO_5$).

Description White tablets.

Identification (1) The retention time of principal peak of the substance being examined in the chromatogram obtained in the Assay is identical with that of the principal peak in the chromatogram of the reference solution.

(2) To 10 powdered tablets add 25 ml of methanol, shake for 30 minutes to dissolve dexamethasone and filter. Evaporate the filtrate on water bath to dryness. The residue complies with the test for Identification (3) described under Dexamethasone.

Content uniformity Comply with the requirements for content uniformity (Appendix X E). Triturate 1 tablet with 2 drops of methanol in a mortar and transfer to a 25 ml volumetric flask with mobile phase in several portions, shake thoroughly to dissolve dexamethasone and dilute with mobile phase to volume, then filter and take the successive filtrate as the test solution. Carry out the method as described under Assay. Calculate the content of $C_{22}H_{29}FO_5$.

Other requirements Comply with the general requirements for tablets (Appendix I A).

Assay Weigh accurately and powder 20 tablets. Wet an accurately weighed quantity of the powder equivalent to 1.5 mg of dexamethasone with 4 drops of methanol in a 50 ml volumetric flask, add mobile phase and shake thoroughly to dissolve dexamethasone and dilute with mobile phase to volume, mix well and filter, take the successive filtrate as test solution. Dissolve 15 mg of dexamethasone CRS, weighed accurately, with 2 ml of methanol in a 50 ml volumetric flask and dilute with mobile phase to volume, mix well, then dilute with mobile phase to produce a solution of 30 μ g of dexamethasone CRS per ml as reference solution.

Carry out the Assay as described under Dexamethasone.

Category As described under Dexamethasone.

Strength 0.75 mg

Storage Preserve in tightly closed containers and protected from light.

Dextran 20

Dextran 20 is a high polymer of glucose produced by the fermentation of sucrose by a certain strain of *Leuconostoc mesenteroides* (L.-M-1226). It has an average molecular mass (M_w) of about 16000 to 24000.

Description A white powder; odourless; tasteless. Very soluble in hot water, insoluble in ethanol.

Specific optical rotation $+190^\circ$ to $+200^\circ$, in an aqueous solution of 10 mg per ml, measured at 25°C (Appendix VI E).

Identification Dissolve 0.2 g in 5 ml of water, add 2 ml of sodium hydroxide TS and a few drops of copper sulfate TS, a pale blue precipitation is produced which changes to brown on heating.

Chloride Dissolve 0.1 g in 50 ml of water by heating and cool. Carry out the limit test for chlorides (Appendix VIII A), using 10 ml. Any opalescence produced is not more pronounced than that of a reference solution using 5.0 ml of sodium chloride standard solution (0.25%).

Nitrogen Transfer 0.2 g to a 50 ml Kjeldahl flask, add 1 ml of sulfuric acid and heat until the substance being examined becomes a black oily mass, cool, add 2 ml of 30% hydrogen peroxide solution and heat until the solution is clear (if the solution is not clear, add 0.5 ml to 1.0 ml of 30% hydrogen peroxide solution and continue heating). Cool to below 20°C , add 10 ml of water and adjust to alkaline by adding dropwise 5% sodium hydroxide solution. Transfer the solution to 50 ml Nessler cylinder and wash the flask with water, add the washings to the Nessler cylinder and then add water to volume. Add slowly 2 ml of alkaline potassium mercuric-iodide TS with shaking and maintain the temperature below 20°C . Any colour produced is not more intense than that of a reference solution using 1.4 ml of ammonium sulfate standard solution (dissolve 0.4715 g of ammonium sulfate, previously dried at 105°C to constant weight and accurately weighed, in water and dilute to volume in a 100 ml volumetric flask, mix well. Dilute 1 ml, accurately measured, to 100 ml with water immediately before use. Each ml is equivalent to 10 μg of N) in place of the substance being examined (0.007%).

Loss on drying When dried at 105°C for 6 hours, loses not more than 5.0% of its weight (Appendix VIII L).

Residue on ignition Not more than 0.5% (Appendix VIII N); using 1.5 g.

Heavy metals Carry out the limit test for heavy metals (Appendix VIII H, method 2), using the residue obtained in the Test for Residue on ignition: not more than 0.0008%.

Molecular mass and molecular mass distribution Dissolve a quantity of substance being examined in the mobile phase to produce a solution of 10 mg per ml. Shake then stand over night at room temperature, as the test solution. Repeat the operation using series of dextran CRS with known molecular mass, as the reference solution. Carry out the method for

size exclusion chromatography (Appendix H), using specific gel column for polysaccharides, and 0.71% sodium sulfate solution containing 0.2% sodium azide as the mobile phase and a differential refractometer as detector. The column temperature is at 35°C and flow rate is 0.5 ml per minute. Dissolve separately a quantity of glucose and dextran 2000 in the mobile phase to produce a solution of 10 mg per ml. Inject 20 μl into the column, record the retention time t_T and t_0 . The retention time of the test solution and the reference solution (t_R) are all between t_T and t_0 . The number of the theoretical plates of the column is not less than 5000, calculated with reference to the peak of glucose. Inject 20 μl of the reference solutions and the test solution separately into the column, record the chromatogram. The data is processed by special software for GPC. The average molecular mass of the 10% high fraction is not more than 70000, The average molecular mass of the 10% low fraction is not less than 3500.

Category Plasma volume extender.

Storage Preserve in tightly closed containers, stored in a dry place.

Preparation (1) Dextran 20 Glucose Injection
(2) Dextran 20 Sodium Chloride Injection

Dextran 20 Glucose Injection

Dextran 20 Glucose Injection is a sterile solution of dextran 20 in Glucose Injection. It contains not less than 95.0% and not more than 105.0% of the labelled amount of dextran 20 and glucose ($\text{C}_6\text{H}_{12}\text{O}_6 \cdot \text{H}_2\text{O}$) respectively.

Description A clear, colourless, slightly viscous liquid, sometimes with a slight opalescence; taste, sweet.

Identification (1) To 1 ml add 2 ml of sodium hydroxide TS and a few drops of copper sulfate TS, a pale blue precipitate is produced, which turns to brown on heating.
(2) Add dropwise 1 ml to a warm alkaline copper tartrate TS, a red precipitate of cuprous oxide is produced.

pH value 3.5-6.5 (Appendix VI H).

Heavy metals Transfer 20 ml, accurately measured, to a crucible and evaporate to dryness, carry out the limit test for heavy metals (Appendix VIII H, method 2): not more than 0.00015%.

Undue toxicity Complies with the test for undue toxicity (Appendix XI C), by intravenous injection.

Bacterial endotoxin Carry out the test for bacterial endotoxin (Appendix V D): less than 0.5 EU per ml.

Allergen Complies with the test of allergen (Appendix XI K).

Molecular mass and molecular mass distribution Carry out the method for Molecular mass and molecular mass distribution described under Dextran 20. It has a weight average molecular mass (M_w) of about 16000 to 24000, the weight average molecular mass of the 10% high fraction is not more than 70000, and the weight average molecular mass of the 10% low fraction is not less than 3500.

Other requirements Complies with the general requirements for injections (Appendix I B).

Assay *Dextran 20* Transfer 10 ml, accurately measured, to a 25 ml (for 6% injection) or 50 ml (for 10% injection) volumetric flask, add water to volume and mix well. Carry

out the determination of optical rotation (Appendix VI E), calculate the content of dextran according to the following formula:

$$C = 0.5128 \times (a - 0.4975C_1)$$

Where C is the weight of dextran 20 in 100 ml of injection (g);

a is optical rotation \times dilution factor 2.5 for 6% injection or 5.0 for 10% injection;

C_1 is content of glucose in 100 ml of injection determined under Assay (g).

Glucose Transfer 2 ml, accurately measured, to a stoppered conical flask, add 25 ml, accurately measured, of iodine solution (0.1 mol/L) VS and add dropwise 50 ml of sodium hydroxide solution (0.1 mol/L) VS with constant shaking. Allow to stand in a dark place for 30 minutes, add 5 ml of dilute sulfuric acid TS, titrate with sodium thiosulfate (0.1 mol/L) VS, add 2 ml of starch IS towards the end of titration, continue the titration until the blue colour disappears. Perform a blank determination, using 0.12 g (6% injection) or 0.20 g (10% injection) of dextran 20, and make any necessary correction. Each ml of iodine (0.1 mol/L) VS is equivalent to 9.909 mg of $C_6H_{12}O_6 \cdot H_2O$.

Category As described under Dextran 20.

Strength (1) 10% Dextran 20 Glucose Injection 100 ml: 10 g of dextran 20 + 5 g of glucose; 250 ml: 25 g of dextran 20 + 12.5 g of glucose; 500 ml: 50 g of dextran 20 + 25 g of glucose
(2) 6% Dextran 20 Glucose Injection 100 ml: 6 g of dextran 20 + 5 g of glucose; 250 ml: 15 g of dextran 20 + 12.5 g of glucose; 500 ml: 30 g of dextran 20 + 25 g of glucose

Storage Preserve in a place below 25°C.

Dextran 20 Sodium Chloride Injection

Dextran 20 Sodium Chloride Injection is a sterile solution of dextran 20 in Sodium Chloride Injection. It contains not less than 95.0% and not more than 105.0% of the labelled amount of dextran 20 and sodium chloride (NaCl) respectively.

Description A clear, colourless, slightly viscous liquid, sometimes with a slight opalescence; taste, salty.

Identification (1) Complies with test (1) for Identification described under Dextran 20 Glucose Injection.
(2) Yields the reactions characteristic of sodium salts and chlorides (Appendix IV).

pH value 4.0-7.0 (Appendix VI H).

Molecular mass and molecular mass distribution Carry out the method for Molecular mass and molecular mass distribution described under Dextran 20. It has a weight average molecular mass (M_w) of about 16000 to 24000, the weight average molecular mass of the 10% high fraction is not more than 70000, and the weight average molecular mass of the 10% low fraction is not less than 3500.

Heavy metals, Undue toxicity, Bacterial endotoxin, Allergen Complies with the corresponding requirements described under Dextran 20 Glucose Injection.

Other requirements Complies with the general requirements for injection (Appendix I B).

Assay *Dextran 20* Transfer 10 ml, accurately measured, to a 25 ml (for 6% injection) or 50 ml (for 10% injection)

volumetric flask, add water to volume and mix well. Carry out the determination of optical rotation (Appendix VI E), calculate the content of dextran according to the following formula:

$$C = 0.5128a$$

Where C is the weight of dextran 20 (g) in 100 ml of injection;

a is optical rotation \times dilution factor 2.5 for 6% injection or 5.0% for 10% injection.

Sodium chloride Measure accurately 10 ml to a conical flask, add a few drops of potassium chromate IS, titrate with silver nitrate (0.1 mol/L) VS. Each ml of silver nitrate (0.1 mol/L) VS is equivalent to 5.844 mg of sodium chloride.

Category As described under Dextran 20.

Strength (1) 10% Dextran 20 Sodium Chloride Injection 100 ml: 10 g dextran 20 + 0.9 g sodium chloride; 250 ml: 25 g dextran 20 + 2.25 g sodium chloride; 500 ml: 50 g dextran 20 + 4.5 g sodium chloride
(2) 6% Dextran 20 Sodium Chloride Injection 100 ml: 6 g dextran 20 + 0.9 g sodium chloride; 250 ml: 15 g dextran 20 + 2.25 g sodium chloride; 500 ml: 30 g dextran 20 + 4.5 g sodium chloride

Storage Preserve in a place below 25°C.

Dextran 40

Dextran 40 is a high polymer of glucose produced by the fermentation of sucrose by a certain strain of *Leuconostoc mesenteroides* (L.-M-1226). It has an average molecular mass (M_w) of about 32000 to 42000.

Description A white powder; odourless; tasteless. Very soluble in hot water, insoluble in ethanol.

Specific optical rotation Complies with the test described under Dextran 20.

Identification Complies with the test for Identification described under Dextran 20.

Molecular mass and molecular mass distribution Carry out the method described under Dextran 20. The average molecular mass of the 10% high fraction is not more than 120000. The average molecular mass of the 10% low fraction is not less than 5000.

Chloride, Nitrogen, Loss on drying, Residue on ignition, Heavy metals Complies with the corresponding requirements described under Dextran 20.

Category Plasma volume extender.

Storage Preserve in tightly closed containers, stored in a dry place.

Preparation (1) Dextran 40 Glucose Injection
(2) Dextran 40 Sodium Chloride Injection

Dextran 40 Glucose Injection

Dextran 40 Glucose Injection is a sterile solution of dextran 40 in Glucose Injection. It contains not less than 95.0% and not more than 105.0% of the

labelled amount of dextran 40 and glucose ($C_6H_{12}O_6 \cdot H_2O$).

Description A clear, colourless and slightly viscous liquid, sometimes with a slight opalescence; taste, sweet.

Identification Complies with the tests for Identification described under Dextran 20 Glucose Injection.

Molecular mass and molecular mass distribution Carry out the method described under Dextran 20 Glucose Injection. The average molecular mass is about 32000 to 42000. The average molecular mass of the 10% high fraction is not more than 120000. The average molecular mass of the 10% low fraction is not less than 5000.

pH value, Heavy metals, Undue toxicity, Bacterial endotoxin, Allergen Complies with the corresponding requirements described under Dextran 20 Glucose Injection.

Other requirements Complies with the general requirements for injections (Appendix I B).

Assay Carry out the Assay described under Dextran 20 Glucose Injection, using dextran 40 instead of dextran 20 in the blank determination.

Category As described under Dextran 40.

Strength (1) 10% dextran 40 Glucose Injection 100 ml: 10 g of dextran 40 + 5 g of glucose; 250 ml: 25 g of dextran 40 + 12.5 g of glucose; 500 ml: 50 g of dextran 40 + 25 g of glucose
(2) 6% Dextran 40 Glucose Injection 100 ml: 6 g of dextran 40 + 5 g of glucose; 250 ml: 15 g of dextran 40 + 12.5 g of glucose; 500 ml: 30 g of dextran 40 + 25 g of glucose

Storage Stored in a place below 25°C.

Dextran 40 Sodium Chloride Injection

Dextran 40 Sodium Chloride Injection is a sterile solution of dextran 40 in Sodium Chloride Injection. It contains not less than 95.0% and not more than 105.0% of the labelled amount of dextran 40 and sodium chloride (NaCl).

Description A clear, colourless and slightly viscous liquid, sometimes with a slight opalescence; taste, salty.

Identification Complies with the tests for Identification described under Dextran 20 Sodium chloride Injection.

pH value 4.0-7.0 (Appendix VI H).

Molecular mass and molecular mass distribution Carry out the method described under Dextran 20 Glucose Injection. The average molecular mass is about 32000 to 42000. The average molecular mass of the 10% high fraction is not more than 120000. The average molecular mass of the 10% low fraction is not less than 5000.

Heavy metals, Undue toxicity, Bacterial endotoxin, Allergen Complies with the corresponding requirements described under Dextran 20 Glucose Injection.

Other requirements Complies with the general requirements for injections (Appendix I B).

Assay Carry out the Assay described under Dextran 20 Sodium Chloride Injection.

Category As described under Dextran 40.

Strength (1) 10% dextran 40 Glucose Injection 100 ml: 10

g of dextran 40 + 0.9 g of sodium chloride; 250 ml: 25 g of dextran 40 + 2.25 g of sodium chloride; 500 ml: 50 g of dextran 40 + 4.5 g of sodium chloride

(2) 6% Dextran 40 Sodium Chloride Injection 100 ml: 6 g of dextran 40 + 0.9 g of sodium chloride; 250 ml: 15 g of dextran 40 + 2.25 g of sodium chloride; 500 ml: 30 g of dextran 40 + 4.5 g of sodium chloride

Storage Stored in a place below 25°C.

Dextran 70

Dextran 70 is a high polymer of glucose produced by the fermentation of sucrose by a certain strain of *Leuconostoc mesenteroides* (L.-M-1226). It has an average molecular mass (M_w) of about 64000 to 76000.

Description A white powder; odourless; tasteless. Very soluble in hot water, insoluble in ethanol.

Specific optical rotation Complies with the test described under Dextran 20.

Identification Complies with the test for Identification described under Dextran 20.

Molecular mass and molecular mass distribution Carry out the method described under Dextran 20. The average molecular mass of the 10% high fraction is not more than 185000. The average molecular mass of the 10% low fraction is not less than 15000.

Chloride, Nitrogen, Loss on drying, Residue on ignition, Heavy metals Complies with the corresponding requirements described under Dextran 20.

Category Plasma volume extender.

Storage Preserve in tightly closed containers, stored in a dry place.

Preparation (1) Dextran 70 Glucose Injection
(2) Dextran 70 Sodium Chloride Injection

Dextran 70 Glucose Injection

Dextran 70 Glucose Injection is a sterile solution of dextran 70 in Glucose Injection. It contains not less than 95.0% and not more than 105.0% of the labelled amount of dextran 70 and glucose ($C_6H_{12}O_6 \cdot H_2O$).

Description A clear, colourless and slightly viscous liquid, sometimes with a slight opalescence; taste, sweet.

Identification Complies with the tests for Identification described under Dextran 20 Glucose Injection.

Molecular mass and molecular mass distribution Carry out the method described under Dextran 20 Glucose Injection. The average molecular mass is about 64000 to 76000. The average molecular mass of the 10% high fraction is not more than 185000. The average molecular mass of the 10% low fraction is not less than 15000.

pH value, Heavy metals, Undue toxicity, Bacterial endotoxin, Allergen Complies with the corresponding requirements described under Dextran 20 Glucose Injection.

Other requirements Complies with the general requirements for injections (Appendix I B).

Assay Carry out the Assay described under Dextran 20 Glucose Injection, using dextran 70 instead of dextran 20 in the blank determination.

Category As described under Dextran 70.

Strength 500 ml: 30 g of dextran 70 and 25 g of glucose

Storage Stored in a place below 25°C.

Dextran 70 Sodium Chloride Injection

Dextran 70 Sodium Chloride Injection is a sterile solution of dextran 70 in Sodium Chloride Injection. It contains not less than 95.0% and not more than 105.0% of the labelled amount of dextran 70 and sodium chloride (NaCl).

Description A clear, colourless and slightly viscous liquid, sometimes with a slight opalescence; taste, salty.

Identification Complies with the tests for Identification described under Dextran 20 Sodium Chloride Injection.

pH value 4.0-7.0 (Appendix VI H).

Molecular mass and molecular mass distribution Carry out the method described under Dextran 20 Glucose Injection. The average molecular mass is about 64000 to 76000. The average molecular mass of the 10% high fraction is not more than 185000. The average molecular mass of the 10% low fraction is not less than 15000.

Heavy metals, Undue toxicity, Bacterial endotoxin, Allergen Complies with the corresponding requirements described under Dextran 20 Glucose Injection.

Other requirements Complies with the general requirements for injections (Appendix I B).

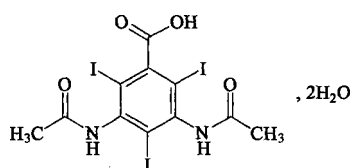
Assay Carry out the Assay described under Dextran 20 Sodium Chloride Injection.

Category As described under Dextran 70.

Strength 500 ml: 30 g of dextran 70 + 4.5 g of sodium chloride

Storage Stored in a place below 25°C.

Diatrizoic Acid



$C_{11}H_9I_3N_2O_4 \cdot 2H_2O$ 649.95 [500978-11-5]

Diatrizoic Acid is 3,5-bis (acetyl amino)-2,4,6-triiodo-benzoic acid, dihydrate. It contains not less than 98.5% of $C_{11}H_9I_3N_2O_4$, calculated on the dried basis.

Description A white powder; odourless; taste, slightly sour. Very slightly soluble in water; soluble in ammonia solution or solution of alkali hydroxides.

Identification (1) Heat about 10 mg in a crucible, violet iodine vapour is evolved.

(2) Carry out the method for thin-layer chromatography (Appendix V B), using silica gel HF_{254} as the coating substance and a mixture of *n*-butanol-glacial acetic acid-water (4:1:5) as the mobile phase. Apply separately to the plate 10 μ l each of (1) a 1 mg per ml solution of the substance being examined in methanol containing 0.08% of sodium hydroxide; (2) a 1 mg per ml solution of diatrizoic acid CRS in the same solvent. After developing and removal of the plate, examine it under an ultraviolet light (254 nm). The principal spots obtained with the two solutions are identical in position.

(3) The infrared absorption spectrum (Appendix IV C) is concordant with the reference spectrum of diatrizoic acid (Appendix XVI).

Colour of alkaline solution Dissolve 4.8 g in sodium hydroxide TS to produce 10 ml. The solution is not more intensely coloured than a reference solution prepared by mixing 5 ml of reference solution Y_3 or OR_2 with 5 ml of water.

Acidity Shake 1.0 g with 20 ml of water for a few minutes, filter, the filtrate has a pH value of 2.5-3.5 (Appendix VI H).

Free iodine To 2.0 ml of the solution obtained in the test for Colour of alkaline solution, add water to produce 10 ml and add dilute acetic acid until the solution is acid to litmus paper. Add 0.5 g of potassium iodide, shake to dissolve it, add 1 ml of starch IS and mix well. Any colour produced is not more intense than, or different from, that of a reference obtained by repeating the operation using 1 ml of water instead of 1 ml of starch IS.

Halides Dissolve 2.0 g in 4 ml of sodium hydroxide TS, add 30 ml of water, then add dropwise 3 ml of dilute nitric acid, stir for a few minutes to precipitate diatrizoic acid and filter. Wash the residue with a small quantity of water, combine the washings with the filtrate and add water to produce 50 ml, mix well. Filter again, if necessary. Carry out the limit test for chlorides (Appendix VIII A) using 20 ml of the filtrate. Any opalescence produced is not more intense than that of a reference using 4.0 ml of sodium chloride standard solution (0.005%).

Iodide To 20 ml of the filtrate obtained in the test for Halides, add 1 ml of chloroform, 3 ml of dilute nitric acid and 1 ml of strong hydrogen peroxide solution, shake and allow to stand. The chloroform layer is not more intensely coloured than that of a reference obtained by repeating the operation using 20 ml of dilute potassium iodide solution (to 2.0 ml of 0.0013% potassium iodide solution, add water to produce 20 ml) instead of the filtrate (0.0025%).

Assay Dissolve 1.0 g in 5 ml of dilute hydrochloric acid and sodium hydroxide TS, add water to produce 100 ml, mix well. To 10 ml of the solution add 5 ml of sodium nitrite solution (0.1 mol/L) and 10 ml of hydrochloric acid solution (9 → 100), mix well and allow to stand for 10 minutes, add 5 ml of 2.5% ammonium sulfamate solution, mix well and allow to stand for 5 minutes. Add 2 ml of alkaline β -naphthol TS, 15 ml of sodium hydroxide TS and sufficient water to produce 50 ml, mix well. Measure the absorbance at 485 nm (Appendix IV A); not greater than 0.25.

Loss on drying When dried at 130°C to constant weight, loses not more than 6.0% of its weight (Appendix VIII L).

Residue on ignition Not more than 0.1% (Appendix VIII N), using 1.0 g.

Iron To the residue obtained in the test for Residue on

ignition add 1 ml of hydrochloric acid, evaporate on a water bath to dryness. To the residue add 1 ml of dilute hydrochloric acid and a quantity of water, heat on a water bath and filter. Wash the crucible with a small quantity of water, combine the washings with the filtrate and add water to produce 25 ml. Carry out the limit test for iron (Appendix VIII G), any colour produced is not more intense than that of a reference using 1.0 ml of iron standard solution (0.001%).

Heavy metals Carry out the limit test for heavy metals (Appendix VIII H, method 2), using 1.0 g: not more than 0.001%.

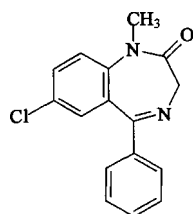
Assay Weigh accurately about 0.4 g, add 30 ml of sodium hydroxide TS and 1.0 g of powdered zinc, heat under reflux for 30 minutes, allow to cool, wash tube of the condenser with a small quantity of water and filter. Wash the flask and the filter with three portions of 15 ml each of water. Combine the washings with the filtrate, add 5 ml of glacial acetic acid and 5 drops of eosin sodium IS, titrate with silver nitrate (0.1 mol/L) VS. Each ml of silver nitrate (0.1 mol/L) VS is equivalent to 20.46 mg of $C_{16}H_{13}ClN_2O$.

Category Diagnostic aid.

Storage Preserve in tightly closed containers, protected from light.

Preparation (1) Meglumine Diatrizoate Injection
(2) Sodium Diatrizoate Injection

Diazepam



$C_{16}H_{13}ClN_2O$ 284.74

[439-14-5]

Diazepam is 7-chloro-1,3-dihydro-1-methyl-5-phenyl-2H-1,4-benzodiazepin-2-one. It contains not less than 98.5% of $C_{16}H_{13}ClN_2O$, calculated on the dried basis.

Description A white or almost white crystalline powder; odourless; taste, slightly bitter. Freely soluble in acetone or chloroform; soluble in ethanol; practically insoluble in water.

Melting range 130-134°C (Appendix VI C).

Specific absorbance Measure the absorbance of a solution of 10 µg per ml in 5% sulfuric acid in methanol at 284 nm (Appendix IV A), the value of A (1%, 1cm) is 440-468.

Identification (1) Dissolve about 10 mg in 3 ml of sulfuric acid, the solution exhibits yellowish-green fluorescence when examined under an ultraviolet light at 365 nm.

(2) The light absorption of a solution of 5 µg per ml in 0.5% methanolic sulfuric acid solution exhibits maxima at 242 nm, 284 nm and 366 nm; the absorbance at 242 nm is about 0.51 and that at 284 nm is about 0.23 (Appendix IV A).

(3) The infrared absorption spectrum (Appendix IV C) is concordant with the reference spectrum of diazepam (Appendix XVI).

(4) Carry out the method for oxygen flask combustion

(Appendix VII C) with 20 mg, using 5 ml of 5% sodium hydroxide solution as the absorbing liquid. When the combustion is completed, acidify the solution with dilute nitric acid and boil gently for two minutes. The solution yields the reactions characteristic of chlorides (Appendix III).

Clarity and colour of ethanol solution A solution of 0.1 g in 20 ml of ethanol is clear and colourless. Any colour produced is not more intense than reference Solution Y₁ (Appendix IX A, method 1).

Chloride Shake 1.0 g with 50 ml of water for 10 minutes and filter. Carry out the limit test for chlorides (Appendix VIII A), using 25 ml of the filtrate. Any opalescence produced is not more intense than that of a reference using 7.0 ml of sodium chloride standard solution (0.014%).

Related substances Carry out the method for high performance liquid chromatography (Appendix V D), using a column packed with octadecylsilane bonded silica gel and a mixture of methanol-water (85:15) as the mobile phase. Detection wavelength is at 254 nm, and the number of theoretical plates of the column is not less than 1500, calculated with reference to the peak of diazepam. Dissolve a quantity of diazepam in methanol to produce the test solution, 0.45 mg per ml. Measure accurately 1 ml of the test solution to 100 ml volumetric flask and dilute with methanol to the volume, mix well to produce the reference solution. Inject accurately 20 µl of the reference solution into the column, adjust the attenuation so that the principal peak height in the chromatogram is 20% -25% of the full scale of the chart. Inject accurately 20 µl each of the test and reference solution into the column separately. Record the chromatogram for twice the retention time of the principal peak. The sum of the areas of all peaks other than the p p p g solution is not greater than 0.3 of the principal peak area of the reference solution (3/10).

Loss on drying When dried at 105°C to constant weight, loses not more than 0.5% of its weight (Appendix VIII L).

Residue on ignition Not more than 0.1% (Appendix VIII N).

Assay Dissolve about 0.2 g, accurately weighed, in a mixture of 10 ml of glacial acetic acid and 10 ml of acetic anhydride, add 1 drop of crystal violet IS. Titrate with perchloric acid (0.1 mol/L) VS until a green colour is produced. Each ml of perchloric acid (0.1 mol/L) VS is equivalent to 28.47 of $C_{16}H_{13}ClN_2O$.

Category Anxiolytic and anticonvulsant agent.

Storage Preserve in tightly closed containers.

Preparation (1) Diazepam Injection
(2) Diazepam Tablets

Diazepam Injection

Diazepam Injection is a sterile solution of diazepam in Water for Injection. It contains not less than 90.0% and not more than 110.0% of the labelled amount of diazepam ($C_{16}H_{13}ClN_2O$).

Description A clear, almost colourless to yellowish-green liquid.

Identification (1) To 2 ml add dropwise dilute potassium iodobismuthate TS, an orangish-red precipitate is produced. (2) The retention time of principal peak in the chromatogram obtained with substance being examined in the Assay is identical with that of diazepam CRS, treated similarly.

pH value 6.0-7.0 (Appendix VI H).

Colour of solution Not more intense than reference solution YG₆ (Appendix IX A, method 1).

Related substances Dissolve a quantity in methanol to produce two solutions containing 1 mg per ml (solution 1) and 5 µg per ml (solution 2) respectively. Carry out the method described under Assay. Inject 10 µl of solution (2) into the column, adjust the attenuation so that the principal peak height is about 10% of the full scale of the chart. Inject accurately 10 µl each of solution (1) and (2) into the column separately, record the chromatogram for four times of the retention time of the principal peak. The sum of the peak areas corresponding impurities is not greater than the principal peak area of solution (2).

Other requirements Complies with the general requirements for injections (Appendix I B).

Assay Carry out the method for high performance liquid chromatography (Appendix V D), using a column packed with octadecylsilane bonded silica gel and a mixture of methanol-water (70 : 30) as the mobile phase. Detection wavelength is 254 nm, and the number of theoretical plates of the column is not less than 1500, calculated with reference to the peak of diazepam. The resolution factor between the peaks of diazepam and internal standard complies with related requirements.

Internal standard solution Dissolve 50 mg of naphthalene in methanol in a 25 ml volumetric flask and dilute to volume, mix well.

Procedure Dissolve a quantity equivalent to 10 mg of diazepam, accurately weighed, in a 50 ml volumetric flask. Add 10 ml of internal standard solution and dilute with methanol to the volume, mix well. Inject accurately 10 µl of the resulting solution into the column. Repeat the operation, using 10 mg of diazepam CRS instead of the substance being examined, accurately weighed, calculate the content of C₁₆H₁₃ClN₂O.

Category As described under Diazepam.

Strength 2 ml : 10 mg

Storage Preserve in well closed containers, protected from light.

Diazepam Tablets

Diazepam Tablets contain not less than 90.0% and not more than 110.0% of the labelled amount of diazepam (C₁₆H₁₃ClN₂O).

Description White tablets.

Identification (1) Shake a quantity of the powdered tablets equivalent to about 10 mg of diazepam with 10 ml of acetone to dissolve diazepam, filter, evaporate the filtrate to dryness. Dissolve the residue in 3 ml of sulfuric acid with shaking, the solution exhibits yellowish-green fluorescence when examined under an ultraviolet light at 365 nm.

(2) The light absorption of the solution obtained in Assay exhibits three maxima at 242 nm, 284 nm and 366 nm (Appendix IV A).

Related substances Shake a quantity of the powdered tablets equivalent to 200 mg of diazepam with 5 ml of acetone, filter, use the successive filtrate as solution (1). Dilute solution (1) with acetone to 0.20 mg per ml as solution (2). Carry out the method for thin-layer chromatography (Appendix V B), using silica gel GF₂₅₄ as the coating

substance, and a mixture of ethyl acetate-hexane (1:1) as the mobile phase. Apply to the plate separately 5 µl each of solution (1) and (2). After the developing and removal of the plate, allow it to dry. Examine under an ultraviolet light (254 nm). Any spot other than the principal spot in the chromatogram obtained with solution (1) is not more intense than the principal spot obtained with solution (2).

Content uniformity Comply with the requirements (Appendix X E). Shake 1 tablet in a 100 ml volumetric flask with 5 ml of water, after the tablet is disintegrated, add about 60 ml of 0.5% sulfuric acid in methanol, shake well to dissolve diazepam, dilute with 0.5% sulfuric acid in methanol to volume, mix well. Filter, measure accurately 10 ml of the successive filtrate into a 25 ml volumetric flask, dilute with 0.5% sulfuric acid in methanol to volume and mix well. Measure the absorbance at 284 nm (Appendix IV A). Calculate the content of C₁₆H₁₃ClN₂O, taking 454 as the value of A (1%, 1 cm).

Dissolution Carry out the dissolution test (Appendix X C, method 1), using 800 ml of hydrochloric acid solution (9→1000) as the dissolution medium, adjust the rotational speed of the basket to 100 rpm. Withdraw 10 ml of the solution at exact 20 minutes and filter. Measure the absorbance of the successive filtrate at 242 nm (Appendix IV A). Calculate the dissolution of C₁₆H₁₃ClN₂O from each tablet, taking 1018 as the value of A (1%, 1 cm), not less than 75% of the labelled amount is dissolved.

Other requirements Comply with the general requirements for tablets (Appendix I A).

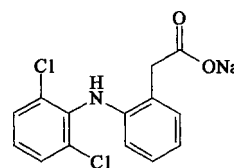
Assay Weigh accurately and powder 20 tablets. Weigh accurately a quantity of the powder equivalent to about 10 mg of diazepam in a 100 ml volumetric flask, add 5 ml of water and mix well. Allow to stand for 15 minutes, add about 60 ml of 0.5% sulfuric acid in methanol, shake thoroughly to dissolve diazepam, add 0.5% sulfuric acid in methanol to volume, mix well. Filter, measure accurately 10 ml of the successive filtrate to 100 ml volumetric flask, dilute with 0.5% sulfuric acid in methanol to volume and mix well. Measure the absorbance of the solution at 284 nm (Appendix IV A), calculate the content of C₁₆H₁₃ClN₂O, taking 454 as the value of A (1%, 1 cm).

Category As described under Diazepam.

Strength (1) 2.5 mg (2) 5 mg

Storage Preserve in tightly closed containers.

Diclofenac Sodium



C₁₄H₁₀Cl₂NNaO₂ 318.13

[15307-79-6]

Diclofenac Sodium is sodium 2-[(2,6-dichlorophenyl) amino] phenyl acetate. It contains not less than 98.5% of C₁₄H₁₀Cl₂NNaO₂, calculated on the dried basis.

Description A white or almost white crystalline powder; irritant to nose and hygroscopic. Freely soluble in ethanol; sparingly soluble in water;

insoluble in chloroform.

Identification (1) The light absorption of a solution of 20 µg per ml in water exhibits a maximum at 276 nm in range of 240-340 nm (Appendix IV A).

(2) The infrared absorption spectrum (Appendix IV C) is concordant with the reference spectrum of diclofenac sodium (Appendix XVI).

(3) Mix about 50 mg with 0.2 g sodium carbonate and ignite until charred, cool. Dissolve the residue in 5 ml of water, boil and filter. The filtrate yields the reaction characteristic of chlorides (Appendix III).

(4) The residue obtained by igniting yields the reaction characteristic of sodium salts (Appendix III).

Acidity or alkalinity Dissolve 0.5 g in 50 ml of water, pH 6.5-7.5 (Appendix VI H).

Clarity and colour of ethanol solution Dissolve 0.5 g in 10 ml of ethanol; any opalescence produced is not more pronounced than that of an equal volume of reference suspension 1 (Appendix IX B); any colour produced is not more intense than that of an equal volume of reference solution Y₃ (Appendix IX A).

Chloride Dissolve 0.5 g in 48 ml of water, add 2 ml of dilute nitric acid dropwise, mix thoroughly and filter. Carry out the limit test for chloride (Appendix VIII A), using 25 ml of the filtrate. Any opalescence produced is not more pronounced than that of a reference solution using 5 ml of sodium chloride standard solution (0.02%).

Related substances Carry out the method for thin-layer chromatography (Appendix V B), using silica gel GF₂₅₄ as the coating substance and a mixture of ethyl acetate-chloroform-glacial acetic acid (25:25:0.2) as the mobile phase. Apply separately to the plate 10 µl each of two solutions of the substance being examined in ethanol containing (1) 10 mg per ml, (2) 0.1 mg per ml. After developing and removal of the plate, dry it in air and examine under ultraviolet light at 254 nm. Any spot in the chromatogram other than the principal spot obtained with solution (1) is not more intense than the principal spot obtained with solution (2).

Loss on drying When dried to constant weight at 105°C, loses not more than 1.0% of its weight (Appendix VIII L).

Heavy metals Dissolve 2.0 g in 45 ml of water by heating gently, add slowly 5 ml of dilute hydrochloric acid with constant shaking and filter. Carry out the limit test for heavy metals (Appendix VIII H), using 25 ml filtrate; not more than 0.001%.

Assay Dissolve about 0.5 g, accurately weighed, in 50 ml of water by gently heating, cool, add 10 drops of a mixture of methyl-red and bromocresol-green IS, titrate with sulfuric acid (0.05 mol/L) VS until the colour of the solution changes to pale yellowish-green. Each ml of sulfuric acid (0.05 mol/L) VS is equivalent to 31.81 mg of C₁₄H₁₀Cl₂NNaO₂.

Category Anti-inflammatory and analgesic non-steroids anti-inflammatory agent.

Storage Preserve in tightly closed containers, protected from light.

Preparation Diclofenac Sodium Enteric-coated Tablets

Diclofenac Sodium and Codeine Phosphate Tablets

Diclofenac Sodium and Codeine Phosphate Tablets contain not less than 90.0% and not more than 110.0% of the labelled amount of diclofenac sodium (C₁₄H₁₀Cl₂NNaO₂) and codeine phosphate (C₁₈H₂₁NO₃ · H₃PO₄ · 1 $\frac{1}{2}$ H₂O) in each tablet.

Formula	Diclofenac sodium	25 g
	Codeine Phosphate (C ₁₈ H ₂₁ NO ₃ · H ₃ PO ₄ · 1 $\frac{1}{2}$ H ₂ O)	15 g
	Excipient	a quantity
	to make	1000 tablets

Description White or almost white tablets.

Identification Weigh a quantity of the powdered tablets equivalent to about 10 mg of diclofenac sodium and 6 mg of codeine phosphate respectively into a 100 ml separator, add 5 ml of 0.1 mol/L sodium hydroxide solution, shake thoroughly, extract with 30 ml of chloroform, wash the chloroform layer with 0.1 mol/L sodium hydroxide solution, transfer the chloroform layer into conical flask and evaporate in vacuum to dryness, the residue is used for identification sample of codeine phosphate; combine the washing and aqueous layer, filter into a 100 ml volumetric flask, dilute with water to volume (equivalent to about 10 mg of diclofenac sodium) and mix well, the aqueous solution is used for identification of diclofenac sodium. (1) The light absorption of the aqueous solution exhibits a maximum at 276 nm (Appendix IV A).

(2) To the residue add 0.5 ml of sulfuric acid containing 2.5 mg of selenic acid, a green colour is produced immediately which turns to blue gradually.

(3) Dissolve a quantity of the powdered tablets equivalent to about 25 mg of diclofenac sodium and 15 mg of codeine phosphate in methanol and dilute to produce a solution containing 2.5 mg of diclofenac sodium and 1.5 mg of codeine phosphate per ml as the test solution. Dissolve a quantity of diclofenac sodium and codeine phosphate CRS in methanol to produce solutions of 2.5 mg of diclofenac sodium per ml and 1.5 mg of codeine phosphate per ml as the reference solutions respectively. Carry out the method for thin-layer chromatography (Appendix V B), using silica gel GF₂₅₄ as the coating substance and a mixture of ethyl acetate-methanol-concentrated ammonia solution (85:10:5) as the mobile phase. Apply separately to the plate 10 µl of each of the above three solutions, after developing and removal of the plate, dry it in air and examine under ultraviolet light at 254 nm. The two principal spots in the chromatogram obtained with the test solution correspond in position to the principal spots obtained with the reference solutions. Then spray with dilute potassium iodobismuthate TS, the colour of the spot of codeine phosphate turns to orange-red.

Content uniformity Comply with the requirements for content uniformity (Appendix X E). To 1 tablet in a 50 ml volumetric flask add 5 ml of water and shake, after the tablet is disintegrated, add 10 ml of ethanol and a quantity of water, sonicate for 15 minutes, dilute with water to volume, shake thoroughly and filter through a membrane filter, use the successive filtrate as the test solution. Carry out the procedure as described under the Assay, beginning at

the words "Inject 10 μ l of the test solution into the column...". Calculate the content of $C_{14}H_{10}Cl_2NNaO_2$ and $C_{18}H_{21}NO_3 \cdot H_3PO_4 \cdot 1\frac{1}{2}H_2O$ respectively.

Dissolution Carry out the dissolution test (Appendix X C, method 2), using 500 ml of water as the dissolution medium, adjust the rotational speed of the paddle to 100 rpm. Withdraw 5 ml of the solution after exactly 45 minutes and filter through a membrane. Use the successive filtrate as the test solution. Dilute 5 ml of the reference solution as described under the Assay, accurately measured, in a 50 ml volumetric flask, with water to volume and mix well as the reference solution. Measure accurately 25 μ l each of the test solution and the reference solution, carry out the method as described under the Assay. Calculate the dissolution of $C_{14}H_{10}Cl_2NNaO_2$ and $C_{18}H_{21}NO_3 \cdot H_3PO_4 \cdot 1\frac{1}{2}H_2O$ from each tablet. Not less than 75% of the labelled amount is dissolved.

Other requirements Comply with the general requirements for tablets (Appendix I A).

Assay Carry out the method for high performance liquid chromatography (Appendix V D), using a column packed with octadecylsilane bonded silica gel and a mixture of 0.04 mol/L sodium heptanesulfonate solution-acetonitrile (1:1.2) as the mobile phase (adjust to pH 6.1 ± 0.2 with acetic acid). Detection wavelength is 280 nm and the number of the theoretical plates of the column is not less than 800, calculated with reference to the peak of codeine phosphate. The resolution factor between the peaks of codeine phosphate and diclofenac sodium is more than 2.0.

procedure Weigh accurately and powder 20 tablets. Weigh accurately a quantity of the powdered tablets equivalent to about 25 mg of diclofenac sodium and 15 mg of codeine phosphate to 50 ml volumetric flask, add about 40 ml of 20% (V/V) ethanol solution, sonicate for 15 minutes, dilute to volume with 20% (V/V) ethanol solution, shake thoroughly and filter through a membrane filter, use the successive filtrate as the test solution. Inject 10 μ l of the test solution into the column, record the peak areas correspondingly obtained in the chromatogram. Weigh accurately about 25 mg of diclofenac sodium CRS and 15 mg of codeine phosphate CRS to 50 ml volumetric flask, dissolve with 20% (V/V) ethanol solution and dilute to volume, mix well as the reference solution. Repeat the operation, using the reference solution instead of the test solution. Calculate the content of $C_{14}H_{10}Cl_2NNaO_2$ and $C_{18}H_{21}NO_3 \cdot H_3PO_4 \cdot 1\frac{1}{2}H_2O$ respectively with respect to the peak areas obtained in the chromatogram by the external standard method. The coefficient 1.068 is used in the calculation of the content of codeine phosphate.

Category Analgetic.

Storage Preserve in tightly closed containers, protected from light.

Diclofenac Sodium Enteric-coated Tablets

Diclofenac Sodium Enteric-coated Tablets contain not less than 90.0% and not more than 110.0% of labelled amount of diclofenac sodium ($C_{14}H_{10}Cl_2NNaO_2$).

Description Enteric-coated tablets with white or almost

white core.

Identification (1) Weigh a quantity of the powdered tablets with enteric-coating removed equivalent to about 0.25 g of diclofenac sodium, add 10 ml of ethanol with shaking and filter, using the filtrate as test solution. Dissolve a quantity of diclofenac sodium CRS in ethanol to produce a solution of 25 mg per ml as reference solution. Carry out the thin-layer chromatography (Appendix V B), using silica gel GF₂₅₄ as the coating substance and a mixture of ethyl acetate-chloroform-glacial acetic acid (25:25:0.2) as the mobile phase. Apply separately to the plate 10 μ l each of above two solutions. After developing and removal of the plate, dry it in air and examine under ultraviolet light at 254 nm. The colour and position of the principal spot in the chromatogram obtained with the test solution correspond to the principal spot obtained with the reference solution.

(2) The light absorption of the solution obtained in Assay exhibits a maximum at 284 nm in range of 240-300 nm (Appendix IV A).

(3) Yields the reaction characteristic of sodium salts (Appendix III).

Drug Release Comply with the requirements for drug release test [Appendix X D, method 2 (2)], with the apparatus of dissolution test method 1 and using 1000 ml of 0.1 mol/L hydrochloric acid solution as the release medium and adjust the rotational speed of the paddle to 100 rpm. Withdraw a quantity of the solution at 2 hours and filter. Take the successive filtrate as test solution (1). Immediately put the basket into the 1000 ml of preliminary heated to 37.0°C of phosphate BS (pH 6.8), with the same rotational speed of the basket. Withdraw a quantity of the solution at 45 minutes and filter. Transfer accurately 5 ml of the successive filtrate to a 10 ml volumetric flask and dilute with phosphate BS (pH 6.8) to the volume, mix well as test solution (2). Dissolve 20 mg of diclofenac sodium CRS, accurately weighed, and dilute with water to the volume of a 100 ml volumetric flask, mix well as the solution A. Transfer accurately 2 ml of the solution A to a 100 ml volumetric flask and dilute with 0.1 mol/L hydrochloric acid solution to the volume, mix well as reference solution of test solution (1). Transfer accurately 5 ml of the solution A, to a 100 ml volumetric flask and dilute with phosphate BS (pH 6.8) to the volume, mix well as reference solution of test solution (2). Measure the absorbances of the resulting solution at 276 nm (Appendix IV A), calculate the dissolution of $C_{14}H_{10}Cl_2NNaO_2$ from each tablet.

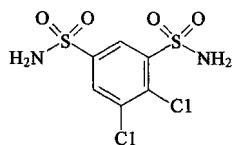
Other requirements Comply with the general requirements for tablets (Appendix I A).

Assay Weigh and powder finely 20 tablets with enteric-coating removed or without enteric-coating removed (for film enteric-coated tablets). Weigh accurately a quantity of the powdered tablets equivalent to about 50 mg of diclofenac sodium into a 100 ml volumetric flask and dissolve in 70 ml of ethanol with shaking. Add ethanol to volume, shake thoroughly and filter. Measure accurately 2 ml of successive filtrate and transfer to a 100 ml volumetric flask, add ethanol to volume and mix well. Carry out the method for spectrophotometry (Appendix IV A), and measure the absorbance at 284 nm. Repeat the operation, weigh accurately 50 mg of diclofenac sodium CRS instead of the substance being examined. Calculate the content of ($C_{14}H_{10}Cl_2NNaO_2$).

Category, Storage As described under diclofenac sodium.

Strength 25 mg

Diclofenamide



$C_6H_4Cl_2N_2O_4S_2$ 305.15

[120-07-8]

Diclofenamide is 4,5-dichloro-1,3-benzene-disulfonamide. It contains not less than 98.0% of $C_6H_4Cl_2N_2O_4S_2$, calculated on the dried basis.

Description A white or almost white crystalline powder; almost odourless; taste, slightly bitter. Soluble in ethanol; practically insoluble in water or chloroform; freely soluble in alkali solutions.

Melting range 238-242°C (Appendix VI C).

Identification (1) Heat to melt a small quantity with a quantity of sodium carbonate or sodium hydroxide; the gas evolved turns moistened red litmus paper blue; ignite until the mixture is incinerated, the residue yields the reactions characteristic of chlorides and sulfates (Appendix III).

(2) The light absorption of a solution of 0.10 mg per ml in 0.4% sodium hydroxide solution exhibits maxima at 284 nm and 294 nm; the absorbance is about 0.43 and 0.36, respectively (Appendix IV A).

(3) The infrared absorption spectrum (Appendix IV C) is concordant with the reference spectrum of diclofenamide (Appendix XVI).

Clarity of alkaline solution A solution of 1.0 g in 10 ml of sodium hydroxide TS is clear.

Chloride To 0.25 g add 25 ml of water, shake for 5 minutes and filter, carry out the limit test for chlorides (Appendix VIII A), using the filtrate. Any opalescence produced is not more pronounced than that of a reference using 7.0 ml of sodium chloride standard solution (0.028%).

Loss on drying When dried to constant weight at 105°C, loses not more than 1.0% of its weight (Appendix VIII L).

Residue on ignition Not more than 0.1% (Appendix VII N).

Heavy metals Not more than 0.001%, using 1.0 g (Appendix VIII H, method 3).

Assay Carry out the determination of nitrogen (Appendix VII D, method 1), using about 0.3 g, accurately weighed. Each ml of sulfuric acid (0.05 mol/L) VS is equivalent to 15.26 mg of $C_6H_4Cl_2N_2O_4S_2$.

Category Carbonic anhydrase inhibitor.

Storage Preserve in tightly closed containers, protected from light.

Preparation Diclofenamide Tablets

Diclofenamide Tablets

Diclofenamide Tablets contain not less than 93.0% and not more than 107.0% of the labelled amount of diclofenamide ($C_6H_4Cl_2N_2O_4S_2$).

Description White tablets.

Identification (1) Comply with test (1) for Identification described under Diclofenamide, using a quantity of the powdered tablets equivalent to 0.2 g of diclofenamide.

(2) The light absorption of the solution obtained in the Assay exhibits maxima at 284 nm and 294 nm (Appendix IV A).

Other requirements Comply with the general requirements for tablets (Appendix I A).

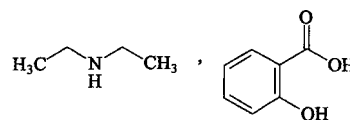
Assay Weigh accurately, and powder 10 tablets. To a quantity of the powder, accurately weighed, equivalent to about 50 mg of diclofenamide in a 100 ml volumetric flask add 50 ml of 0.4% sodium hydroxide solution and shake thoroughly. Add 0.4% sodium hydroxide solution to volume and mix well. Filter, transfer accurately 20 ml of the successive filtrate to another 100 ml volumetric flask, add 0.4% sodium hydroxide solution to volume and mix well. Measure the absorbance of the resulting solution at 284 nm (Appendix IV A). Calculate the content of $C_6H_4Cl_2N_2O_4S_2$, taking 43.4 as the value of A (1%, 1 cm).

Category As described under Diclofenamide.

Strength 25 mg

Storage Preserve in tightly closed containers, protected from light.

Diethylamine Salicylate



$C_{11}H_{17}NO_3$ 211.26

Diethylamine Salicylate is the salicylate of diethylamine. It contains $C_{11}H_{17}NO_3$ not less than 99.0%, calculated on the dried basis.

Description A white crystalline powder; odourless; taste, sweet and slight bitter; hygroscopic. Very soluble in water; freely soluble in ethanol, chloroform or acetone; slightly soluble in ether.

Melting range 99-102°C (Appendix VI C).

Identification (1) To an aqueous solution, add 1 drop of ferric trichloride TS; a violet colour is produced.

(2) To about 0.1 g add 5 ml of sodium hydroxide TS, heat; the characteristic odour of ammonia is perceived, the vapor turns moistened red litmus paper to blue.

(3) The light absorption of a solution of 20 µg per ml in ethanol, exhibits two maxima at 227 nm and 297 nm, a minimum at 257 nm.

(4) The infrared absorption spectrum (Appendix IV C) is concordant with the reference spectrum of diethylamine salicylate (Appendix XVI).

Clarity of solution Dissolve 0.50 g in 25 ml of water, the solution is clear.

Acidity Dissolve 0.25 g in 10 ml of water, pH 5.0-6.5 (Appendix VI H).

Loss on drying When dried to constant weight at 80°C, loses not more than 0.5% of its weight (Appendix VIII L).

Residue on ignition Not more than 0.1% (Appendix VII N).

Heavy metals Dissolve 1.0 g in a quantity of water, add 2

ml of acetate BS (pH 3.5), dilute with water to 25 ml, carry out the limit test for heavy metals (Appendix VIII H, method 1): not more than 0.001%.

Assay Dissolve about 0.2 g, accurately weighed, in 10 ml of glacial acetic acid, add 1 drop of crystal violet IS, titrate with perchloric acid (0.1 mol/L) VS, until the colour changes to bluish-green. Perform a blank determination and make any necessary correction. Each ml of perchloric acid (0.1 mol/L) VS is equivalent to 21.13 mg of $C_{11}H_{17}NO_3$.

Category Anti-inflammatory and analgesic.

Storage Preserve in tightly closed containers, protected from light.

Preparation Diethylamine Salicylate Cream

Diethylamine Salicylate Cream

Diethylamine Salicylate Cream contains not less than 90.0% and not more than 110.0% of labelled amount of diethylamine salicylate ($C_{11}H_{17}NO_3$).

Description A white to faintly yellow cream.

Identification (1) Mix a quantity of the ointment equivalent to 0.2 g diethylamine salicylate with 10 ml of water, stir thoroughly to dissolve diethylamine salicylate, the filtrate complies with the tests (1) and (2) for Identification described under Diethylamine Salicylate.

(2) The solution obtained in the Assay complies with test (3) for Identification described under Diethylamine Salicylate.

Acidity or alkalinity Mix 3.0 g with 10 ml of water, stir thoroughly, pH 6.5-7.5 (Appendix VI H).

Other requirements Comply with the general requirements for cream (Appendix I F).

Assay Dissolve a quantity equivalent to about 20 mg of diethylamine salicylate in a beaker with 20 ml of ethanol by stirring. Transfer to a 100 ml volumetric flask, dilute with ethanol to volume and mix well. Transfer accurately 10 ml of the solution to a 100 ml volumetric flask, dilute to volume and mix well. Measure the absorbance of the resulting solution at 297 nm (Appendix IV A) and calculate the content of $C_{11}H_{17}NO_3$, taking 186 as the value of A (1%, 1 cm).

Category As described under Diethylamine Salicylate.

Strength (1) 20 g : 2 g (2) 20 g : 4 g (3) 30 g : 3 g (4) 30 g : 6 g

Storage Preserve in tightly closed containers, protected from light.

98.0% of $C_{10}H_{21}N_3O \cdot C_6H_8O_7$, calculated on the dried basis.

Description A white, crystalline powder; odourless; taste, sour and bitter; slightly hygroscopic. Very soluble in water; sparingly soluble in ethanol; insoluble in acetone, chloroform or ether.

Melting range 135-139°C (Appendix VI C).

Identification (1) Dissolve 0.2 g in 2 ml of water, make alkaline with sodium hydroxide TS and extract with 5 ml of chloroform. Evaporate the chloroform extract to dryness and add 2 ml of ammonium molybdate-sulfuric acid TS, heat in a water bath; a blue precipitate is produced.

(2) The infrared absorption spectrum (Appendix IV C) is concordant with the reference spectrum of diethylcarbamazine citrate (Appendix XVI).

(3) The water layer remaining in the above test yields the reaction characteristic of citrates (Appendix III).

N-methylpiperazine Carry out the method for thin-layer chromatography (Appendix V B), using silica gel G as the coating substance and a mixture of chloroform-methanol-ammonia solution (13:5:1) as the mobile phase. Apply separately to the plate 10 μ l each of two solutions in methanol containing (1) 50 mg of the substance being examined per ml, (2) 50 μ g of N-methylpiperazine CRS per ml. After developing and removal of the plate, dried it in the air and visualize in iodine vapour. Any spot other than the principal spot in the chromatogram obtained with solution (1) is not more intense than the principal spot obtained with solution (2).

Loss on drying When dried at 105°C to constant weight, loses not more than 0.5% of its weight (Appendix VIII L).

Residue on ignition Not more than 0.1% (Appendix VIII N).

Heavy metals Dissolve 2.0 g in 20 ml of water, add 1.0 ml of 1 mol/L hydrochloric acid solution and sufficient water to produce 25 ml, carry out the limit test for heavy metals (Appendix VIII H, method 1): not more than 0.001%.

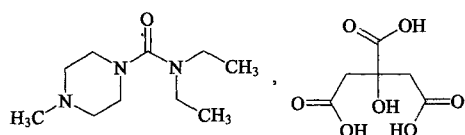
Assay Dissolve about 0.3 g, accurately weighed, in 1 ml of acetic anhydride and 10 ml of glacial acetic acid, add 1 drop of crystal violet IS and titrate with perchloric acid (0.1 mol/L) VS until the colour changes to blue. Perform a blank determination and make any necessary correction. Each ml of perchloric acid (0.1 mol/L) VS is equivalent to 39.14 mg of $C_{10}H_{21}N_3O \cdot C_6H_8O_7$.

Category Antifilaria drug.

Storage Preserve in tightly closed containers, stored in a dry place.

Preparation Diethylcarbamazine Citrate Tablets

Diethylcarbamazine Citrate



$C_{10}H_{21}N_3O \cdot C_6H_8O_7$ 391.42

[1642-54-2]

Diethylcarbamazine Citrate is 4-methyl-N, N-diethyl-1-piperazinecarboxamide, 2-hydroxy-1,2,3-propanetricarboxylate. It contains not less than

Diethylcarbamazine Citrate Tablets

Diethylcarbamazine Citrate Tablets contain not less than 95.0% and not more than 105.0% of the labelled amount of diethylcarbamazine citrate ($C_{10}H_{21}N_3O \cdot C_6H_8O_7$).

Description White tablets.

Identification To a quantity of the powdered tablets equivalent to about 0.2 g of diethylcarbamazine citrate add 10 ml of water, shake to dissolve diethylcarbamazine citrate, filter. The filtrate complies with the tests (1) and (3) for Identification described under Diethylcarbamazine Citrate.

Other requirements Comply with the general requirements for tablets (Appendix I A).

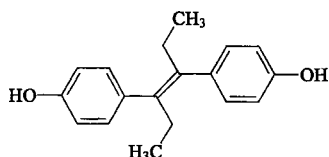
Assay Weigh accurately and powder 20 tablets. To an accurately weighed quantity of the powder equivalent to about 0.25 g of diethylcarbamazine citrate in a conical flask with stopper add 0.20 g of tartaric acid (powdered and dried at 105°C for 2 hours before use) and 10 ml of glacial acetic acid, boil gently for 3-5 minutes and cool. Add 5 ml of acetic anhydride and 1 drop of crystal violet IS and mix well. Titrate with perchloric acid (0.1 mol/L) VS, shaking vigorously for 2 minutes toward the end of the titration, until the colour of the solution changes to blue. Perform a blank determination and make any necessary correction. Each ml of perchloric acid (0.1 mol/L) VS is equivalent to 39.14 mg of $C_{10}H_{21}N_3O \cdot C_6H_8O_7$.

Category As described under Diethylcarbamazine Citrate.

Strength (1) 50 mg (2) 100 mg

Storage Preserve in tightly closed containers, stored in a dry place.

Diethylstilbestrol



$C_{18}H_{20}O_2$ 268.36

[56-53-1]

Diethylstilbestrol is α, α' -diethyl-(*E*)-4,4'-stilbenediol. It contains not less than 97.0% and not more than 103.0% of $C_{18}H_{20}O_2$, calculated on the dried basis.

Description Colourless crystals or a white crystalline powder; almost odourless.

Soluble in ethanol, ether or fatty oil; slightly soluble in chloroform; practically insoluble in water; soluble in dilute sodium hydroxide solutions.

Melting point 169-172°C (Appendix VI C).

Identification (1) Dissolve about 10 mg in 1 ml of sulfuric acid; the solution is orangish-yellow in colour; the colour disappears on diluting with 10 ml of water.

(2) In the Assay, the retention time of the two principal peaks in the chromatogram obtained with the test preparation corresponds with that of the two principal peaks in the chromatogram obtained with the reference preparation.

(3) The infrared absorption spectrum (Appendix IV C) is concordant with the reference spectrum of diethylstilbestrol (Appendix XVI).

Acidity or alkalinity Dissolve 0.10 g in 5.0 ml of 70% ethanol, the solution is neutral to litmus paper.

Related substances Carry out the method as described under Assay. Dissolve a quantity of the substance being examined in a mixture of ethanol-water (1:1) to produce a solution of about 0.5 mg per ml (1). Transfer accurately 1 ml of solution (1) to a 50 ml volumetric flask and dilute with the mixture of ethanol-water (1:1) to volume, shake well as solution (2). Inject 10 μ l of solution (2) into the column. Adjust the attenuation so that the principal peak height in the chromatogram is about 20% of full scale of the chart. Then inject separately 10 μ l of solution (1) and (2) into the

column, and record the chromatogram for twice of the retention time of the peak of *cis*-isomer. There are no more than 4 other peaks except the *trans*-isomer and *cis*-isomer peaks in the chromatogram of solution (1), the area of any one is not greater than half of the sum of the area of *trans*-isomer and 1.26 times of the area of *cis*-isomer of solution (2), the sum of the areas of all peaks other than the *trans*-isomer and *cis*-isomer peaks is not greater than 3/4 of the sum of the area of *trans*-isomer and 1.26 times of the area of *cis*-isomer of solution (2).

Loss on drying when dried to constant weight at 105°C, loses not more than 0.5% of its weight (Appendix VIII L).

Residue on ignition Not more than 0.1% (Appendix VIII N).

Assay Carry out the method for high performance liquid chromatography (Appendix V D), using a column packed with octadecylsine bonded silica gel and a mixture of methanol-water (80:20) as the mobile phase. Detection wavelength is 254 nm and the number of theoretical plates of the column is not less than 1000, calculated with reference to the peak of *trans*-isomer of diethylstilbestrol. Dissolve about 10 mg of diethylstilbestrol CRS in 50 ml of chloroform, allow it to stand in dark place for not less than 5 hours. Evaporate chloroform of 5.0 ml of the resulting solution and dissolve the residue in 25 ml of the mixture of ethanol-water (1:1). Inject 10 μ l of the solution into the column, record the chromatogram, the relative retention time between *trans*-isomer and *cis*-isomer of diethylstilbestrol is 1:1.33. The resolution factor between the peak of *trans*-isomer and *cis*-isomer is not less than 10.

Procedure Dissolve a quantity of diethylstilbestrol CRS, accurately weighed, in a mixture of ethanol-water (1:1) and dilute to produce a solution of about 0.1 mg per ml, inject 10 μ l into the column and record the chromatogram. Repeat the operation, using the substance being examined instead of the diethylstilbestrol CRS. Calculate the content of $C_{18}H_{20}O_2$ with respect to the sum of the peak areas of *trans*-isomer and *cis*-isomer obtained in the chromatogram by the external standard method (the peak area of *cis*-isomer multiplied by 1.26).

Category Estrogen

Storage Preserve in tightly closed containers, protected from light.

Preparation (1) Diethylstilbestrol Injection
(2) Diethylstilbestrol Tablets

Diethylstilbestrol Injection

Diethylstilbestrol Injection is a sterile solution of diethylstilbestrol in oil. It contains not less than 90.0% and not more than 110.0% of the labelled amount of diethylstilbestrol ($C_{18}H_{20}O_2$).

Description A clear, faint yellow to pale yellow oily liquid.

Identification In the Assay, the retention time of the two principal peaks in the chromatogram obtained with the test preparation corresponds with that of the two principal peaks in the chromatogram obtained with the reference preparation.

Other requirements Complies with the general requirements for injections (Appendix I B).

Assay Carry out the Assay as described under Diethylstilbestrol. Measure accurately a quantity of the substance being examined, dilute with ether to produce a solution of

about 200 μg per ml and shake well. Measure accurately 5 ml of the solution into a tube with plug for centrifugation. Evaporate ether in the bath of warm water and extract 5 times with methanol (Each 5 ml before the fifth time and 3 ml in the fifth time), at each time shake for 10 minutes and centrifugate for 15 minutes. Collect the methanol layer in a 25 ml volumetric flask and dilute with methanol to volume, mix well. Inject 10 μl into the column and record the chromatogram. Dissolve a quantity of diethylstilbestrol CRS, accurately weighed, with methanol to produce a solution of about 40 μg per ml, and repeat the operations of the above solution. Calculate the content of $\text{C}_{18}\text{H}_{20}\text{O}_2$ with respect to the sum of the peak areas of *trans*-isomer and *cis*-isomer obtained in the chromatogram by the external standard method (the peak area of *cis*-isomer multiplied by 1.26).

Category As described under Diethylstilbestrol.

Strength (1) 1 ml : 0.5 mg (2) 1 ml : 1 mg
(3) 1 ml : 2 mg (4) 1 ml : 3 mg

Storage Preserve in tightly closed containers, protected from light.

Diethylstilbestrol Tablets

Diethylstilbestrol Tablets contain not less than 90.0% and not more than 110.0% of the labelled
..... μl 1 1 $\text{C}_{18}\text{H}_{20}\text{O}_2$..

Description White tablets.

Identification (1) Place a quantity of the powdered tablets equivalent to about 20 mg of diethylstilbestrol in a separator. Add 15 ml of water containing 2 drops of hydrochloric acid, extract with 30 ml of ether, evaporate the ether extract to dryness. The residue complies with tests (1) for Identification described under Diethylstilbestrol.

(2) In the Assay, the retention time of the principal peak in the chromatogram obtained with the test preparation corresponds with that of the principal peak in the chromatogram of the reference preparation.

Content uniformity Comply with the requirements (Appendix X E). Triturate 1 tablet with ethanol-water (1:1) and transfer to a 25 ml volumetric flask in portions with dehydrated ethanol, dissolve the diethylstilbestrol by ultrasonical treatment, cool, dilute with dehydrated ethanol to the volume, shake well, filter and use the successive filtrate as the test solution. Dissolve a quantity of diethylstilbestrol CRS, accurately weighed, in ethanol-water (1:1) and dilute to produce a solution with the same concentration as the test solution. Carry out the procedure as described under Assay using above two solutions, calculate the content of $\text{C}_{18}\text{H}_{20}\text{O}_2$.

Dissolution Carry out the dissolution test (Appendix X C, method 3), using 250 ml of 0.1% lauryl sodium sulfate solution as the dissolution medium, adjust the rotational speed of the paddle to 100 rpm. Withdraw 5 ml of the solution at exact 45 minutes and filter, take the successive filtrate as the test solution. Dissolve about 10 mg of diethylstilbestrol CRS, accurately weighed, with a mixture of ethanol-water (1:1) in a 250 ml volumetric flask and dilute to volume, shake well. Measure a quantity of the solution and dilute with the dissolution medium to produce a solution of about 2 μg (for strength 0.5 mg), 4 μg (for strength 1 mg), 8 μg (for strength 2 mg), 12 μg (for strength 3 mg) per ml as the reference solution. Carry out the method described under the Assay. Inject separately 50

μl of the test and the reference solution into the column and record the chromatogram. Calculate the dissolution of $\text{C}_{18}\text{H}_{20}\text{O}_2$ from each tablet with respect to the sum of the peak areas of *trans*-isomer and *cis*-isomer obtained in the chromatogram by the external standard method (the peak area of *cis*-isomer multiplied by 1.26). Not less than 75% of the labelled amount is dissolved.

Other requirements Comply with the general requirements for tablets (Appendix I A).

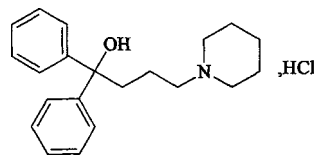
Assay Weigh accurately and powder 20 tablets. Weigh accurately a quantity of the powder, add a quantity of the mixture of ethanol-water (1:1), and supersonic until diethylstilbestrol is dissolved. Dilute with the mixture to produce a solution of about 0.1 mg per ml and filter, take 10 μl of the successive filtrate as the test solution. Carry out the method described under the Assay of Diethylstilbestrol. Calculate the content of $\text{C}_{24}\text{H}_{31}\text{FO}_6$ with respect to the peak area obtained in the chromatogram by the external standard method.

Category As described under Diethylstilbestrol.

Strength (1) 0.5 mg (2) 1 mg (3) 2 mg (4) 3 mg

Storage Preserve in tightly closed containers, protected from light.

Difenidol Hydrochloride



$\text{C}_{21}\text{H}_{27}\text{NO} \cdot \text{HCl}$ 345.91

[3254-89-5]

Difenidol Hydrochloride is α , α -diphenyl-1-piperidine-butanol hydrochloride. It contains not less than 98.5% of $\text{C}_{21}\text{H}_{27}\text{NO} \cdot \text{HCl}$, calculated on the dried basis.

Description A white crystalline powder; odourless; taste, astringent.

Freely soluble in methanol; soluble in ethanol; sparingly soluble in water or chloroform.

Melting range 217-222°C, with decomposition (Appendix VI C).

Identification (1) To 1-2 mg add 1 ml of water and 0.5 ml of sulfuric acid, a yellow colour is produced, which disappears on mixing well.

(2) Dissolve about 5 mg in 1 ml of a 1% solution of citric acid in acetic anhydride and warm in a water bath for about 3 minutes, a rose-red colour is produced.

(3) The light absorption of the solution obtained in the test for Alkene exhibits maxima at 258 nm and 252 nm, a minimum at 244 nm (Appendix IV A).

(4) The infrared absorption spectrum (Appendix IV C) is concordant with the reference spectrum of difenidol hydrochloride (Appendix XVI).

(5) The aqueous solution yields the reaction characteristic of chlorides (Appendix III).

Acidity Dissolve 0.10 g in 10 ml of water, pH 5.0-7.0 (Appendix VI H).

Alkene The light absorbance of a 0.30 mg per ml of the solution in ethanol at 251 nm is not greater than 0.36

(Appendix IV A).

Loss on drying When dried to constant weight at 105°C, loses not more than 0.5% of its weight (Appendix VIII L).

Residue on ignition Not more than 0.1% (Appendix VIII N).

Assay Dissolve 0.25 g, accurately weighed, in 40 ml of glacial acetic acid, add 5 ml of mercuric acetate TS and 1 drop of crystal violet IS. Titrate with perchloric acid (0.1 mol/L) VS until the colour changes to blue. Perform a blank determination and make any necessary correction. Each ml of perchloric acid (0.1 mol/L) VS is equivalent to 34.59 mg of $C_{21}H_{27}NO \cdot HCl$.

Category Antiemetic.

Storage Preserve in tightly closed containers.

Preparation Difenidol Hydrochloride Tablets

Difenidol Hydrochloride Tablets

Difenidol Hydrochloride Tablets contain not less than 90.0% and not more than 110.0% of the labelled amount of difenidol hydrochloride ($C_{21}H_{27}NO \cdot HCl$).

Description Sugar-coated or film coated tablets with white core.

Identification Triturate four tablets, add 20 ml of ethanol and shake to dissolve difenidol hydrochloride. Filter and evaporate the filtrate to dryness. Use the residue for the following tests.

(1) Complies with tests (1) and (2) for Identification described under Difenidol Hydrochloride.

(2) Dissolve the residue in water, add a few drops of dilute nitric acid and silver nitrate TS, a white curdy precipitate is produced.

Dissolution Comply with the dissolution test (Appendix X C, method 2), using 900 ml water as the dissolution medium, rotate the paddle at 50 rpm. Withdraw a quantity of solution at exact 30 minutes and filter. Take the successive filtrate as test solution. Carry out the method for high performance liquid chromatography (Appendix V D), using a column packed with octadecylsilane bonded silica gel and a mixture of 0.5% triethylamine solution (adjust with phosphoric acid to pH of 4.0)-methanol (40 : 60) as the mobile phase. Detection wavelength is 220 nm and the number of theoretical plates of the column is not less than 1500, the resolution factor between the peaks of difenidol and the impurities complies with the related requirements. Inject accurately 20 μ l of the test solution into the column, record the chromatogram. Repeat the operation, dissolve a quantity of difenidol hydrochloride CRS, weigh accurately, in water to produce a solution of 25 μ g per ml. Calculate the dissolution of $C_{21}H_{27}NO$ from each tablet, with respect to the peak area obtained in the chromatogram by the external standard method. Not less than 75% of the labelled amount is dissolved.

Other requirements Comply with the general requirements for tablets (Appendix I A).

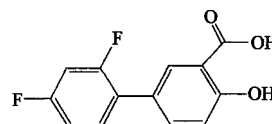
Assay Moisten 10 tablets with ethanol to a fine powder, triturate and extract with three successive portions of ethanol, 20 ml, 15 ml and 15 ml. Filter, wash with a small amount of ethanol and evaporate the combined filtrates to dryness, then dry at 105°C for 1 hour. Carry out the Assay described under Difenidol Hydrochloride beginning at

the words "Dissolve in 40 ml of glacial acetic acid, ...". Each ml of perchloric acid (0.1 mol/L) VS is equivalent to 34.59 mg of $C_{21}H_{27}NO \cdot HCl$.

Category, Storage As described under Difenidol Hydrochloride.

Strength 25 mg

Diflunisal



$C_{13}H_8F_2O_3$ 250.20

Diflunisal is 2',4'-difluoro-4-hydroxy-3-biphenylcarboxylic acid. It contains not less than 98.5% of $C_{13}H_8F_2O_3$, calculated on the dried basis.

Description A white or almost white crystal or crystalline powder; odourless.

Freely soluble in methanol, soluble in ethanol, slightly soluble in chloroform, practically insoluble in water.

Identification (1) Dissolve about 2 mg in 10 ml of ethanol, add 1 drop of ferric chloride TS, a dark purple colour is produced.

(2) Dissolve a quantity, in 0.1 mol/L hydrochloric acid in ethanol to produce a solution of 20 μ g per ml. The light absorption of the resulting solution exhibits two maxima at 251 nm and 315 nm (Appendix IV A).

The ratio of the absorbance at 251 nm to that at 315 nm is 4.2-4.6.

(3) The infrared absorption spectrum (Appendix IV C) is concordant with the reference spectrum of diflunisal (Appendix XXIII)

Related substances A Carry out the method for thin-layer chromatography (Appendix V B), using silica GF₂₅₄ as the coating substance and a mixture of *n*-hexane-dioxane-glacial acetic acid (85 : 10 : 5) as the mobile phase. Apply separately to the plate 5 μ l each of two solutions in methanol containing (1) 10 mg per ml, (2) 50 μ g per ml of the substance being examined. After developing and removal of the plate, dry it in air and examine under ultra-violet light at 254 nm. Any spot in the chromatogram other than the principal spot obtained with solution (1) is not more intense than the principal spot obtained with solution (2).

Related substances B Carry out the method for high performance liquid chromatography (Appendix V D), using a column packed with octadecylsilane bonded silica gel and a mixture of water-methanol-acetonitrile-glacial acetic acid (55 : 23 : 30 : 2) as the mobile phase. Detection wavelength is 254 nm and the number of the theoretical plates of the column is not less than 2000, calculated with reference to the peak of diflunisal. Inject 20 μ l of solution (2), obtained under the related substances A, into the column. Adjust the attenuation so that the principal peak height in the chromatogram is 20%-25% of full scale of the chart. Inject separately 20 μ l each of the solution (2) and the solution (1), obtained under the related substances A, into the column, and record the chromatograms for twice the retention time of the principal peak. The sum of the areas of all peaks other than the principal peak in the chromatogram obtained from the solution (1) is not greater than the area of the principal peak in the chromatogram obtained from solution (2).

Loss on drying When dried in vacuum over phosphorous pentoxide to constant weight at 60°C, loses not more than 0.3% of its weight (Appendix VIII L).

Fluoride Weigh accurately about 13 mg. Carry out the limit test for fluoride (Appendix VIII E). The fluoride content is not less than 14.5% and not more than 15.5%.

Residue on ignition Not more than 0.1% (Appendix VIII N), using 1.0 g.

Heavy metals Carry out the limit test for heavy metals (Appendix VIII H, method 2), using the residue obtained under the test for Residue on ignition; not more than 0.001%.

Assay Dissolve about 0.45 g, accurately weighed, in 80 ml of methanol, add 10 ml of water and 8-9 drops of phenol red IS (dissolve 0.1 g phenol red in 1.4 ml of 0.2 mol/L sodium hydroxide solution and 5 ml of 90% ethanol, slightly warm to dissolve diflunisal, add 20% ethanol to 250 ml), titrate with sodium hydroxide (0.1 mol/L) VS. Perform a blank determination and make any necessary correction. Each ml of sodium hydroxide (0.1 mol/L) VS is equivalent to 25.02 mg of $C_{13}H_8F_2O_3$.

Category Non-steroid anti-inflammatory drug.

Storage Preserve in tightly closed containers, protected from light.

Preparation Diflunisal capsules

Diflunisal Capsules

Diflunisal capsules contain not less than 90.0% and not more than 110.0% of the labelled amount of Diflunisal ($C_{13}H_8F_2O_3$).

Description Capsules contain white or almost white fine granules.

Identification (1) Shake a quantity of the contents of the capsules, equivalent to about 2 mg of diflunisal, with 10 ml of ethanol, add 1 drop of ferric chloride TS, a dark purple colour is produced.

(2) Dilute a quantity of the test solution obtained under the Assay with 0.1 mol/L hydrochloric acid solution in ethanol to produce a solution of about 20 µg per ml. The light absorption of the resulting solution exhibits two maxima at 251 nm and 315 nm (Appendix IV A).

(3) Take a quantity of the contents, equivalent to about 5 mg of diflunisal, add 5 ml of methanol to dissolve diflunisal with shaking, filter and take the filtrate as test solution. To a quantity of diflunisal CRS, dissolve in methanol to produce a solution of 10 mg per ml as reference solution. Carry out the method for thin-layer chromatography (Appendix V B), using silica GF₂₅₄ as the coating substance and a mixture of carbon tetrachloride-acetone-glacial acetic acid (20:2:1) as the mobile phase. Apply separately to the plate 5 µl each of above two solutions. After developing and removal of the plate, dry it in air and examine under ultra-violet at 254 nm. The colour and position of the principal spot in the chromatogram obtained with the test solution correspond to the principal spot obtained with the reference solution.

Dissolution Carry out the method for dissolution test (Appendix X C, method 2), using 900 ml of 0.1 mol/L trihydroxymethylaminomethane BS (Dissolve 121 g of trihydroxymethylaminomethane in 9000 ml of water, adjust to pH 7.2 with 25% citric acid solution, dilute to 10000 ml with water) as the dissolution medium and adjust the rotation speed of the basket to 50 rpm. Withdraw 10 ml of

the solution at exact 30 minutes and filter. Dilute a quantity of the successive filtrate, accurately measured, with dissolution medium to produce a solution of about 30 µg per ml as test solution. Dissolve diflunisal CRS in dissolution medium to produce a solution of about 30 µg per ml as reference solution. Measure the absorbances of the two resulting solutions at 306 nm (Appendix IV A). Calculate the dissolution of $C_{13}H_8F_2O_3$ from each capsule. Not less than 80% of the labelled amount is dissolved.

Other requirements Comply with the general requirements for capsules (Appendix I E).

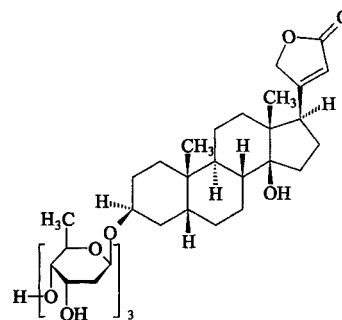
Assay Triturate the mixed contents obtained under the test for Weight variation. Weigh accurately a quantity, equivalent to about 0.1 g of diflunisal, transfer to a 100 ml volumetric flask, add a quantity of 0.1 mol/L of hydrochloric acid in ethanol, treated with ultrasonicator for 10 minutes to dissolve diflunisal, cool to room temperature, dilute to volume with the same solution, shake thoroughly and filter. Transfer accurately 5 ml of the successive filtrate to a 100 ml volumetric flask, add 0.1 mol/L of hydrochloric acid in ethanol to volume and mix well as test solution. Measure the absorbance of the resulting solution at 315 nm (Appendix IV A). Dissolve a quantity of diflunisal CRS, accurately weighed, in 0.1 mol/L of hydrochloric acid in ethanol to produce a solution of 50 µg per ml, measure the absorbance in the same manner. Calculate the content of $C_{13}H_8F_2O_3$.

Category As described under Diflunisal.

Strength 0.25 g

Storage Preserve in tightly closed containers.

Digitoxin



$C_{41}H_{64}O_{13}$ 764.95

[71-63-6]

Digitoxin is 3β - [(O - 2,6 - dideoxy - β - D - ribo - hexopyranosyl - (1→4) - O - 2,6 - dideoxy - β - D - ribo - hexopyranosyl - (1→4) - 2,6 - dideoxy - β - D - ribo - hexopyranosyl) oxy] - 14β - hydroxy - 5β - card - 20 (22) - enolide. It contains not less than 90.0% of $C_{41}H_{64}O_{13}$, calculated on the dried basis.

Description A white or almost white crystalline powder; odourless.

Sparingly soluble in chloroform; slightly soluble in ethanol or ether; insoluble in water.

Identification Dissolve about 1 mg in a test tube with 2 ml of glacial acetic acid containing ferric chloride (to 10 ml of glacial acetic acid add 1 drop of ferric chloride TS), add slowly alongside the test tube wall 2 ml of sulfuric acid to form a subjacent layer, a brown ring develops at the interface and a pale green, then blue, colour passes to the

glacial acetic acid layer.

Clarity of chloroform solution To 0.10 g in a cylinder with stopper add 5 ml of chloroform, shake for 10 minutes and allow to stand for 1 hour, the solution is clear.

Digitonin Dissolve 10 mg in 2 ml of ethanol, add 2 ml of a solution of cholesterol in ethanol (1→200), shake gently, no precipitate is formed in 10 minutes.

Loss on drying When dried to constant weight at 105°C, loses not more than 1.0% of its weight (Appendix VIII L).

Assay Reference preparation Weigh accurately a quantity of digitoxin CRS previously dried to constant weight at 105°C, add a mixture of benzene* (Add a quantity of water to redistilled benzene of reagent grade, shake until saturated, separate the benzene layer.)-chloroform (4:1) to produce a solution of 40 µg per ml.

Chromatographic column Select a chromatographic tube about 200 mm long and about 25 mm in internal diameter. Insert a layer of purified cotton wool. Mix 1 ml of water with 2 g of purified kieselguhr (boil 150 g of chromatographic kieselguhr in 1000 ml of dilute hydrochloric acid for 10 minutes, cool and filter, wash thoroughly with water until the washing is neutral to pH test paper, dry at 105°C and ignite at 500°C for 2 hours and cool), transfer the mixture to the chromatographic tube in divided quantities and tamp lightly each time with a flat head glass rod. Mix 3 g of purified kieselguhr with a mixture of 2 ml of formamide and 1 ml of water and transfer to the chromatographic tube in similar manner. Cover with a pledget of purified cotton wool and tamp lightly.

Procedure Dissolve about 10 mg, accurately weighed, in 10 ml of chloroform in a 50 ml volumetric flask, dilute with benzene* to volume, mix well. Transfer 10 ml, accurately measured, to the prepared chromatographic column and elute with a mixture of benzene*-chloroform (3:1) at a rate not exceeding 4 ml per minute. Collect nearly 250 ml of eluate in a 250 ml volumetric flask, stop the elution, add chloroform to volume and mix well.

Transfer accurately 25 ml of the eluate and 5 ml of the Reference re aration to two conical flasks res ectivel , evaporate each to dryness on a water bath. To each residue add 0.5 ml of ethanol, evaporate to dryness and cool. To each flask add 5 ml of ethanol, insert the stoppers tightly and allow to stand at 22-25°C for 15 minutes, shaking frequently. Add accurately to each flask 3 ml of freshly prepared alkaline trinitrophenol TS, mix well and allow to stand at 22-25°C for 30 minutes, measure separately the absorbances at 495 nm (Appendix IV B). Calculate the content of digitoxin.

Category Cardiotonic glycoside.

St—g Preserve in tightly closed containers.

Preparation Digitoxin Tablets

Digitoxin Tablets

Digitoxin Tablets contain not less than 90.0% and not more than 110.0% of the labelled amount of digitoxin ($C_{41}H_{64}O_{13}$).

Description White tablets.

Identification To a quantity of the powdered tablets equivalent to about 1 mg of digitoxin in a cylinder with stopper, add 5 ml of chloroform and insert the stopper, shake occasionally, filter. Evaporate the filtrate to dryness

on a water bath, the residue complies with test for Identification described under Digitoxin.

Content uniformity To 1 tablet in a 25 ml volumetric flask add 15 ml of methanol-water (1:1), carry out the procedure described under Assay, beginning at the words "shake for 1 hour to dissolve digitoxin..." and calculate the content of $C_{41}H_{64}O_{13}$. The limit of content deviation is $\pm 20\%$. The results comply with the requirements. (Appendix X E).

Other requirements Comply with the general requirements for tablets (Appendix I A).

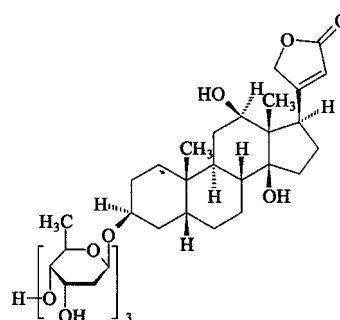
Assay Weigh accurately and powder 20 tablets. To a quantity of the powder equivalent to about 0.4 mg of digitoxin, accurately weighed, in a 100 ml volumetric flask, add 60 ml of methanol-water (1:1), shake for 1 hour, dilute with methanol-water (1:1) to volume, mix well. Filter through a membrane filter with a porosity not greater than 0.8 µm, discard the initial filtrate, take the successive filtrate as test preparation. Dissolve a quantity of digitoxin CRS, accurately weighed, in a mixture of methanol-water (1:1) to produce a solution of 4 µg per ml and use it as reference preparation. Measure accurately 1 ml each of the solutions to two 10 ml volumetric flasks. To each flask add 3 ml of a 0.1% ascorbic acid solution in methanol and 0.2 ml of hydrogen peroxide (0.009 mol/L) VS (standardized immediately before use), mix well after addition of each reagent. Add hydrochloric acid to volume, mix well and allow to stand for exact 30 minutes. Measure the fluorescence of the two solutions (Appendix IV E), at an excitation wavelength of 400 nm and an emission wavelength of 565 nm and calculate the content of $C_{41}H_{64}O_{13}$.

Category As described under Digitoxin.

Strength 0.1 mg

Storage Preserve in tightly closed containers.

Digoxin



$C_{41}H_{64}O_{14}$ 780.95

[20830-75-5]

Digoxin is 3-[(O-2,6-dideoxy-β-D-ribohexopyranosyl-(1→4)-O-2,6-dideoxy-β-D-ribohexopyranosyl-(1→4)-2,6-dideoxy-β-D-ribohexopyranosyl)oxy]-12β, 14β-dihydroxy-5β-card-20(22)-enolide. It contains not less than 95.0% of $C_{41}H_{64}O_{14}$, calculated on the dried basis.

Description White crystals or a crystalline powder; odourless; taste, bitter. Freely soluble in pyridine; slightly soluble in dilute ethanol; very slightly soluble in chloroform; insoluble in water or ether.

Specific optical rotation +9.5° to +12.0°, in a solution of

20 mg per ml in pyridine (Appendix VI E).

Identification (1) Dissolve about 1 mg in 1 ml of glacial acetic acid containing ferric chloride (to 10 ml of glacial acetic acid add 1 drop of ferric chloride TS), add slowly along the wall of test tube 1 ml of sulfuric acid to form two layers; a brown ring is formed at the junction of the liquids and the upper layer acquires an indigo colour on standing.

(2) Dissolve separately the substance being examined and digoxin CRS in methanol-chloroform (1:1) to produce two solutions of 2.5 mg per ml. Carry out the method for ascending paper chromatography (Appendix V A), apply separately 10 μ l each of the two solutions to the paper, previously soaked in a freshly prepared formamide-acetone (3:7) solution for more than 5 minutes and dried before use; using a freshly prepared saturated solution of formamide in chloroform (mix 25 volumes of chloroform and 1 volume of formamide, shake thoroughly, allow to stand, separate the chloroform layer and filter through cotton wool) as the mobile phase. After developing and removal of the paper, dry it at 100°C and examine under ultraviolet light at 365 nm, no spot is obtained in the chromatogram; spray with freshly prepared trichloroacetic acid solution in chloroform (dissolve 6 g of trichloroacetic acid in 25 ml of chloroform, add 0.5 ml of 30% hydrogen peroxide solution, mix well), dry it again at 100°C and cool. Examine under ultraviolet light at 365 nm, the principal spot in the chromatogram obtained with the substance being examined corresponds in both fluorescence and position to that of the principal spot obtained with digoxin CRS.

(3) The infrared absorption spectrum (Appendix IV C) is concordant with the reference spectrum of digoxin (Appendix XVI).

Clarity of solution A solution of 0.50% (w/v) in methanol-chloroform (1:1) is clear.

Related substances Dissolve a quantity of the substance being examined with dilute ethanol to produce a solution of 1 mg per ml as the test solution. Transfer 2 ml of the test solution, accurately measured, into 100 ml volumetric flask, dilute with dilute ethanol to volume, mix well as the reference solution (1). Dissolve an accurately weighed quantity of digitoxin CRS with dilute ethanol to produce a solution of 0.02 mg per ml as the reference solution (2). Carry out the method described under Assay. Inject 20 μ l of the reference solution (1) into the column, adjust the attenuation so that the principal peak height in the chromatogram is 20% full scale of the chart. Inject separately 20 μ l each of solutions, accurately measured, into column, and record the chromatogram for three times the retention time of the principal peak. If the peak appeared which the retention time is identical with that of the peak of digitoxin in the test solution chromatogram, calculate the content of digitoxin with respect to the peak area obtained in the chromatogram by the external standard method. The content of digitoxin is not more than 2.0%. The area of any peak other than the principal and solvent peak obtained with test solution is not more than the area of the principal peak in the chromatogram obtained with reference solution (1). The sum of the area of all peaks other than the principal peak obtained with test solution is not greater than the twice of the area of the principal peak in the chromatogram obtained with reference solution (1).

Loss on drying When dried in vacuum at 105°C for 1 hour, loses not more than 1.0% of its weight (Appendix VIII L).

Assay Carry out the method for high performance liquid chromatography (Appendix V D), using a column packed with octadecylsilane bonded silica gel and a mixture of acetonitrile-water (10:90) as the mobile phase A, a mixture of acetonitrile-water (60:40) as the mobile phase

B. The flow rate is 1.5 ml/min and detection wavelength is 230 nm. The number of theoretical plates of the column is not less than 2000, calculated with reference to the peak of digoxin.

Time (minute)	mobile phase A	mobile phase B
0	60%	40%
5	60%	40%
15	0%	100%
15.1	60%	40%
20	60%	40%

Procedure Dissolve an accurately weighed quantity of the substance being examined with dilute ethanol to produce a solution of 0.1 mg per ml as the test solution. Inject accurately 20 μ l of the resulting solution into the column. Repeat the operation, using digoxin CRS instead of the substance being examined. Calculate the content of $C_{41}H_{64}O_{14}$ with respect to the peak area obtained in the chromatogram by the external standard method.

Category Cardiotonic.

Storage Preserve in tightly closed containers.

Preparation (1) Digoxin Injection (2) Digoxin Tablets

Digoxin Injection

Digoxin Injection is a sterile solution of digoxin in Water for Injection. It contains not less than 90.0% and not more than 110.0% of the labelled amount of digoxin ($C_{41}H_{64}O_{14}$).

Description A clear, colourless or almost colourless liquid.

Identification (1) Mix 1 ml of the injection with 1 ml of glacial acetic acid containing ferric chloride (to 10 ml of glacial acetic acid add 1 drop of ferric chloride TS) in a small test tube and add slowly along the wall of test tube, 1 ml of sulfuric acid to form two layers, a brown ring is formed at the junction of the liquids, and the upper layer acquires an indigo colour on standing.

(2) The retention time of principal peaks of the substance being examined in the chromatogram obtained in the Assay is identical with that of digoxin CRS.

pH value 6.5-7.5 (Appendix VI H).

Other requirements Complies with the general requirements for injections (Appendix I B).

Assay Carry out the method for high performance liquid chromatography (Appendix V D), using a column packed with octadecylsilane bonded silica gel and a mixture of acetonitrile-water (32:68) as the mobile phase. Maintain the column temperature at 30°C, detection wavelength is 230 nm. The number of theoretical plates of the column is not less than 1500, calculated with reference to the peak of digoxin.

Procedure Transfer accurately 2 ml of the injection equivalent to 0.5 mg of digoxin to a 5 ml volumetric flask. Dilute to volume with dilute ethanol, mix well. Inject accurately 20 μ l into the column. Dissolve an accurately weighed quantity of digoxin CRS with dilute ethanol, dilute to produce a solution of about 0.1 mg per ml. Repeat the operation. Calculate the content of $C_{41}H_{64}O_{14}$ with respect to the peak area obtained in the chromatogram by the external standard method.

Category As described under Digoxin.

Strength 2 ml : 0.5 mg

Storage Preserve in well closed containers, protected from light.

Digoxin Tablets

Digoxin Tablets contain not less than 90.0% and not more than 110.0% of the labelled amount of digoxin ($C_{41}H_{64}O_{14}$).

Description White tablets.

Identification (1) To a quantity of the powdered tablets equivalent to about 0.25 mg of digoxin add 10 ml of glacial acetic acid containing ferric chloride (to 10 ml of glacial acetic acid add 1 drop of ferric chloride TS). Shake for a few minutes, filter through a sintered glass filter. To the filtrate add slowly, along the wall of test tube, 1 ml of sulfuric acid to form two layers; a brown ring is formed at the junction of the liquids and the upper layer acquires an indigo colour on standing.

(2) The retention time of principal peak of the substance being examined in the chromatogram obtained in the Assay is identical with that of digoxin CRS.

Content uniformity Shake 1 tablet with 10 ml of water in a 25 ml volumetric flask to disintegrate. Add 10 ml of ethanol, make digoxin dissolve for 30 minutes, by ultrasonic generator. Dilute with dilute ethanol to volume and mix well. Filter through a filter membrane with a porosity not greater than $0.45 \mu\text{m}$. Discard the initial filtrate, using the successive filtrate as the test preparation. Weigh accurately a quantity of digoxin CRS, add dilute ethanol to produce a solution of $10 \mu\text{g}$ per ml as the reference preparation. Complete the procedure described under Assay. Calculate the content of $C_{41}H_{64}O_{14}$ of each tablet. The limit of content variation is $\pm 20\%$. The results comply with the requirements (Appendix X E).

Dissolution Carry out the dissolution test (Appendix X C, method 3), using 250 ml of the solution (to 6 ml of dilute hydrochloric acid add water to produce 250 ml) as the dissolution medium, adjust the rotational speed of the paddle to 100 rpm. Withdraw the solution at exact 60 minutes and filter through a filter membrane with a porosity not greater than $0.45 \mu\text{m}$, use the successive filtrate as the test solution. Dissolve an accurately weighed quantity of digoxin CRS in 50 ml volumetric flask with 80% ethanol, dilute to volume with the dissolution medium to produce a solution of $1 \mu\text{g}$ per ml as the reference solution. Transfer accurately 1 ml each of the test solution and the reference solution to a 10 ml volumetric flask, add 3 ml of 0.1% ascorbic acid solution in methanol, 0.20 ml of hydrogen peroxide (0.009 mol/L) VS (standardized immediately before use), shake after each addition, then add dilute hydrochloric acid to volume and mix well. Allow to stand in the dark at 30°C for 2 hours and immediately carry out the method for Fluorometry (Appendix IV E). Measure the fluorescence of the two solution using an excitation wavelength of 360 nm and an emission wavelength of 485 nm. Calculate the dissolution of $C_{41}H_{64}O_{14}$ from each tablet, not less than 65% of the labelled amount is dissolved.

Other requirements Comply with the general requirements for tablets (Appendix I A).

Assay Carry out the method for high performance liquid chromatography (Appendix V D), using a column packed with octadecylsilane bonded silica gel and a mixture of

acetonitrile-water (32:68) as the mobile phase. Maintain the column temperature at 30°C , detection wavelength is 230 nm. The number of theoretical plates of the column is not less than 1500, calculated with reference to the peak of digoxin.

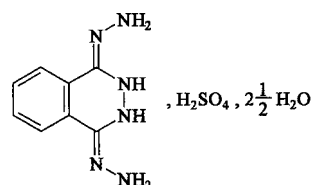
Procedure Weigh accurately and powder 20 tablets, weigh accurately a quantity of powder equivalent to 2.5 mg of digoxin in a 25 ml volumetric flask. To make digoxin dissolved for 30 minutes by ultrasonic generator, and cool, dilute to volume with ethanol, mix well and filter membrane with a porosity not greater than $0.45 \mu\text{m}$. Inject accurately $20 \mu\text{l}$ of the successive filtrate into the column. Dissolve an accurately weighed quantity of digoxin CRS with dilute ethanol, dilute to produce a solution of 0.1 mg per ml. Repeat the operation, Calculate the content of $C_{41}H_{64}O_{14}$ with respect to the peak area obtained in the chromatogram by the external standard method.

Category As described under Digoxin.

Strength 0.25 mg

Storage Preserve in tightly closed containers.

Dihydralazine Sulfate



$C_8H_{10}N_6 \cdot H_2SO_4 \cdot 2\frac{1}{2}H_2O$ 333.32 [484-23-1]

Dihydralazine Sulfate is 1,4-dihydrazinophthalazine sulfate hemipentahydrate. It contains not less than 98.0% of $C_8H_{10}N_6 \cdot H_2SO_4$, calculated on the dried basis.

Description A white to pale yellow crystalline powder, and the anhydrous base is yellow powder; odourless; taste, slightly bitter.

Sparingly soluble in boiled water; slightly soluble in water or ethanol.

Melting range $241-245^\circ\text{C}$, with decomposition (Appendix VI C).

Identification (1) Filter the solution obtained under the Assay finished, wash the precipitate with water and dry it at 105°C , the melting range is $150-156^\circ\text{C}$ (Appendix VI C).

(2) To the saturated aqueous solution add alkaline mercuric potassium iodide TS, a brownish black precipitate is produced. To another portion of the solution add ferric chloride TS, a blue colour is produced.

(3) The saturated aqueous solution yields the reaction characteristic of sulfates (Appendix III).

Free hydrazine Dissolve 2.0 mg in water to produce a solution of 0.4 mg per ml. To 5 ml of the solution add 4 ml of freshly prepared *p*-dimethylaminobenzaldehyde solution (dissolve 0.2 g of *p*-dimethylaminobenzaldehyde in a mixture of 60 ml of hydrochloric acid and 40 ml of water), allow to stand for 3 minutes. Measure the absorbance of the resulting solution at 450 nm; not more than 0.05 (Appendix IV A).

Loss on drying When dried in vacuum to constant weight at 80°C , loses not more than 12.0%-15.0% (Appendix VIII

L).

Residue on ignition Not more than 0.1% (Appendix VIII N).

Assay Dissolve about 0.3 g, accurately weighed, in 50 ml of water and 10 ml of hydrochloric acid solution (1→2) by gently heating, cool to room temperature. Carry out the method for dead-stop titration (Appendix VII A), titrate with sodium nitrite (0.1 mol/L) VS. Each ml of sodium nitrite (0.1 mol/L) VS is equivalent to 14.41 mg of $C_8H_{10}N_6 \cdot H_2SO_4$.

Category Antihypertensive.

Storage Preserve in tightly closed containers, protected from light.

Preparation Dihydralazine Sulfate Tablets

Dihydralazine Sulfate Tablets

Dihydralazine Sulfate Tablets contain not less than 90.0% and not more than 110.0% of the labelled amount of dihydralazine sulfate ($C_8H_{10}N_6 \cdot H_2SO_4$).

Description Sugar-coating tablets with white to pale yellow core.

Identification (1) Powder the tablets with the sugar coating removed. To a quantity of the powdered tablets equivalent to about 25 mg of dihydralazine sulfate add 20 ml of water, shake well and filter. The filtrate complies with tests (2), (3) for Identification described under Dihydralazine Sulfate.

(2) To a quantity of the powdered tablets obtained under the identification (1) equivalent to about 50 mg of dihydralazine sulfate add 20 ml of water and 3 ml of dilute hydrochloric acid, shake and filter. To the filtrate add an excess of sodium nitrite solution (0.1 mol/L), a precipitate is produced. Filter, wash the precipitate with water and dry at 105°C, it melts in a range of 148-156°C.

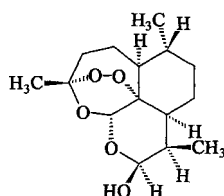
Other requirements Comply with the general requirements for tablets (Appendix I A).

Assay Weigh accurately and powder 40 tablets. Weigh accurately a quantity of the powdered tablets equivalent to about 0.2 g of dihydralazine sulfate. Carry out the method for the Assay described under Dihydralazine Sulfate. Each ml of sodium nitrite (0.1 mol/L) VS is equivalent to 14.41 mg $C_8H_{10}N_6 \cdot H_2SO_4$.

Category, Storage As described under Dihydralazine Sulfate.

Strength (1) 12.5 mg (2) 25 mg

Dihydroartemisinin



$C_{15}H_{24}O_5$ 284.35

Dihydroartemisinin is (3R, 5 α S, 6R, 8 α S, 9R, 12S, 12 α R) - octahydro - 3,6,9 - trimethyl - 3,12 - epoxy-12H-pyrano [4,3-j]-1,2-benzodioxepin-10 (3H)-ol. It contains not less than 98.0% and not more than 102.0% of $C_{15}H_{24}O_5$, calculated on the dried basis.

Description White needle crystals; odourless; taste, bitter. Freely soluble in chloroform; soluble in acetone; sparingly soluble in methanol or ethanol; practically insoluble in water.

Melting range 145-150°C, with decomposition (Appendix VI C).

Identification (1) Dissolve about 10 mg of dihydroartemisinin in 1 ml of dehydrated ethanol, add 2 ml of potassium iodide TS and 4 ml of dilute sulfuric acid TS, mix well, add a few drops of starch IS; a bluish purple colour is produced.

(2) To 3-4 drops of dihydroartemisinin in chloroform solution (1→10), previously volatilizing completely the chloroform, add 1 drop of a solution of 2% vanillin in sulfuric acid; a red colour is produced which changes gradually to brown on standing.

(3) A solution of 20 mg per ml in chloroform is dextrorotatory (Appendix VI E).

(4) The infrared absorption spectrum (Appendix IV C) is concordant with the reference spectrum of dihydroartemisinin (Appendix XVI).

Related substances Carry out the method for thin-layer chromatography (Appendix V B), using silica gel G as the coating substance and a mixture of benzene-ethyl acetate (8:2) as the mobile phase. Apply separately to the plate 10 μ l each of two solutions in chloroform containing (1) 20 mg per ml (2) 0.4 mg per ml of the substance being examined. After developing and removal of the plate, allow it to dry in air, spray with a solution of 2% vanillin in sulfuric acid. Not more than a secondary spot is obtained in the chromatogram obtained with solution (1) and no secondary spot is more intense than the principal spot obtained with solution (2) (2%).

Loss on drying When dried in vacuum over phosphorous pentoxide to constant weight at 105°C, loses not more than 0.5% of its weight (Appendix VIII L).

Residue on ignition Not more than 0.1% (Appendix VIII N), using 1.0 g.

Heavy metals Carry out the limit test for heavy metals (Appendix VIII H, method 2), using the residue obtained in the test for Residue on ignition; not more than 0.001%.

Assay Dissolve about 10 mg of dihydroartemisinin, accurately weighed, in ethanol in a 50 ml volumetric flask, dilute with ethanol to volume, mix well and allow to stand for 2 hours, as the test solution. Dissolve about 10 mg, accurately weighed, of dihydroartemisinin CRS, in ethanol in a 50 ml volumetric flask and dilute with ethanol to volume. Mix well and allow to stand for 2 hours as the reference solution.

To 1 ml of each of the two solutions, accurately measured, to 10 ml of 2% sodium hydroxide solution and mix well. Dilute with 2% sodium hydroxide solution to volume, mix well, warm the two solutions in a water bath at 60°C for 30 minutes and cool to room temperature. Use a mixture of 2% sodium hydroxide solution-ethanol (4:1) as a blank and measure the absorbances of the resulting solutions at 238 nm (Appendix IV A). Calculate the content of $C_{15}H_{24}O_5$.

Category Antimalarial.

Storage Preserve in tightly closed containers, stored in a cool place and protected from light.

Preparation Dihydroartemisinin Tablets

Dihydroartemisinin Tablets

Dihydroartemisinin Tablets contain not less than 90.0% and not more than 110.0% of the labelled amount of dihydroartemisinin ($C_{15}H_{24}O_5$).

Description White tablets.

Identification (1) Dissolve a quantity of the powdered tablets equivalent to about 20 mg of dihydroartemisinin in 2 ml of dehydrated ethanol and filter. To the filtrate add 2 ml of potassium iodide TS and 4 ml of dilute sulfuric acid TS, mix well, add a few drops of starch IS; a bluish-purple colour is produced.

(2) To a quantity of the powdered tablets equivalent to about 20 mg of dihydroartemisinin add 10 ml of chloroform, shake to dissolve dihydroartemisinin and filter. Evaporate the filtrate to about 2 ml and use the solution as the test solution. Dissolve dihydroartemisinin CRS in chloroform to produce a solution of 10 mg per ml as reference solution. Carry out the method for thin-layer chromatography (Appendix V B), using silica gel G as the coating substance and a mixture of benzene-ethyl acetate (8:2) as the mobile phase. Apply separately to the plate 10 μ l each of the two solutions. After developing and removal of the plate, dry it in air and spray with a solution of 2% vanillin in sulfuric acid. The colour and position of the principal spot in the chromatogram obtained with the test solution corresponds to the principal spot in the chromatogram obtained with reference solution.

Related substances Carry out the method for thin-layer chromatography (Appendix V B), using silica gel G as the coating substance and a mixture of benzene-ethyl acetate (8:2) as the mobile phase. Apply to the plate 10 μ l each of two solutions in chloroform containing (1) 20 mg per ml (2) 0.6 mg per ml of the substance being examined. After developing and removal of the plate, dry it in air, spray with a solution of 2% vanillin in sulfuric acid. Not more than a secondary spot in the chromatogram is obtained with solution (1), and no secondary spot is more intense than the principal spot obtained with solution (2) (3%).

Dissolution Carry out the dissolution test (Appendix X C, method 3), using 250 ml of a mixture of 0.15% sodium hydroxide solution-ethanol (4:1) as the dissolution medium, adjust the rotational speed of the paddle to 50 rpm. Withdraw 5 ml of the solution at exact 30 minutes and filter. Transfer accurately 2 ml of the successive filtrate, to a 10 ml volumetric flask, dilute with 2% sodium hydroxide solution to volume and use this solution as the test solution. Dissolve a quantity of dihydroartemisinin CRS in ethanol to produce a solution of about 0.4 mg per ml and allow it to stand for 2 hours. Transfer accurately 2 ml of the solution in a 10 ml volumetric flask, dilute with 0.15% sodium hydroxide solution to volume, warm the solution in water bath at 37°C for 30 minutes and dilute 2 ml of the solution, accurately measured, with 2% sodium hydroxide solution to 10 ml as the reference solution. Warm the two solutions in water bath at 60°C for 30 minutes, cool to room temperature. Measure the absorbances of the resulting solutions at 241 nm (Appendix IV A). Calculate the dissolution of $C_{15}H_{24}O_5$ form each tablet. Not less than 70% of the labelled amount is dissolved.

Other requirements Comply with the general requirement

for tablets (Appendix I A).

Assay Weigh accurately and powder 10 tablets. Transfer an accurately weighed quantity of the powder equivalent to about 10 mg of dihydroartemisinin to a 50 ml volumetric flask, add a quantity of ethanol, shake to dissolve dihydroartemisinin, dilute with ethanol to volume and mix well. Allow it to stand for 2 hours, filter and use the successive filtrate, as the test solution. Dissolve about 10 mg of dihydroartemisinin CRS, accurately weighed, in ethanol in a 50 ml volumetric flask and dilute with ethanol to volume. Mix well and allow it to stand for 2 hours, as the reference solution.

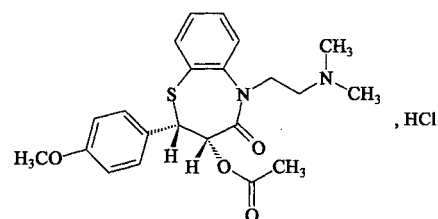
To 1 ml of each of the two solutions, accurately measured, in two 10 ml volumetric flasks add accurately 1 ml of ethanol, mix well, dilute with 2% sodium hydroxide solution and mix well. Warm the solutions in a water bath at 60°C for 30 minutes, cool to room temperature. Use a mixture of 2% sodium hydroxide solution-ethanol (4:1) as a blank and measure the absorbances of the resulting solutions at 238 nm (Appendix IV A). Calculate the content of $C_{15}H_{24}O_5$.

Category As described under Dihydroartemisinin.

Strength 20 mg

Storage Preserve in tightly closed containers, stored in a dry place and protected from light.

Diltiazem Hydrochloride



$C_{22}H_{26}N_2O_4S \cdot HCl$ 450.99

[33286-22-5]

Diltiazem Hydrochloride is (+) - cis - 5 - [2-(dimethylamino) ethyl]-2-(4-methoxyphenyl)-3-(acetoxy) - 2,3 - dihydro - 1,5-benzothiazepin-4 (5H)-one Hydrochloride. It contains not less than 98.5% of $C_{22}H_{26}N_2O_4S \cdot HCl$, calculated on the dried basis.

Description White or almost white crystals or a crystalline powder; odourless; taste, bitter. Freely soluble in water, methanol or chloroform; practically insoluble in ether or benzene.

Melting range 210-215°C, with decomposition (Appendix VI C).

Specific optical rotation +115° to +120°, in a solution of 10 mg per ml in water (Appendix VI E).

Identification (1) Dissolve about 50 mg in 1 ml of hydrochloric acid solution (9→100), add 1 ml of ammonium thiocyanate TS, 1 ml of 2.8% cobaltous nitrate solution and 5 ml of chloroform, shake thoroughly. Allow to stand, a blue colour is produced in the chloroform layer.

(2) The light absorption of a 10 μ g per ml solution in hydrochloric acid solution (0.01 mol/L) exhibits a maximum at 236 nm (Appendix IV A).

(3) The infrared absorption spectrum (Appendix IV C) is concordant with the reference spectrum of diltiazem hydrochloride (Appendix XVI).

(4) Carry out the method of Oxygen flask combustion (Appendix VII C), using about 30 mg, with 20 ml of water as absorbing liquid. The solution yields the reaction characteristic of sulfates (Appendix III).

(5) The aqueous solution yields the reaction characteristic of chlorides (Appendix III).

Acidity Dissolve 0.20 g in 20 ml of water, pH 4.3-5.3 (Appendix VI H).

Clarity of solution Dissolve 1.0 g in 20 ml of water, the solution is clear.

Sulfate Carry out the limit test for sulfates (Appendix VII B), using 1.0 g. Any opalescence produced is not more intense than that of a reference using 2.4 ml of potassium sulfate standard solution (0.024%).

Related substances Carry out the method described under the Assay of Diltiazem Hydrochloride Tablets. Dissolve the substance being examined in the mobile phase to produce a solution of (1) 1.0 mg per ml, (2) 5.0 µg per ml. Carry out the method described under Assay for Diltiazem Hydrochloride Tablets. Inject 20 µl of solution (2) into the column, adjust the attenuation so that the principal peak height is about 20% of the full scale of the chart. Inject separately 20 µl each of solution (1) and (2) into the column, record the chromatogram for twice the retention time of the principal peak; the sum of peak areas of the solution (1) due to impurities is not greater than that of the principal peak area of the solution (2).

Loss on drying When dried to constant weight at 105°C, loses not more than 0.5% of its weight (Appendix VIII L).

Residue on ignition Not more than 0.1% (Appendix VIII N).

Heavy metals Carry out the limit test for heavy metals (Appendix VIII N, method 2), using 2.0 g; not more than 0.001%.

Arsenic To 1.0 g in a 100 ml Kjeldahl flask add 5 ml of nitric acid and 2 ml of sulfuric acid, cover the mouth of the flask with a small funnel, heat cautiously until white fumes are evolved. Cool, add 2 ml of nitric acid and heat again, repeat the addition of nitric acid and heating once more, then add 2 ml of strong hydrogen peroxide solution and heat, repeat the addition of hydrogen peroxide solution and heating until the solution is colourless or faintly yellowish. Cool, add 2 ml of saturated ammonium oxalate solution, heat until white fumes are evolved again. Cool, add water to 5 ml and carry out the limit test for arsenic (Appendix VIII J, method 1); not more than 0.0002%.

Assay Dissolve about 0.3 g, accurately weighed, in 2 ml of anhydrous formic acid, add 30 ml of acetic anhydride, 5 ml of mercuric acetate TS and 2 drops of naphtholbenzein IS. Titrate with perchloric acid (0.1 mol/L) VS until the colour changes to green. Perform a blank determination and make any necessary correction. Each ml of perchloric acid (0.1 mol/L) VS is equivalent to 45.10 mg of $C_{22}H_{26}N_2O_4S \cdot HCl$.

Category Calcium channel blocker.

Storage Preserve in tightly closed containers, protected from light.

Preparation Diltiazem Hydrochloride Tablets

Diltiazem Hydrochloride Tablets

Diltiazem Hydrochloride Tablets contain not less

than 93.0% and not more than 107.0% of the labelled amount of diltiazem hydrochloride ($C_{22}H_{26}N_2O_4S \cdot HCl$).

Description White tablets.

Identification (1) To a quantity of the powdered tablets equivalent to 60 mg of diltiazem hydrochloride, add 10 ml of hydrochloric acid solution (9→100), shake thoroughly to dissolve diltiazem hydrochloride and filter. The filtrate complies with test (1) for Identification described under Diltiazem Hydrochloride.

(2) Dilute 1 ml of the filtrate obtained in the test for Identification (1) with water to 500 ml, mix well. The light absorption of the solution exhibits a maximum at 236 nm (Appendix IV A).

(3) The retention time of the principal peak of the substance being examined in the chromatogram obtained in the Assay is concordant with that of diltiazem hydrochloride CRS.

Related substances Dissolve the substance being examined in ethanol to produce solutions of (1) 1.0 mg per ml, (2) 5.0 µg per ml. Carry out the method described under Assay. Inject 20 µl of solution (2) into the column, adjust the attenuation so that the principal peak height is 20% of the full scale of the chart. Inject separately 20 µl each of solution (1) and (2) into the column, record the chromatogram for twice the retention time of the principal peak. The sum of the areas of all peaks other than the principal peak obtained with solution (1) is not greater than twice of the area of the principal peak obtained with solution (2).

Content uniformity Comply with the requirements (Appendix X E). Dissolve 1 tablet in a 100 ml volumetric flask in 50 ml of ethanol with ultrasonic treatment, dilute to volume with ethanol and mix well. Filter, dilute a quantity of the successive filtrate, accurately measured, with ethanol to produce a solution of 0.1 mg per ml as test solution. Carry out the method described under Assay using the resulting solution.

Dissolution Carry out the dissolution test (Appendix X C, method 2), using 900 ml of water as the dissolution medium, adjust the rotational speed of the paddle to 75 rpm. Withdraw 10 ml of the solution at exact 30 minutes and 180 minutes respectively and add immediately 10 ml of the water to the vessel to compensate the volume. Filter and dilute the successive filtrate with water as the test solution, to produce two solutions of 8 µg per ml respectively. Dissolve a quantity of diltiazem hydrochloride CRS, in water to produce a solution of 8 µg per ml and use it as the reference solution. Measure the absorbance of the solutions at 240 nm separately (Appendix IV A), calculate the dissolution of diltiazem hydrochloride each tablet for 6 tablets. The amount of diltiazem hydrochloride dissolved in 30 minutes not more than 60% and in 180 minutes not less than 80%.

Other requirements Comply with the general requirements for tablets (Appendix I A).

Assay Carry out the method for high performance liquid chromatography (Appendix V D), using a column of octadecylsilane bonded silica gel and a mixture of buffer solution (Dissolve 1.16 g of *d*-Camphor sulfonic acid in 0.01 mol/L sodium acetate solution and dilute to 1000 ml, adjust pH to 6.2 with 0.01 mol/L sodium hydroxide solution)-acetonitrile-methanol (50 : 25 : 25) as the mobile phase. Detection wavelength is 240 nm and the number of theoretical plates is not less than 1200; calculated with reference to diltiazem.

Procedure Weigh accurately and powder 20 tablets. To an accurately weighed quantity of the powder equivalent to 10 mg of diltiazem hydrochloride in a 100 ml volumetric flask,

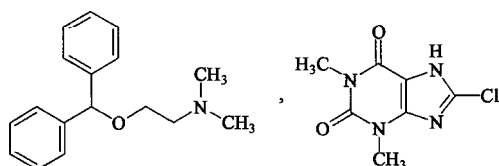
add 50 ml of ethanol, dissolve diltiazem hydrochloride with ultrasonic treatment for 10 minutes, Dilute to volume with ethanol, mix well and filter. Inject 20 μ l of the successive filtrate into the column and record the chromatogram. Dissolve a quantity of accurately weighed diltiazem hydrochloride CRS in ethanol and dilute to produce a solution of about 0.10 mg per ml. Inject 20 μ l of the resulting solution into the column and calculate the content of $C_{22}H_{26}N_2O_4S \cdot HCl$ with respect to the peak area obtained in the chromatogram by the external standard method.

Category As described under Diltiazem Hydrochloride.

Strength (1) 30 mg (2) 45 mg (3) 60 mg
(4) 90 mg (5) 120 mg

Storage Preserve in tightly closed containers, protected from light.

Dimenhydrinate



$C_{24}H_{28}ClN_5O_3$ 469.97

[523-87-5]

Dimenhydrinate is 8-chloro-3,7-dihydro-1,3-dimethyl-1H-purine-2,6-dione, compound with 2-(diphenylmethoxy)-N,N-dimethylethanamine (1 : 1). It contains not less than 53.0% and not more than 55.5% of diphenhydramine ($C_{17}H_{21}NO$), and not less than 44.0% and not more than 47.0% of 8-chlorotheophylline ($C_7H_7ClN_4O_2$), calculated on the dried basis.

Description A white, crystalline powder; odourless. Freely soluble in ethanol or chloroform; slightly soluble in water or ether.

Melting range 102-107°C (Appendix VI C).

Identification (1) Dissolve about 0.2 g in 15 ml of dilute ethanol in a separator, add a mixture of 15 ml of water and 2 ml of concentrated ammonia solution and extract with 20 ml of ether. Wash the extract with 5 ml of water, discard the water layer. To the ether layer add 5 ml of dilute hydrochloric acid, shake well and allow to stand. Separate the acid layer, expel the residual ether with a current of air. Add 10 ml of water and add dropwise trinitrophenol TS with vigorous stirring until crystallisation is complete, filter. The crystals, after recrystallisation from ethanol and dried at 80°C for 30 minutes, melt at 128-132°C (Appendix VI C). (2) To 0.1 g add 1 ml of hydrochloric acid and 0.1 g of potassium chlorate, and evaporate to dryness on a water bath. Add a few drops of ammonia TS to the residue, a purple colour is produced.

(3) The infrared absorption spectrum (Appendix VI C) is concordant with the reference spectrum of dimenhydrinate (Appendix XVI)

Related Substances Carry out the method for high performance liquid Chromatography (Appendix X D), using a column packed with octadecylsilane bonded silica gel and a mixture of methanol-triethylamine BS (1:1) as mobile phase. Detection wavelength is 225 nm, and the number of theoretical plates of the column is not less than 2000,

calculated with reference to the peaks of diphenhydramine. Dissolve a quantity of substance being examined in mobile phase to produce two solutions of 0.4 mg per ml (test solution) and 6 μ g per ml (reference solution), respectively. Inject 10 μ l of the reference solution into the column, adjust the attenuation so that the height of the peak corresponding 8-chlorotheophylline is not less than 10% of the full scale of the chart. Inject separately 10 μ l each of the test solution and the reference solution, both accurately measured, into the column, record the chromatogram for twice the retention time of principal peak of diphenylhydramine. The sum of peak areas due to the impurities is not greater than the principal peak area of the reference solution.

Chloride To 0.30 g in a 200 ml volumetric flask add 50 ml of water, 3 ml of ammonia TS and 6 ml of 10% ammonium nitrate solution and heat on a water bath for 5 minutes. Add accurately 25 ml of silver nitrate (0.1 mol/L) VS, shake well and heat again on a water bath for 15 minutes with frequent shaking. Cool, dilute with water to volume, mix well and allow to stand for 15 minutes. Filter the solution with a piece of dry filter paper and discard the initial filtrate. To 25 ml of the successive filtrate in a 50 ml Nessler cylinder and 10 ml of dilute nitric acid and dilute with water to 50 ml, mix well. Allow the solution to stand in the dark place for 5 minutes. Carry out the limit test for chlorides (Appendix VIII A). Any opalescence produced is not more pronounced than that of a reference using 1.5 ml of sodium chloride standard solution (0.04%).

Loss on drying When dried in vacuum over phosphorous pentoxide to constant weight, loses not more than 0.5% of its weight (Appendix VIII L).

Residue on ignition Not more than 0.1% (Appendix VIII N); using 1.0 g.

Heavy metals Carry out the limit test for heavy metals (Appendix VIII H, method 2), using the residue obtained in Residue on ignition; not more than 0.001%.

Assay diphenhydramine Dissolve about 0.3 g, accurately weighed, in 15 ml of glacial acetic acid by warming gently. Cool, add 1 drop of crystal violet IS and titrate with perchloric acid (0.1 mol/L) VS until the colour changes to blue. Perform a blank determination and make any necessary correction. Each ml of perchloric acid (0.1 mol/L) VS is equivalent to 25.54 mg of $C_{17}H_{21}NO$.

8-chlorotheophylline To 0.3 g, accurately weighed, in a 200 ml volumetric flask, add 50 ml of water, 3 ml of ammonia TS and 6 ml of 10% ammonium nitrate solution, warm on a water bath for 5 minutes. Add accurately 25 ml of silver nitrate (0.1 mol/L) VS, mix well, and warm on a water bath for 15 minutes with shaking, cool, add water to volume, mix well, and allow to stand for 15 minutes. Filter and discard the initial filtrate. Measure accurately 100 ml of the successive filtrate, acidify with nitric acid, add further 3 ml of nitric acid and 2 ml of ferric ammonium sulfate IS, titrate with ammonium thiocyanate (0.1 mol/L) VS. Each ml of silver nitrate (0.1 mol/L) VS is equivalent to 21.46 mg of $C_7H_7ClN_4O_2$.

Category Antihistamine agent.

Storage Preserve in tightly closed containers, stored in a dry place.

Preparation Dimenhydrinate Tablets

Dimenhydrinate Tablets

Dimenhydrinate Tablets contain not less than 90.0% and not more than 110.0% of the labelled amount of dimenhydrinate ($C_{24}H_{28}ClN_5O_3$). The content of 8-chlorotheophylline ($C_7H_7ClN_4O_2$) is not less than 4.4% and not more than 4.9% of the content of dimenhydrinate.

Description White tablets.

Identification (1) Triturate a quantity of the powdered tablets equivalent to about 0.4 g of dimenhydrinate with 40 ml of warm ethanol, filter and evaporate the filtrate to dryness. The residue complies with tests for Identification described under Dimenhydrinate.

(2) In the Assay, the retention time of the two principal peaks in the chromatogram obtained with the test preparation corresponds with that of the two principal peaks in the chromatogram obtained with the reference preparation.

Dissolution Carry out the dissolution test (Appendix X C, method 2), using 900 ml of water as the dissolution medium, adjust the rotational speed of the paddle to 50 rpm. Withdraw 10 ml of the solution at exact 45 minutes and filter. Transfer accurately 5 ml of the successive filtrate into a 20 ml (for strength 50 mg) or 10 ml (for strength 25 mg) volumetric flask and dilute with water to volume, shake well. Measure the absorbance at 278 nm (Appendix IV A). Dissolve a quantity of dimenhydrinate CRS, weighed accurately, in water to produce a solution of about 14 µg per ml and measure the absorbance at 278 nm. Calculate the dissolution of $C_{18}H_{20}O_2$ from each tablet. Not less than 75% of the labelled amount is dissolved.

Other requirements Comply with the general requirements for tablets (Appendix I A).

Assay Carry out the method for high performance liquid chromatography (Appendix X D), using a column packed with octadecylsilane bounded silica gel and a mixture of methanol-triethylamine BS (1 : 1) as the mobile phase. Detection wavelength is 225 nm, and the number of theoretical plates of the column is not less than 2000, calculated with reference to the peak of diphenhydramine. The resolution factors between the peaks of 8-chlorotheophylline, internal standard and diphenhydramine comply with the related requirements.

Internal Standard Solution Dissolve about 0.1 g of anisic acid in 10 ml of methanol in a 250 ml volumetric flask and dilute with the mobile phase to volume, mix well.

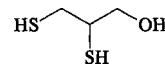
Procedure Dissolve a quantity of dimenhydrinate CRS, accurately weighed, in the internal standard solution to produce a solution of about 0.4 mg per ml. Inject 5-10 µl into the column. Calculate the response factor, taking 45.7 as the percentage of 8-chlorotheophylline in dimenhydrinate. Weigh accurately and powder 20 tablets. To an accurately weighed quantity of the powder equivalent to about 20 mg of dimenhydrinate in a 50 ml volumetric flask, add a quantity of internal standard solution and subject to ultrasonic treatment. Add internal standard solution to volume, mix well and filter. Discard the initial filtrate and inject 5-10 µl of the successive filtrate into the column. Calculate the content of $C_7H_7ClN_4O_2$ and that of $C_{24}H_{28}ClN_5O_3$ in the tablets.

Category As described under Dimenhydrinate.

Strength (1) 25 mg (2) 50 mg

Storage Preserve in tightly closed containers, stored in a dry place.

Dimercaprol



$C_3H_8OS_2$ 124.23

[59-52-9]

Dimercaprol is 2,3-dimercapto-1-propanol. It contains not less than 98.5% (g/g) of $C_3H_8OS_2$.

Description A colourless or almost colourless, mobile, clear liquid; odour, characteristic, alliaceous.

Very soluble in methanol, ethanol or benzyl benzoate; soluble in water; insoluble in fatty oil; miscible with fatty oils when dissolved in benzyl benzoate.

Relative density 1.235-1.255 at 25°C (Appendix VI A).

Identification (1) Mix 1 drop in 2 ml of water, add a few drops of lead acetate TS; a yellow precipitate is produced.

(2) Heat with sodium carbonate; an odour of acrolein is perceptible.

(3) The infrared absorption spectrum (Appendix IV C) is concordant with the reference spectrum of dimercaprol (Appendix XVI).

Stability Heat at 140°C for 2 hours, carry out the procedure described under Assay, loses not more than 4.0% of the content.

Acidity Shake 1.0 g with 10 ml of water to prepare a saturated solution and filter; pH 5.0-7.0 (Appendix VI H).

Bromine Weigh 40 mg on an ashless filter paper, carry out the method for oxygen flask combustion (Appendix VII C), using a mixture of 15 ml of 2.0% sodium hydroxide solution and 15 drops of 30% hydrogen peroxide solution as the absorbing liquid. When the combustion is complete, wash the stopper and the platinum wire with 20 ml of water. Combine the washing with the absorbing liquid, boil for 2 minutes and cool. Transfer the solution to a 50 ml Nessler cylinder, neutralize with nitric acid solution (1→2) and add 2 ml of nitric acid solution in excess. Then add 1.0 ml of silver nitrate TS and water to produce 50 ml, mix well and allow to stand in a dark place for 10 minutes. Any opalescence produced is not more pronounced than that of a reference solution prepared in the same manner, using 4.0 ml of sodium bromide standard solution (dissolve 12.88 mg of sodium bromide in water to produce 1000 ml. Each ml is equivalent to 10 µg of Br) in place of the substance being examined (0.10%).

Assay Mix about 0.1 g, accurately weighed, with 10 ml of ethanol. Titrate with iodine (0.05 mol/L) VS until the solution becomes persistently pale yellow. Perform a blank determination and make any necessary correction. Each ml of iodine (0.05 mol/L) VS is equivalent to 6.211 mg of $C_3H_8OS_2$.

Category Antidote.

Storage Preserve in tightly closed containers, protected from light.

Preparation Dimercaprol Injection

Dimercaprol Injection

Dimercaprol Injection is a sterile solution of dimercaprol in oil. It contains not less than 95.0% and not more than 105.0% of the labelled amount of dimercaprol ($C_3H_8OS_2$).

Benzyl benzoate is added as a solubilizing agent.

Description A clear, colourless to pale yellow, oily liquid.

Identification Shake 0.3 ml with 10 ml of water and add a few drops of lead acetate TS; a yellow precipitate is produced.

Other requirements Complies with the general requirements for injections (Appendix I B).

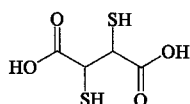
Assay Transfer 1 ml, accurately measured with a "to contain" pipet to a conical flask, wash the inner wall of the pipet with 10 ml, in portions, of a mixture of chloroform-dehydrated ethanol (1:3) add the washings to the conical flask and mix well. Titrate with iodine (0.05 mol/L) VS until the solution becomes persistently pale yellow. Perform a blank determination and make any necessary correction. Each ml of iodine (0.05 mol/L) VS is equivalent to 6.211 mg of $C_3H_8OS_2$.

Category As described under Dimercaprol.

Strength (1) 1 ml:0.1 g (2) 2 ml:0.2 g

Storage Preserve in well closed containers, protected from light.

Dimercaptosuccinic Acid



$C_4H_6O_4S_2$ 182.22

[304-55-2]

Dimercaptosuccinic Acid is 2,3-dimercaptosuccinic acid. It contains not less than 98.5% of $C_4H_6O_4S_2$, calculated on the dried basis.

Description White or almost white crystals or a crystalline powder; with an odour resembling that of mercapto compound. Slightly soluble in methanol or ethanol; practically insoluble in water or chloroform.

Melting range 190-194°C, with decomposition (Appendix VI C).

Identification (1) To about 0.2 g add 2 ml of water and a quantity of sodium bicarbonate TS to dissolve the substance being examined and make the solution neutral, add 1 ml of lead acetate TS; a pale yellow precipitate is produced.

(2) To about 0.2 g add 2 ml of water and a quantity of sodium hydroxide TS to dissolve the substance being examined and make the solution alkaline, add dropwise sodium nitroprusside TS; a violet-red colour is produced.

(3) The infrared absorption spectrum (Appendix IV C) is concordant with the reference spectrum of dimercaptosuccinic acid (Appendix XVI).

Acidity A suspension of 1.0 g in 20 ml of water, pH 2.5-3.0 (Appendix VI H).

Loss on drying When dried to constant weight at 105°C,

loses not more than 1.0 % of its weight (Appendix VIII L).

Residue on ignition Not more than 0.1 % (Appendix VIII N), using 1.0 g.

Heavy metals Carry out the limit test for heavy metals (Appendix VIII H, method 2), using the residue obtained in the test for Residue on ignition; not more than 0.001 %.

Assay Weigh accurately about 0.05 g into a conical flask with stopper, add 30 ml of ethanol to dissolve the substance being examined. Add 2 ml of diluted nitric acid, and 25 ml of silver nitrate (0.1 mol/L) VS, accurately measured, shake vigorously. Heat in a water bath for 2 to 3 minutes, cool, and filter. Wash the conical flask and precipitate with water until the washings yield no reaction characteristic of silver. Combine the filtrate and washings, add 2 ml of nitric acid and 2 ml of ferric ammonium sulfate IS, titrate with ammonium thiocyanate (0.1 mol/L) VS. Perform a blank determination and make any necessary correction. Each ml of silver nitrate (0.1 mol/L) VS is equivalent to 4.556 mg of $C_4H_6O_4S_2$.

Category Antidote.

Storage Preserve in tightly closed containers, protected from light and stored in a cool place.

Preparation Dimercaptosuccinic Acid Capsules

Dimercaptosuccinic Acid Capsules

Dimercaptosuccinic Acid Capsules contain not less than 90.0 % and not more than 110.0 % of the labelled amount of dimercaptosuccinic acid ($C_4H_6O_4S_2$).

Identification A quantity of the contents of the capsules equivalent to about 200 mg of dimercaptosuccinic acid complies with the test (1) and (2) for Identification described under Dimercaptosuccinic Acid.

Loss on drying The contents of the capsules, when dried to constant weight at 105°C, loses not more than 1.0 % of their weight (Appendix VIII L).

Other requirements Comply with the general requirements for capsules (Appendix I E).

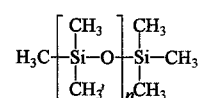
Assay Weigh accurately a quantity of the mixed contents in the test for Weight variation equivalent to about 50 mg of dimercaptosuccinic acid, carry out the method for Assay described under Dimercaptosuccinic Acid. Each ml of silver nitrate (0.1 mol/L) VS is equivalent to 4.556 mg of $C_4H_6O_4S_2$.

Category As described under Dimercaptosuccinic Acid.

Strength 0.25 g

Storage Preserve in tightly closed containers, protected from light and stored in a cool and dry place.

Dimethicone



[9006-65-9]

Dimethicone is a polymer of dimethylsiloxane.

Description A clear, colourless oily liquid; odourless or almost odourless; tasteless. Miscible with chloroform, ether, benzene, toluene or xylene; insoluble in water or ethanol.

Relative density 0.970-0.980 (Appendix VI A).

Refractive index 1.400-1.410 (Appendix VI F).

Viscosity Kinematic viscosity 500-1000 mm²/s, at 25°C (Appendix VI G, method 1, using a capillary tube; 2 mm in internal diameter).

Identification (1) Ignite gently 0.5 g with 0.5 ml each of sulfuric acid and nitric acid in a crucible. A white fibrous matter is formed and finally a white residue is produced.

(2) The infrared absorption spectrum (Appendix IV C) is concordant with the reference spectrum of dimethicone (Appendix XVI).

Acidity or alkalinity Mix 5 ml each of ethanol and chloroform, add 1 drop of phenolphthalein IS, and sodium hydroxide (0.02 mol/L) VS dropwise until a slight pink colour is produced. Add 1.0 g of the substance being examined and mix well. If the solution is colourless, add 0.15 ml of sodium hydroxide (0.02 mol/L) VS, a pink colour is produced; if the colour of the solution is pink, add 0.15 ml of sulfuric acid (0.01 mol/L) VS, the colour disappears.

Loss on drying When dried to constant weight at 150°C for 3 hours, loses not more than 1.0% of its weight (Appendix VIII L).

Category Antifoaming agent.

Storage Preserve in tightly closed containers.

Preparation (1) Dimethicone Aerosol
(2) Dimethicone Tablets

Dimethicone Aerosol

Dimethicone Aerosol contains not less than 80.0% and not more than 120.0% of the labelled amount of dimethicone. The concentration of dimethicone in the liquid is not less than 0.65% (g/g) and not more than 1.00% (g/g).

Description A clear, colourless to pale yellow liquid with an odour resembling that of peppermint.

Identification The oily liquid obtained in the Assay complies with test (2) for Identification described under Dimethicone.

Other requirements Complies with the general requirements for aerosols, powders for spray and preparations for nebulisation except total number of discharge per container, content of active ingredient in a unit spray and deposition of the emitted dose (Appendix I L).

Assay To 3 containers, weigh accurately, punch a small hole on the aluminium cover and insert syringe needle connecting to a rubber tubing, but does not contact the liquid surface. Dip the other end of the tubing in water to expel the propellants slowly. Remove the aluminium covers and transfer the contents of each container separately to 3 evaporating dishes previously dried to constant weight at 110°C with a small quantity of chloroform. Wash each container with 20 ml of chloroform in portions, transfer the washings to the evaporating dish, evaporate on a water bath and dry to constant weight at 110°C, and weigh accurately to calculate the weight of dimethicone in each container. Wash

and dry the container valve and aluminium cover, and weigh accurately to get the weight of the contents of each container. Calculate the concentration of dimethicone in g/g. The results comply with the requirements.

Category As described under Dimethicone.

Strength Total amount of each container, 18 g, containing 0.15 g of dimethicone

Storage Preserve in well closed containers, stored in a dark and cool place.

Dimethicone Tablets

Dimethicone Tablets contain not less than 90.0% and not more than 110.0% of the labelled amount of dimethicone; not less than 45.0% of the labelled amount of aluminium hydroxide calculated as aluminium oxide (Al₂O₃).

Formula	Dimethicone	50 g
	Aluminium hydroxide	80 g
	Glucose	600 g
	To make	1000 tablets (50 mg) or 2000 tablets (25 mg)

Description White or almost white tablets.

Identification (1) The oily liquid obtained in the Assay complies with tests of Identification described under Dimethicone.

(2) Dissolve a quantity of powdered tablets equivalent to about 0.5 g of aluminium hydroxide with 10 ml of dilute hydrochloric acid by heating and filter. The filtrate yields the reactions characteristic of aluminium salts (Appendix III).

Other requirements Comply with the general requirements for tablets (Appendix I A).

Assay *Dimethicone* Weigh accurately and powder 20 tablets (50 mg strength) or 40 tablets (25 mg strength). Extract a quantity of the powder equivalent to about 0.2 g of dimethicone with 8 quantities of 15 ml of chloroform. Combine the extracts, filter and wash the residue with chloroform, evaporate the combined filtrate and washing to dryness in a crucible, dried previously at 110°C to constant weight, on a water bath. Dry the residue to constant weight at 110°C and weigh accurately. Calculate the content of dimethicone.

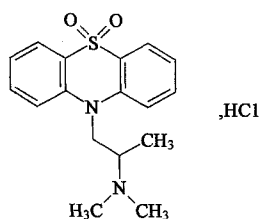
Aluminium oxide To a quantity, accurately weighed, of the above powder equivalent to about 0.4 g of aluminium hydroxide add 10 ml each of hydrochloric acid and water. Heat on a water bath for 5 minutes to produce a solution, allow it to cool and filter. Transfer the filtrate to a 100 ml volumetric flask, wash the residue with water and combine the washings with the filtrate, dilute with water to volume and shake well. Carry out the Assay described under Aluminium Hydroxide, using 20 ml, accurately measured, of the resulting solution, beginning at the words "neutralize with ammonia TS until a precipitate is just produced...". Calculate the content. Each ml of disodium edetate (0.05 mol/L) VS is equivalent to 2.549 mg of Al₂O₃.

Category As described under Dimethicone.

Strength (1) 25 mg (2) 50 mg

Storage Preserve in tightly closed containers, stored at dry place.

Dioxopromethazine Hydrochloride



$C_{17}H_{20}N_2O_2S \cdot HCl$ 352.88

Dioxopromethazine Hydrochloride is 10-(2-Dimethylamino-isopropyl) phenothiazine-5, 5-dioxide monohydrochloride. It contains not less than 99.0% of $C_{17}H_{20}N_2O_2S \cdot HCl$, calculated on the dried basis.

Description A white to slightly yellow powder or crystalline powder; odourless; taste, bitter. Soluble in water; very slightly soluble in ethanol.

Specific absorbance Measure the absorbance of a solution of 10 μg per ml in hydrochloric acid solution (0.1 mol/L) at 264 nm (Appendix IV A), the value of A (1%, 1 cm) is 350-370.

Identification (1) The light absorption of a solution of 10 μg per ml in hydrochloric acid (0.1 mol/L) exhibits four maxima at 227 nm, 264 nm, 290.5 nm and 328 nm; the absorbance at 328 nm is 0.15-0.18 (Appendix IV A). (2) The infrared absorption spectrum (Appendix IV C) is concordant with the reference spectrum of dioxopromethazine hydrochloride (Appendix XVI). (3) The aqueous solution yields the reactions characteristic of chlorides (Appendix III).

Acidity Dissolve 0.5 g in 25 ml of water, pH 4.2-5.1 (Appendix VI H).

Clarity and colour of solution Dissolve 0.2 g in 10 ml of water, the solution is clear and colourless or almost clear and colourless.

Sulfate Carry out the limit test for sulfates (Appendix VIII B), using 1.2 g. Any opalescence produced is not more pronounced than that of the reference solution using 3 ml of potassium sulfate standard solution (0.025%).

Related substances Carry out the method for thin-layer chromatography (Appendix V B), using silica gel GF₂₅₄ as the coating substance and a mixture of toluene-acetone-concentrated ammonia solution (70 : 29 : 1) as the mobile phase. Apply separately to the plate 20 μl of each of two solutions in methanol containing (1) 10 mg, (2) 50 μg of the substance being examined per ml. After developing and removal of the plate, dry it in air and examine under ultraviolet light at 254 nm. Any spot, other than the principal spot, in the chromatogram obtained with solution (1) is not more intense than the principal spot obtained with solution (2).

Loss on drying When dried to constant weight at 105°C, loses not more than 0.5% of its weight (Appendix VIII L).

Residue on ignition Not more than 0.1% (Appendix VIII N), use 1.0 g.

Heavy metals Carry out the limit test for heavy metals (Appendix VIII H, method 2), using the residue obtained in the test for Residue on ignition; not more than 0.001%.

Assay Dissolve about 0.3 g, accurately weighed, in 25 ml of glacial acetic acid and 10 ml of mercuric acetate TS by warming, cool to room temperature, add 1-2 drop of crystal violet IS, titrate with perchloric acid (0.1 mol/L) VS until the colour changes to blue. Perform a blank determination and make any necessary correction. Each ml of perchloric acid (0.1 mol/L) VS is equivalent to 35.29 mg of $C_{17}H_{20}N_2O_2S \cdot HCl$.

Category Antitussive.

Storage Preserve in tightly closed containers, protected from light.

Preparation Dioxopromethazine Hydrochloride Tablets

Dioxopromethazine Hydrochloride Tablets

Dioxopromethazine Hydrochloride Tablets contain not less than 90.0% and not more than 110.0% of the labelled amount of dioxopromethazine hydrochloride ($C_{17}H_{20}N_2O_2S \cdot HCl$).

Description Sugar-coated tablets with white core.

Identification (1) The light absorption of the solution obtained in Assay exhibits four maxima at 227 nm, 264 nm, 290.5 nm and 328 nm (Appendix IV A).

(2) The aqueous solution yields the reactions characteristic of chlorides (Appendix III).

Content of uniformity Comply with the requirements (Appendix X E). Triturate 1 tablet with 40 ml of hydrochloric acid solution (0.1 mol/L) in portions and transfer to a 50 ml volumetric flask, shake for 15 minutes, add hydrochloric acid solution (0.1 mol/L) to volume, shake thoroughly and filter. Discard the initial filtrate, transfer accurately 5 ml of the successive filtrate to another 50 ml volumetric flask, dilute with hydrochloric acid solution (0.1 mol/L) to volume and mix well. Measure the absorbance of the resulting solution at 264 nm (Appendix IV A), calculate the content of $C_{17}H_{20}N_2O_2S \cdot HCl$, taking 362 as the value of A (1%, 1 cm).

Other requirements Comply with the general requirements for tablets (Appendix I A).

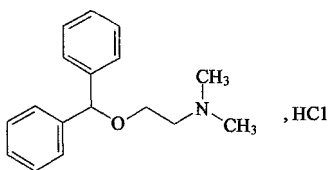
Assay To 12 tablets in a 200 ml volumetric flask add 150 ml of hydrochloric acid solution (0.1 mol/L), shake to dissolve dioxopromethazine hydrochloride, dilute with hydrochloric acid solution (0.1 mol/L) to volume and mix well. Filter, discard the initial filtrate, transfer accurately 5 ml of the successive filtrate to a 100 ml of volumetric flask, dilute with hydrochloric acid solution (0.1 mol/L) to volume and mix well. Measure the absorbance of the resulting solution at 264 nm (Appendix IV A), calculate the content of $C_{17}H_{20}N_2O_2S \cdot HCl$, taking 362 as the value of A (1%, 1 cm).

Category As described under Dioxopromethazine Hydrochloride.

Strength 5 mg

Storage Preserve in tightly closed containers, protected from light.

Diphenhydramine Hydrochloride



$C_{17}H_{21}NO \cdot HCl$ 291.82

[147-24-0]

Diphenhydramine Hydrochloride is *N,N*-dimethyl-2-(diphenyl-methoxy)-ethanamine hydrochloride. It contains not less than 99.0% of $C_{17}H_{21}NO \cdot HCl$, calculated on the dried basis.

Description A white crystalline powder; odourless; taste, bitter and numbing.

Very soluble in water; freely soluble in ethanol or chloroform; sparingly soluble in acetone; very slightly soluble in ether or benzene.

Melting range 167-171°C (Appendix VI C).

Identification (1) To 5 mg add 1 drop of sulfuric acid; a yellow colour, then orange-red, is produced; forms white opalescence on adding water dropwise.

(2) Dissolve 30 mg in 1 ml of water, add 1 ml of hydrochloric acid; a white opalescence is produced, which turns to an oily liquid on boiling and forms a white waxy solid on cooling.

(3) The aqueous solution forms white curdy precipitate on adding silver nitrate TS dropwise.

(4) The light absorption of a 0.5 mg per ml solution in hydrochloric acid solution (0.01 mol/L) exhibits maxima at 253 nm and 258 nm (Appendix IV A).

(5) The infrared absorption spectrum (Appendix IV C) is concordant with the reference spectrum of diphenhydramine hydrochloride (Appendix XVI).

Related substances Carry out the method for thin-layer chromatography (Appendix V B), using silica gel H as the coating substance and a mixture of chloroform-methanol (8:2) as the mobile phase. Apply separately to the plate 5 μ l each of two solutions in methanol containing (1) 20 mg per ml, (2) 0.20 mg per ml of the substance being examined. After developing and removal of the plate, dry it in air and spray with dilute potassium iodobismuthate TS. Any spot other than the principal spot in the chromatogram obtained with solution (1) is not more intense than the principal spot obtained with solution (2).

Loss on drying When dried to constant weight at 105°C, loses not more than 0.5% of its weight (Appendix VIII L).

Residue on ignition Not more than 0.1% (Appendix VIII N).

Assay Dissolve about 0.2 g, accurately weighed, in 20 ml of glacial acetic acid and 4 ml of acetic anhydride, add 4 ml of mercuric acetate TS and 1 drop of crystal violet IS, titrate with perchloric acid (0.1 mol/L) VS until the colour changes to bluish green. Perform a blank determination and make any necessary correction. Each ml of perchloric acid (0.1 mol/L) VS is equivalent to 29.18 mg of $C_{17}H_{21}NO \cdot HCl$.

Category Antihistaminic.

Storage Preserve in tightly closed containers.

Preparation (1) Diphenhydramine Hydrochloride Injection

Diphenhydramine Hydrochloride Injection

Diphenhydramine Hydrochloride Injection is a sterile solution of Diphenhydramine Hydrochloride in Water. It contains not less than 95.0% and not more than 105.0% of the labelled amount of diphenhydramine hydrochloride ($C_{17}H_{21}NO \cdot HCl$).

Description A clear, colourless liquid.

Identification The retention time of principal peak of the substance being examined is identical with that of principal peak of the reference solution in the chromatogram obtained in Assay.

pH value 4.0-6.0 (Appendix VI H).

Other requirements Complies with the general requirements for injections (Appendix I B).

Assay Carry out the method for high performance liquid chromatography (Appendix V D), using a column packed with cyano bonded silica gel and a mixture of acetonitrile-water-triethylamine (50:50:0.5) (Adjust pH to 6.5 by glacial acetic acid) as the mobile phase. Detective Wavelength is 258 nm, and the number of theoretical plates of the column is not less than 5000, calculated with reference to the peak of diphenhydramine hydrochloride. The resolution factor between the peaks of diphenhydramine hydrochloride and adjacent impurities should agree with the requirement.

Procedure Transfer a proper quantity equivalent to about 50 mg of diphenhydramine hydrochloride, accurately measured, to a 100 ml volumetric flask, dilute with water to the volume, mix well and filter, take the successive filtrate as the test solution. Inject 20 μ l into the column, record the chromatogram. Dissolve a quantity of diphenhydramine hydrochloride CRS, accurately weighed, in water to produce a solution of about 0.5 mg per ml, repeat the operations instead of the test solution, calculate the content of $C_{22}H_{28}FN_2O_8P$ with respect to the peak area obtained in the chromatogram by the external standard method.

Category As described under Diphenhydramine Hydrochloride.

Strength 1 ml:20 mg

Storage Preserve in tightly closed containers, protected from light.

Diphenhydramine Hydrochloride Tablets

Diphenhydramine Hydrochloride Tablets contain not less than 93.0% and not more than 107.0% of the labelled amount of diphenhydramine hydrochloride ($C_{17}H_{21}NO \cdot HCl$).

Description Sugar-coated or film-coated tablets with white core.

Identification (1) Extract a quantity of the coating removed and powdered tablets equivalent to about 0.1 g of diphenhydramine hydrochloride with 10 ml of chloroform. Filter and evaporate the filtrate to dryness on a water bath. The residue, dried at 80°C, complies with tests (1), (2) and (3) for Identification described under Diphenhydramine Hydrochloride.

(2) The retention time of principal peak of the substance being examined is identical with that of principal peak of the reference solution in the chromatogram obtained in Assay.

Dissolution Carry out the dissolution test (Appendix X C, method 1), using 500 ml of water as the dissolution medium, adjust the rotational speed of the basket to 100 rpm. Withdraw 5 ml of solution at exact 45 minutes and filter. Discard the initial filtrate, use the successive filtrate as the test preparation. Dissolve a quantity of diphenhydramine hydrochloride CRS in water to produce a solution of about 50 µg per ml as the reference solution, proceed as described under the Assay. Inject separately 50 µl each of the test and reference solution into the column and record the chromatogram. Calculate the dissolution of $C_{17}H_{21}NO \cdot HCl$ from each tablet, not less than 70% of the labelled amount is dissolved.

Related substances Extract a quantity of the powdered tablets equivalent to 50 mg of diphenhydramine hydrochloride with chloroform for 3 times, each of 10 ml. Combine the chloroform extracts, filter and evaporate the filtrate to dryness on a water bath. The residue complies with the test for Related substances described under Diphenhydramine Hydrochloride.

Other requirements Comply with the general requirements for tablets (Appendix I A).

Assay Carry out the method for high performance liquid chromatography (Appendix V D), using a column packed with cyano bonded silica gel and a mixture of acetonitrile-water-triethylamine (50:50:0.5) (Adjust pH to 6.5 by glacial acetic acid) as the mobile phase. Detective Wavelength is 258 nm, and the number of theoretical plates of the column is not less than 5000, calculated with reference to the peak of diphenhydramine hydrochloride. The resolution factor between the peaks of diphenhydramine hydrochloride and adjacent impurities should agree with the requirement.

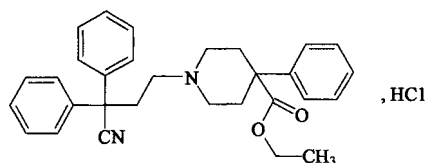
Procedure Weigh accurately and powder 20 tablets removed the coat. To a quantity, weighed accurately, equivalent to about 50 mg of diphenhydramine hydrochloride, to a 100 ml volumetric flask, dissolve and dilute with water to the volume, mix well and filter, take the successive filtrate as the test solution. Inject 20 µl into the volumn, record the chromatogram. Dissolve a quantity of diphenhydramine hydrochloride CRS, accurately weighed, in water to produce a solution of about 0.5 mg per ml, repeat the operations instead of the test solution, calculate the content of $C_{22}H_{23}FN_2O_2 \cdot HCl$ with respect to the peak area obtained in the chromatogram by the external standard method.

Category As described under Diphenhydramine Hydrochloride.

Strength 25 mg

Storage Preserve in tightly closed containers.

Diphenoxylate Hydrochloride



$C_{30}H_{32}N_2O_2 \cdot HCl$ 489.06

[3810-80-8]

Diphenoxylate Hydrochloride is 1-(3,3-diphenylpropyl-3-cyano)-4-phenyl-4-piperidine carboxylic acid ethyl ester hydrochloride. It contains not less than 98.0% of $C_{30}H_{32}N_2O_2 \cdot HCl$, calculated on the dried basis.

Description A white or almost white powder or crystalline powder; odourless.

Freely soluble in chloroform; soluble in methanol; sparingly soluble in ethanol or acetone; practically insoluble in water or ether.

Melting range 221-226°C (Appendix VI C).

Identification (1) The light absorption of a 0.5 mg per ml solution in a mixture of 1 mol/L hydrochloric acid solution methanol (1:99) exhibits maxima at 252 nm, 258 nm and 264 nm. The ratio of absorbance at 258 nm to that at 252 nm is 1.1-1.3 (Appendix IV A).

(2) The infrared absorption spectrum (Appendix IV C) is concordant with the reference spectrum of diphenoxylate hydrochloride (Appendix VI).

(3) The saturated aqueous solution yields the reactions characteristic of chlorides (Appendix III).

Loss on drying When dried to constant weight at 105°C, loses not more than 0.5% of its weight (Appendix VIII L).

Residue on ignition Not more than 0.1% (Appendix VIII N).

Assay Dissolve about 0.4 g, accurately weighed, in 20 ml of glacial acetic acid and 5 ml of mercuric acetate TS, shake thoroughly, add 1 drop of crystal violet IS. Titrate with perchloric acid (0.1 mol/L) VS until the solution becomes blue. Perform a blank determination and make any necessary correction. Each ml of perchloric acid (0.1 mol/L) VS is equivalent to 48.91 mg of $C_{30}H_{32}N_2O_2 \cdot HCl$.

Category Antidiarrhoeal agent.

Storage Preserve in tightly closed containers.

Preparation Compound Diphenoxylate Tablets

Compound Diphenoxylate Tablets

Compound Diphenoxylate Tablets contain 2.25-2.75 mg of diphenoxylate hydrochloride ($C_{30}H_{32}N_2O_2 \cdot HCl$) and 20.0-30.0 µg of atropine sulfate ($C_{17}H_{23}NO_3)_2 \cdot H_2SO_4 \cdot H_2O$ in each tablet.

Formula	Diphenoxylate hydrochloride	2.5 g
	Atropine sulfate	0.025 g

To make	1000 tablets
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Description White tablets.

Identification The retention time of principal peaks of the diphenoxylate hydrochloride and atropine sulfate being examined in the chromatogram obtained in the Assay are identical with that of the diphenoxylate hydrochloride CRS and atropine sulfate CRS.

Content uniformity Comply with the requirements for content uniformity (Appendix X E). Triturate 1 tablet with the mobile phase in the Assay described under Diphenoxylate Hydrochloride in a mortar and transfer with the said mobile phase in portions to a 50 ml volumetric flask, shake thoroughly, dilute to volume with the said mobile phase, mix well and filter. Carry out the Assay described under Diphenoxylate Hydrochloride, using the successive filtrate.

Other requirements Comply with the general requirements for tablets (Appendix I A).

Assay *Diphenoxylate hydrochloride* Carry out the method for high performance liquid chromatography (Appendix V D), using a column packed with octadecylsilane bonded silica gel and a mixture of triethylamine phosphoric acid solution (to 4 ml of triethylamine add 500 ml of water and 2 ml of phosphoric acid,

dilute to 1000 ml with water, mix well)-acetonitrile(45:55), adjust the pH value to 3.1 ± 0.2 , as the mobile phase. Detection wavelength is 230 nm and the number of theoretical plates of the column is not less than 2000, calculated with reference to the peak of diphenoxylate hydrochloride.

Procedure Weigh accurately and powder 50 tablets. Dissolve an accurately weighed quantity of the powdered tablets equivalent to about 2.5 mg of Diphenoxylate hydrochloride in 50 ml volumetric flask with a quantity of the mobile phase, shake thoroughly. Dilute with the mobile phase to volume, mix well and filter. Inject accurately 20 μ l of the successive filtrate into the column. Dilute an accurately weighed quantity of diphenoxylate hydrochloride CRS with mobile phase to produce a solution of 50 μ g per ml. Repeat the operation, calculate the content of $C_{30}H_{32}N_2O_2 \cdot HCl$ with respect to the peak area obtained in the chromatogram by the external standard method.

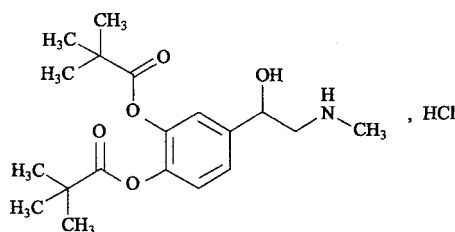
Atropine sulfate Carry out the method for high performance liquid chromatography (Appendix V D), using a column packed with octadecylsilane bonded silica gel and a mixture of triethylamine phosphoric acid solution (to 4 ml of triethylamine add 500 ml of water and 1.8 ml of phosphoric acid, dilute to 1000 ml with water, mix well)-acetonitrile(85:15), adjust the pH value to 5.8 ± 0.2 , as the mobile phase. Detection wavelength is 206 nm and the number of theoretical plates of the column is not less than 3000, calculated with reference to the peak of Atropine sulfate.

Procedure Dissolve an accurately weighed quantity of the powdered tablets equivalent to about 0.5 mg of Atropine sulfate in 50 ml volumetric flask with a quantity of the mobile phase, shake thoroughly. Dilute with the mobile phase to volume, mix well and filter. Inject accurately measured 20 μ l of the successive filtrate into the column. Dilute an accurately weighed quantity of Atropine sulfate CRS with mobile phase to produce a solution of 10 μ g per ml. Repeat the operation, calculate the content of $C_{17}H_{23}NO_3 \cdot H_2SO_4$ with respect to the peak area obtained in the chromatogram by the external standard method and multiply by 1.027.

Category Antidiarrhoeal.

Storage Preserve in tightly closed containers.

Dipivefrin Hydrochloride



$C_{19}H_{29}NO_5 \cdot HCl$ 387.90

[64019-93-8]

Dipivefrin Hydrochloride is (\pm)-3,4-dihydroxy- α [(methylamino) methyl] benzyl alcohol 3,4-dipivalate hydrochloride. It contains not less than 98.5% and not more than 101.5% of $C_{19}H_{29}NO_5 \cdot HCl$, calculated on the dried basis.

Description A white or almost white crystalline powder; odourless; taste, bitter; hygroscopic; deteriorated on exposure to light or air.

Very soluble in water; freely soluble in ethanol; very slightly soluble in ethyl acetate; practically insoluble in petroleum ether.

Melting range 161-166°C (Appendix VI C), melts within a range of 2°C.

Identification (1) Dissolve about 10 mg in 10 ml of sodium hydroxide TS, a pale yellow colour is produced gradually. When examined under ultraviolet light (365 nm), a yellow fluorescence is produced.

(2) The retention time of principal peak of dipivefrin hydrochloride in the substance being examined in the chromatogram obtained in the Assay is identical with that of the principal peak of dipivefrin hydrochloride CRS in the chromatogram of the reference solution.

(3) The infrared absorption spectrum (Appendix IV C) is concordant with the reference spectrum of dipivefrin hydrochloride (No. 335 in Spectra Atlas).

(4) Yields the reactions characteristic of chlorides (Appendix III).

Acidity Dissolve 0.10 g in 10 ml of water, pH5.0-6.5 (Appendix VI H).

Clarity and colour of solution A solution of 100 mg per ml in water is clear and colourless.

Related substances Dissolve a quantity of the substance being examined in the mobile phase to produce a solution of 1 mg per ml as the test solution. Dilute an accurately measured quantity of the test solution with the mobile phase to produce a solution of 10 μ g per ml as the reference solution (1). Dissolve a quantity of (\pm) 3,4-dihydroxy-2'-methylaminoacetophenone-3,4-dipivalate perchlorate in the mobile phase to produce a solution of 5 μ g per ml as the reference solution (2). Carry out the procedure as described under Assay, inject 20 μ l of the reference solution (1) into the column, adjust the attenuation so that the principal peak height in the chromatogram is about 20% of the full scale of the chart. And then inject separately 20 μ l each of the test solution and the two reference solutions into the column, record the chromatogram for twice the retention time of the principal peak. In the chromatogram obtained with the test solution, the peak area of the impurity which has the same retention time as that in the chromatogram obtained with the reference solution (2) is not greater than the peak area in the reference solution (2) (0.5%), the sum of the areas of all peaks other than the principal peak is not greater than the area of the principal peak in the chromatogram obtained with reference solution (1).

Loss on drying When dried in vacuum to constant weight at 60°C, loses not more than 1.0% of its weight (Appendix VIII L).

Residue on ignition Not more than 0.3% (Appendix VIII N), using 1.0 g.

Heavy metals Carry out the limit test for heavy metals (Appendix VIII H, method 2), using the residue obtained in the test for Residue on ignition; not more than 0.0015%.

Assay Carry out the method for high performance liquid chromatography (Appendix V D), using a column packed with octadecylsilane bonded silica gel and a mixture of phosphoric acid (dissolve 13.6 g of potassium dihydrogen phosphate in water and dilute with water to 1000 ml, adjust to pH 3.5 with 10% phosphoric acid)-acetonitrile (60:40) as the mobile phase. Detection wavelength is 254 nm and the number of the theoretical plates of the column is not less than 1500, calculated with reference to the peak of dipivefrin. The resolution factor between the peak of dipivefrin and the adjacent impurity peaks complies with the related requirements.

Procedure Dissolve a quantity of the substance being examined, accurately weighed, in mobile phase to produce a solution of 1 mg per ml as the test solution. Inject 20 μ l of the test solution into the column. Repeat the operation, using dipivefrin hydrochloride CRS instead of the substance being examined. Calculate the content of $C_{19}H_{29}NO_5 \cdot HCl$ with respect to the

peak area obtained in the chromatogram by the external standard method.

Category Ophthalmics.

Storage Preserve in tightly closed containers, stored in a dry place and protected from light.

Preparation Dipivefrin Hydrochloride Eye Drops

Dipivefrin Hydrochloride Eye Drops

Dipivefrin Hydrochloride Eye Drops contain not less than 90.0% and not more than 110.0% of the labelled amount of dipivefrin hydrochloride ($C_{19}H_{29}NO_5 \cdot HCl$).

Description A clear, colourless liquid.

Identification (1) To about 5 ml add 2 ml of sodium hydroxide TS, allow to stand for a few minutes, a pale yellow colour is produced. When examined under ultraviolet light (365 nm), a yellow fluorescence is produced.

(2) The retention time of principal peak of the dipivefrin hydrochloride in the substance being examined in the chromatogram obtained in the Assay is identical with that of the principal peak of dipivefrin hydrochloride CRS in the chromatogram of the reference solution.

pH value 3.5-5.0 (Appendix VI H).

Related substances Carry out the method described under Related substances in Dipivefrin Hydrochloride using the substance being examined as the test solution. In the chromatogram obtained with the test solution, the peak area of the impurity which has the same retention time as that in the chromatogram obtained with the reference solution (2) is not greater than the peak area in the reference solution (2) (0.5%), the sum of the areas of all peaks other than the principal peak is not greater than the area of the principal peak in the chromatogram obtained with reference solution (1).

Other requirements Comply with the general requirements for ophthalmic preparations (Appendix I G).

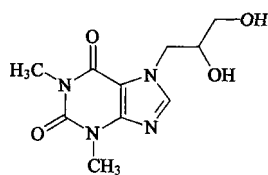
Assay Carry out the method described under Assay in Dipivefrin Hydrochloride, using the substance being examined as the test solution.

Category As described under Dipivefrin Hydrochloride.

Strength (1) 5 ml : 5 mg (2) 8 ml : 8 mg

Storage Preserve in tightly closed containers, stored in a cool place and protected from light.

Diprophylline



$C_{10}H_{14}N_4O_4$ 254.25

[479-18-5]

Diprophylline is 1,3-dimethyl 7-(2,3-dihydroxypropyl)-3,7-dihydro-1H-purine-2,6-dione. It contains not less than 98.0% of $C_{10}H_{14}N_4O_4$, calculated on the

dried basis.

Description A white powder or granules; odourless; taste, bitter.

Freely soluble in water; slightly soluble in ethanol; very slightly soluble in chloroform or ether.

Melting range 160-164°C (Appendix VI C).

Specific absorbance Measure the absorbance of a solution of 10 µg per ml in water at 273 nm (Appendix IV A), the value of A (1%, 1 cm) is 354-376.

Identification (1) Heat under reflux about 1 g in a conical flask with 5 ml of acetic anhydride for 30 minutes and cool. Add 50 ml of water, mix well and rub the flask wall with a glass rod; a white crystalline precipitate is produced gradually. Filter, wash the precipitate with a quantity of water and dry at 105°C for 1 hour. The melting range of the precipitate is 141-147°C (Appendix VI C).

(2) To about 0.1 g add 1 ml of hydrochloric acid and 0.1 g of potassium chlorate, evaporate to dryness on a water bath; a violet colour is produced on exposure to ammonia vapour and the colour disappears by adding a few drops of sodium hydroxide TS.

(3) The infrared absorption spectrum (Appendix IV C) is concordant with the reference spectrum of diprophylline (Appendix XVI).

Acidity or alkalinity Dissolve 0.50 g in 10 ml of water, add 5 drops of bromothymol blue IS; a yellow or green colour is produced. Add 0.20 ml of sodium hydroxide (0.02 mol/L) VS; a blue colour is produced.

Clarity and colour of solution Dissolve 1.0 g in 10 ml of water, shake thoroughly the solution is clear and colourless, any colour produced is not more intense than that of reference solution Y₁ or YG₁ (Appendix IX A, method 1).

Chloride Boil 0.25 g with 5 ml of water and 1.0 ml of sodium hydroxide TS for 30 seconds and cool. Carry out the limit test for chlorides (Appendix VIII A), any opalescence produced is not more pronounced than that of a reference using 7.0 ml of sodium chloride standard solution (0.028%).

Related substances Carry out the method for thin-layer chromatography (Appendix V B), using silica gel GF₂₅₄ as the coating substance and a mixture of chloroform-dehydrated ethanol-concentrated ammonia solution (90:10:1.5) as the mobile phase. Apply separately to the plate 10 µl each of three solutions in methanol-water (30:20) containing (1) 30 mg, (2) 0.45 mg, (3) 0.30 mg of the substance being examined per ml. After developing and removal of the plate, dry in air and examine under ultraviolet light at 254 nm. Any spot other than the principal spot in the chromatogram obtained with solution (1) is not more intense than the principal spot obtained with solution (3), and not more than one of such spot is intense than the principal spot obtained with solution (2).

Loss on drying When dried to constant weight at 105°C, loses not more than 0.5% of its weight (Appendix VIII L).

Residue on ignition Not more than 0.15% (Appendix VIII N).

Heavy metals Dissolve 1.0 g in 2 ml of acetic acid (pH 3.5) and a quantity of water to produce 25 ml, carry out the limit tests for heavy metals (Appendix VIII H, method 1); not more than 0.002%.

Assay Dissolve about 0.2 g, accurately weighed, in 2 ml of anhydrous formic acid, add slowly 50 ml of acetic anhydride and shake for 3 minutes. Add 4-5 drops of sudan IV IS, titrate with perchloric acid (0.1 mol/L) VS until a violet

colour is obtained. Perform a blank determination and make any necessary correction. Each ml of perchloric acid (0.1 mol/L) VS is equivalent to 25.42 mg of $C_{10}H_{14}N_4O_4$.

Category Smooth muscle relaxant.

Storage Preserve in tightly closed containers, stored in a dry place.

Preparation (1) Diprophylline Injection
(2) Diprophylline Tablets

Diprophylline Injection

Diprophylline Injection is a sterile solution of diprophylline in Water for Injection. It contains not less than 90.0% and not more than 110.0% of the labelled amount of diprophylline ($C_{10}H_{14}N_4O_4$).

Description A clear colourless liquid.

Identification (1) To 1 ml add 2 ml of water, mix well, add a few drops of tannic acid TS, a white precipitate is produced.

(2) Evaporate 1 ml to dryness on a water bath, add 1 ml of hydrochloric acid and 0.1 g of potassium chlorate, evaporate to dryness on a water bath, a purple colour is produced on exposure to ammonia vapour and the purple colour disappears on the addition of a few drops of sodium hydroxide TS.

pH value 4.0-7.0 (Appendix VI H).

Other requirements Complies with the general requirements for injections (Appendix I B).

Assay Transfer accurately a quantity equivalent to about 0.25 g of diprophylline into a 250 ml volumetric flask, dilute with water to volume and mix well. Transfer accurately 5 ml of the solution into a 200 ml volumetric flask, dilute with water to volume and mix well. Measure the absorbance at 273 nm (Appendix IV A), calculate the content of $C_{10}H_{14}N_4O_4$, taking 365 as the value of A (1%, 1 cm).

Category As described under Diprophylline.

Strength 2 ml : 0.25 g

Storage Preserve in tightly closed containers, protected from light.

Diprophylline Tablets

Diprophylline Tablets contain not less than 93.0% and not more than 107.0% of the labelled amount of diprophylline ($C_{10}H_{14}N_4O_4$).

Description White tablets.

Identification (1) To a quantity of the powdered tablets equivalent to about 0.5 g of diprophylline add 5 ml of water, shake to dissolve diprophylline. Filter and evaporate 1 ml of the filtrate to dryness on a water bath. The residue complies with test (2) for Identification described under Diprophylline.

(2) The light absorption of the solution obtained in the Assay exhibits a maximum at 273 nm and a minimum at 246 nm (Appendix IV A).

Dissolution Carry out the dissolution test (Appendix X C, method 1), using 900 ml of water as the dissolution medium, adjust the rotational speed of the basket to 100

rpm. withdraw the solution at exact 30 minutes and filter. Dilute 3 ml of the successive filtrate, accurately measured, with water to volume in a 25 ml volumetric flask (0.1 g for strength) or a 50 ml volumetric flask (0.2 g for strength) and mix well. Measure the absorbance of the resulting solution at 273 nm (Appendix IV A). Calculate the dissolution of $C_{10}H_{14}N_4O_4$ from each tablet, taking 365 as the value of A (1%, 1 cm). Not less than 75% of the labelled amount is dissolved.

Other requirements Comply with the general requirements for tablets (Appendix I A).

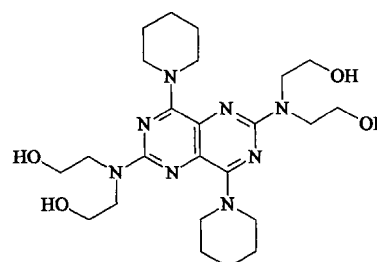
Assay Weigh accurately and powder 10 tablets. Transfer a quantity, accurately weighed, equivalent to about 0.15 g of diprophylline to a 500 ml volumetric flask, add a quantity of water, shake thoroughly and add water to volume. Transfer accurately 10 ml of the successive filtrate to a 200 ml volumetric flask, dilute with water to volume and mix well. Measure the absorbance at 273 nm (Appendix IV A) and calculate the content of $C_{10}H_{14}N_4O_4$, taking 365 as the value of A (1%, 1 cm).

Category As described under Diprophylline.

Strength (1) 0.1 g (2) 0.2 g

Storage Preserve in tightly closed containers, stored in a dry place.

Dipyridamole



$C_{24}H_{40}N_8O_4$ 504.63

[58-32-2]

Dipyridamole is 2, 2', 2'', 2'''-(4,8-dipiperidino-pyrimido [5,4-d] pyrimidin-2,6-diyl) dinitrilo]-tetrakis-ethanol. It contains not less than 98.0% and not more than 102.0% of $C_{24}H_{40}N_8O_4$, calculated on the dried basis.

Description A yellow crystalline powder; odourless; taste, slightly bitter.

Freely soluble in chloroform; soluble in ethanol; slightly soluble in acetone; practically insoluble in water; freely soluble in dilute acid.

Melting range 162-168°C (Appendix VI C).

Identification (1) Dissolve 10 mg in ethanol, a green fluorescence is produced; add a few drops of acid, the fluorescence is disappeared.

(2) Dissolve about 10 mg in 20 ml of dilute hydrochloric acid, add dropwise a 1% solution of potassium chromate, a purple colour is produced, which disappears on shaking; add excess of 1% solution of potassium chromate, no purple colour is produced.

(3) The light absorption of a solution of 10 µg per ml in hydrochloric acid solution (0.01 mol/L) exhibits maxima at 234 nm, 284 nm and 405 nm, the absorbance at 284 nm is about 0.62 (Appendix IV A).

(4) The infrared absorption spectrum (Appendix IV C) is concordant with the reference spectrum of Dipyridamole (Appendix XVI).

Chlorinate compound Carry out the method for oxygen flask combustion (Appendix VII C), using about 20 mg and using 20 ml of a 0.4% solution of sodium hydroxide as the absorbing liquid. When the combustion is complete, shake vigorously the liquid for 15 minutes, add 10 ml of dilute nitric acid and transfer the liquid to a 50 ml Nessler cylinder. Carry out the limit test for chlorides (Appendix VIII A), using the resulting solution. Any opalescence produced is not more pronounced than that of a reference prepared in the same manner using 4.0 ml of sodium chloride standard solution (0.20%).

Related substances Carry out the method for high performance liquid chromatography (Appendix V D), using a column packed with octadecylsilane bonded silica gel and a mixture of dibasic sodium hydrogen phosphate in methanol [Dissolve 250 mg of dibasic sodium phosphate in 250 ml of water, adjust with phosphoric acid (1→3) solution to pH of 4.6 and dilute with methanol to 1000 ml, mix well] as the mobile phase. Detection wavelength is at 288 nm, and the number of theoretical plates of the column is not less than 600, calculated with reference to the peak of dipyridamole. Prepare a solution of 1.0 mg per ml of substance being examined in methanol as the test solution; and dilute the test solution with methanol to produce a solution of 1 µg per ml as the reference solution. Inject 10 µl of the reference solution into the column, adjust the attenuation so that the principal peak height in the chromatogram is about 10% of full scale of the chart. Inject separately 10 µl each of the test solution and the reference solution and record the chromatograph for twice the retention time of principal peak, the sum of the area of all peaks other than the principal peak obtained from the test solution is not greater than the principal peak obtained from the reference solution.

Loss on drying When dried to constant weight at 105°C, loses not more than 0.5% of its weight (Appendix VIII L).

Residue on ignition Not more than 0.1% (Appendix VIII N); use 1.0 g.

Heavy metals Carry out the limit test for heavy metals (Appendix VIII H, method 2), using the residue obtained in Residue on ignition; not more than 0.001%.

Assay Dissolve about 0.3 g, accurately weighed, in 50 ml of dilute hydrochloric acid. Titrate slowly with potassium bromate (0.01667 mol/L) VS, towards the end of titration, shake frequently and titrate in dropwise until no red-violet colour is produced. Each ml of potassium bromate (0.01667 mol/L) VS is equivalent to 25.23 mg of $C_{24}H_{40}N_8O_4$.

Category Anticoagulant; coronary artery dilator.

Storage Preserve in tightly closed containers, protected from light.

Preparation (1) Dipyridamole Injection
(2) Dipyridamole Tablets

Dipyridamole Injection

Dipyridamole Injection is a sterile solution of dipyridamole in Water for Injection. It contains not less than 90.0% and not more than 110.0% of the labelled amount of dipyridamole ($C_{24}H_{40}N_8O_4$).

Description A clear, yellow liquid with fluorescence.

Identification (1) To 2 ml add 2 ml of dilute hydrochloric acid and 1% potassium chromate solution dropwise, a purple colour is produced and disappears on shaking. Add excess 1% potassium chromate solution, the colour is not reproduced.

(2) Dilute 1 ml with 20 ml of water, a greenish fluorescence is produced, which disappears after adding acid.

(3) The light absorption of the solution obtained in the Assay exhibits a maximum at 283 nm (Appendix IV A).

pH value 2.5-4.5 (Appendix VI H).

Other requirements Complies with the general requirements for injections (Appendix I B).

Assay Transfer accurately 5 ml to a 50 ml volumetric flask, dilute with 0.01 mol/L hydrochloric acid solution to volume and mix well. Transfer accurately 2 ml to a 100 ml volumetric flask, dilute to volume and mix well. Measure the absorbance at 283 nm (Appendix IV A), calculate the content of $C_{24}H_{40}N_8O_4$ taking 625 as the value of A (1%, 1 cm).

Category As described under Dipyridamole.

Strength 2 ml : 10 mg

Storage Preserve in tightly closed containers, protected from light.

Dipyridamole Tablets

Dipyridamole Tablets contain not less than 90.0% and not more than 110.0% of the labelled amount of dipyridamole ($C_{24}H_{40}N_8O_4$).

Description Sugar-coated tablets with yellow core.

Identification To a quantity of powdered tablets with coating removed, equivalent to about 0.2 g of dipyridamole, add 20 ml of chloroform and stir to dissolve dipyridamole and filter. Evaporate the filtrate to dryness on a water bath, the residue complies with tests (1), (2) and (3) for Identification described under Dipyridamole.

Content uniformity Comply with the requirements (Appendix X E). Triturate 1 tablet with coating removed. Carry out the determination of content described under Assay, beginning at the words "to a 100 ml volumetric flask...".

Dissolution Carry out the dissolution test (Appendix X C, method 1), using 900 ml of hydrochloric acid solution (9→1000) as the dissolution medium, adjust the rotational speed of the basket to 100 rpm, withdraw 10 ml of the solution at exact 30 minutes and filter, discard the initial filtrate. Measure accurately a quantity of the successive filtrate and dilute with the dissolution medium to produce a solution of 10 µg per ml. Dissolve and dilute an accurately weighed quantity of dipyridamole CRS in the dissolution medium to produce a solution of similar concentration. Measure the absorbance of the resulting solutions at 283 nm (Appendix IV A), and calculate the dissolution of $C_{24}H_{40}N_8O_4$ from each tablet, not less than 80% of the labelled amount is dissolved.

Other requirements Comply with the general requirements for tablets (Appendix I A).

Assay Weigh accurately and powder 20 tablets with coating removed. Transfer accurately a quantity of the powder equivalent to about 50 mg of dipyridamole to a 100 ml volumetric flask, add a quantity of hydrochloric acid (0.01

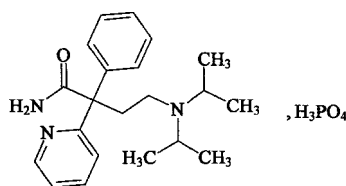
mol/L) VS, shake to dissolve dipyridamole, dilute with hydrochloric acid (0.01 mol/L) VS to volume and mix well. Filter and discard the initial filtrate. Measure accurately a quantity of the successive filtrate, dilute with hydrochloric acid (0.01 mol/L) VS to produce a solution of 10 µg per ml. Measure the absorbance of the solution at 283 nm (Appendix IV A), calculate the content of $C_{21}H_{29}N_3O_4$, taking 625 as the value of A (1%, 1 cm).

Category As described under Dipyridamole.

Strength 25 mg

Storage Preserve in tightly closed containers, protected from light.

Disopyramide Phosphate



$C_{21}H_{29}N_3O \cdot H_3PO_4$ 437.47

[22059-60-5]

Disopyramide Phosphate is α -[2-(Disopropylamino)ethyl]- α -phenyl-2-pyridineacetamide phosphate. It contains not less than 98.5% (for injection) or 98.0% (for oral administration) of $C_{21}H_{29}N_3O \cdot H_3PO_4$, calculated on the dried basis.

Description A white or almost white crystalline powder; odourless; taste, bitter. Freely soluble in water; slightly soluble in ethanol; soluble in glacial acetic acid.

Melting range 206-209°C (for injection) or 205-209°C (for oral administration), with decomposition (Appendix VI C).

Identification (1) The light absorption of a solution of 50 µg per ml in water exhibits a maximum at 261 nm, the absorbance is about 0.47 (Appendix IV A).

(2) The infrared absorption spectrum (Appendix IV C) is concordant with the reference spectrum of disopyramide phosphate (Appendix XVI).

(3) The aqueous solution yields the reactions characteristic of phosphates (Appendix III).

Acidity A solution of 0.10 g in 10 ml of water, pH 4.0-5.0 (Appendix VI H).

Related substances Carry out the method for thin layer chromatography (Appendix V B), using silica HF₂₅₄ with the adhesive of sodium carboxymethylcellulose as the coating substance and a mixture of ethyl acetate-methanol-concentrated ammonia TS (78:20:2) as the mobile phase. Apply to the plate 2 µl of the solution of 0.1 g per ml the substance being examined in 75% ethanol. After developing and removal of the plate, examine under ultraviolet light. No spot other than the principal spot in the chromatogram is obtained.

Loss on drying When dried to constant weight at 105°C, loses not more than 0.5% of its weight (Appendix VIII L).

Heavy metals Dissolve 1.0 g in 20 ml of water and 4 ml of dilute hydrochloric acid, carry out the limit test for heavy metals (Appendix VIII H, method 1); not more than 0.002%.

Assay Dissolve about 0.1 g, accurately weighed, in 10 ml of glacial acetic acid, add 1 drop of crystal violet IS, titrate with perchloric acid (0.1 mol/L) VS until the colour changes to green. Perform a blank determination and make any necessary correction. Each ml of perchloric acid (0.1 mol/L) VS is equivalent to 21.87 mg of $C_{21}H_{29}N_3O \cdot H_3PO_4$.

Category Anti-arrhythmic.

Storage Preserve in tightly closed containers.

Preparation (1) Disopyramide Phosphate Injection
(2) Disopyramide Phosphate Tablets

Disopyramide Phosphate Injection

Disopyramide Phosphate Injection is a sterile solution of disopyramide phosphate in Water for Injection. It contains not less than 95.0% and not more than 105.0% of the labelled amount of disopyramide phosphate ($C_{21}H_{29}N_3O \cdot H_3PO_4$).

Description A clear, colourless liquid.

Identification Complies with the tests (1) and (3) for Identification described under Disopyramide Phosphate.

pH value 4.0-5.0 (Appendix VI H).

Other requirements Complies with the general requirements for injections (Appendix I B).

Assay Evaporate 5 ml (for strength 2 ml:50 mg) or 2 ml (for strength 2 ml:100 mg), accurately measured, on a water bath to dryness, dry at 105°C for 1 hour and cool. Dissolve the residue in 10 ml of glacial acetic acid, add 1 drop of crystal violet IS, titrate with perchloric acid (0.1 mol/L) VS until the colour changes to green. Perform a blank determination and make any necessary correction. Each ml of perchloric acid (0.1 mol/L) VS is equivalent to 21.87 mg of $C_{21}H_{29}N_3O \cdot H_3PO_4$.

Category As described under Disopyramide Phosphate.

Strength (1) 2 ml:50 mg (2) 2 ml:100 mg

Storage Preserve in tightly closed containers.

Disopyramide Phosphate Tablets

Disopyramide Phosphate Tablets contain not less than 95.0% and not more than 105.0% of the labelled amount disopyramide phosphate ($C_{21}H_{29}N_3O \cdot H_3PO_4$).

Description White tablets.

Identification (1) Transfer a quantity of powdered tablets, equivalent to about 5 mg of disopyramide phosphate, to a 100 ml volumetric flask, add a quantity of water and shake to dissolve disopyramide phosphate, dilute with water to volume and filter. The filtrate complies with the test (1) for Identification described under Disopyramide Phosphate.

(2) Shake a quantity of powdered tablets with water, filter, the filtrate yields the reactions characteristic of phosphates (Appendix III).

Other requirements Comply with the general requirements for tablets (Appendix I A).

Assay Weigh accurately and powder 10 tablets. Weigh accurately a quantity of the powder, equivalent to about 0.25

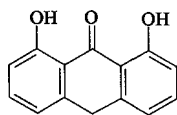
g of disopyramide phosphate, to a 25 ml volumetric flask, add a quantity of glacial acetic acid, shake to dissolve disopyramide phosphate, dilute with glacial acetic acid to volume, mix well and filter. Measure accurately 10 ml of the successive filtrate, carry out the Assay as described under Disopyramide Phosphate. Each ml of perchloric acid (0.1 mol/L) VS is equivalent to 21.87 mg of $C_{21}H_{29}N_3O \cdot H_3PO_4$.

Category As described under Disopyramide Phosphate.

Strength 0.1 g

Storage Preserve in tightly closed containers.

Dithranol



$C_{14}H_{10}O_3$ 226.23

[1143-38-0]

Dithranol is 1,8-dihydroxy-9-anthrone. It contains not less than 95.0% of $C_{14}H_{10}O_3$, calculated on the dried basis.

Description Yellow to slightly yellowish-brown crystals or a powder; odourless.

Soluble in chloroform; very slightly soluble in ethanol; practically insoluble in water; slightly soluble in glacial acetic acid.

Melting range 176-181°C (Appendix VI C).

Identification (1) The light absorption in the range of 240 nm to 400 nm (Appendix IV A) of the solution obtained in the Assay exhibits maxima at 257 nm, 289 nm and 356 nm. The ratio of the absorbance at 257 nm and 289 nm is 1.06-1.10. The ratio of the absorbance at 356 nm and 289 nm is 0.90-0.94.

(2) The infrared absorption spectrum (Appendix IV C) is concordant with the reference spectrum of dithranol (Appendix XVI).

Acidity Shake 1.0 g with 25 ml of water, filter. To 10 ml of the filtrate, add 2 drops of methyl red IS, the solution shows no red colouration.

Dihydroxyanthraquinone The light absorption at 432 nm (Appendix IV A) of a solution of 0.10 mg per ml in chloroform is not greater than 0.12.

Loss on drying When dried to constant weight at 105°C, loses not more than 0.5% of its weight (Appendix VIII L).

Residue on ignition Not more than 0.1% (Appendix VIII N), use 1.0 g.

Heavy metals Carry out the limit test for heavy metals (Appendix VIII H, method 2), using the residue obtained in the Residue on ignition; not more than 0.002%.

Assay Dissolve an accurately weighed quantity in chloroform to produce a solution of about 10 µg per ml and measure the absorbance at 356 nm (Appendix IV A), and calculate the content of $C_{14}H_{10}O_3$, taking 463 as the value of A (1%, 1 cm).

Category Antipsoriatic agent.

Storage Preserve in tightly closed containers, protected from light.

Preparation Dithranol Ointment

Dithranol Ointment

Dithranol Ointment contains not less than 85.0% and not more than 110.0% of the labelled amount of dithranol ($C_{14}H_{10}O_3$).

Description A yellow ointment.

Identification (1) Heat a quantity equivalent to about 0.5 mg of dithranol, with 5 ml of sodium hydroxide TS on a water bath, a red colour is produced.

(2) The light absorption spectrum of the test preparation obtained in the Assay is concordant with that of the reference preparation in the range of 440-470 nm (Appendix IV A).

Other requirements Complies with the general requirements for ointments (Appendix I F).

Assay Weigh accurately a quantity of the ointment equivalent to 2 mg of dithranol in a 50 ml beaker. Add 10 ml of glacial acetic acid and heat on a water bath for 3 minutes with constant stirring. Cool in a cold water bath and allow the ointment base to congeal. Filter the extract into a 50 ml volumetric flask. Repeat the extraction with three 10 ml portions of glacial acetic acid in a similar manner, collecting the filtrates in the same volumetric flask, dilute with glacial acetic acid to volume and mix well. Dissolve an accurately weighed quantity of dithranol CRS and dilute to produce a solution of 40 µg per ml with glacial acetic acid, as the reference solution.

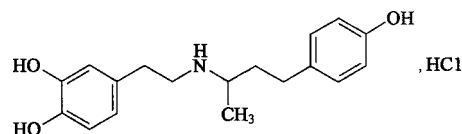
Transfer separately 5 ml each of the test solution and the reference solution, accurately measured, to two 25 ml volumetric flasks. Add to each flask 1 ml of freshly prepared 5% sodium nitrite solution, accurately measured, and mix well. Heat in a boiling water bath for 3 minutes and cool to room temperature immediately. Dilute with glacial acetic acid to volume, mix well and filter if necessary. Measure the absorbance of the two solutions at 450 nm (Appendix IV A) and calculate the content of $C_{14}H_{10}O_3$ in the ointment.

Category As described under Dithranol.

Strength (1) 0.1% (2) 0.5% (3) 1%

Storage Preserve in tightly closed containers, protected from light.

Dobutamine Hydrochloride



$C_{18}H_{23}NO_3 \cdot HCl$ 337.85

[49745-95-1]

Dobutamine hydrochloride is 4-[2-[1-methyl-3-(4-hydroxyphenyl)-propyl]amino]ethyl]-1,2-benzenediol hydrochloride. It contains not less than 98.5% of $C_{18}H_{23}NO_3 \cdot HCl$, calculated on the dried basis.

Description A white or almost white crystalline powder; almost odourless; taste, slightly bitter. The colour deepens on exposure to air or light.

Sparingly soluble in water or dehydrated ethanol; practically insoluble in chloroform.

Melting range 188-193°C (Appendix VI C).

Identification (1) Dissolve 10 mg in 2 ml of water, add 1 drop of ferric chloride TS, the solution becomes green; then add 1 drop of ammonia TS, the colour changes to bluish-violet immediately, then to violet and finally becomes purple.

(2) The light absorption of a 40 µg per ml solution in hydrochloric acid solution (9→1000) exhibits maxima at 220 nm and 278 nm (Appendix IV A).

(3) The infrared absorption spectrum (Appendix VI C) is concordant with the reference spectrum of dobutamine hydrochloride (Appendix XVI).

(4) The aqueous solution yields the reactions characteristic of chlorides (Appendix III).

Clarity of solution A solution of 0.10 g in 10 ml of freshly boiled and cooled water is clear.

Acidity pH of the solution obtained in the test for Clarity of solution is 4.5-6.0 (Appendix VI H).

Loss on drying When dried to constant weight at 105°C, loses not more than 0.5% of its weight (Appendix VIII L).

Residue on ignition Not more than 0.1% (Appendix VIII N); use 1.0 g.

Heavy metals Carry out the limit test for heavy metals (Appendix VIII H, method 2), using the residue obtained in the test for Residue on ignition; not more than 0.002%.

Assay Dissolve about 0.2 g, accurately weighed, in 20 ml of glacial acetic acid by warming, add 5 ml of mercuric acetate TS and 1 drop of crystal violet IS. Titrate with perchloric acid (0.1 mol/L) VS until the solution changes to bluish-green. Perform a blank determination and make any necessary correction. Each ml of perchloric acid (0.1 mol/L) VS is equivalent to 33.78 mg of $C_{18}H_{23}NO_3 \cdot HCl$.

Category β-adreno receptor activator.

Storage Preserve in tightly closed containers, protected from light.

Preparation Dobutamine Hydrochloride Injection

Dobutamine Hydrochloride Injection

Dobutamine Hydrochloride Injection is a sterile solution of dobutamine hydrochloride in Water for Injection. It contains not less than 90.0% and not more than 110.0% of the labelled amount of dobutamine ($C_{18}H_{23}NO_3$).

Description A clear, colourless liquid.

Identification Complies with tests (1), (2) and (4) for Identification described under Dobutamine Hydrochloride.

pH value 2.5-5.0 (Appendix VI H).

Other requirements Complies with the general requirements for injections (Appendix I B).

Assay Dilute an accurately measured quantity with hydrochloric acid solution (9→1000) to produce a solution of 40 µg dobutamine per ml. Measure the absorbance at 278 nm (Appendix IV A) and calculate the content of $C_{18}H_{23}NO_3$, taking 137 as the value of A (1%, 1 cm).

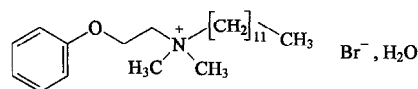
Category As described under Dobutamine Hydrochloride.

Strength 2 ml : 20 mg (calculated as dobutamine)

Storage Preserve in tightly closed containers, protected

from light.

Domiphen Bromide



$C_{22}H_{40}BrNO \cdot H_2O$ 432.49

[538-71-6]

Domiphen Bromide is *N,N*-dimethyl-*N*-(2-phenoxyethyl)-1-dodecanaminium bromide monohydrate. It contains not less than 98.0% of $C_{22}H_{40}BrNO$, calculated on the dried basis.

Description White to pale yellow crystalline flakes; odourless or with a light characteristic odour; taste, bitter; the aqueous solution foams on shaking.

Very soluble in ethanol or chloroform; freely soluble in water; sparingly soluble in acetone; practically insoluble in ether.

Identification (1) Dissolve 50 mg in 10 ml of water, add a few drops of potassium ferricyanide TS, a yellow precipitate is produced.

(2) Dissolve 10 mg in 10 ml of water, add 0.5 ml of eosin solution IS and 100 ml of water, an intense pink colour is produced.

(3) The light absorption of a solution of 0.1 mg per ml in water exhibits maxima at 268 nm and 275 nm (Appendix IV A).

(4) Mix 0.1 g with 0.5 g of sodium carbonate, ignite until it is thoroughly charred, cool. Heat with 5 ml of water to dissolve the residue. Allow to cool, filter, acidify the filtrate with nitric acid, the solution yields the reactions characteristic of bromides (Appendix III).

Acidity Dissolve 0.20 g in 20 ml of water, pH 5.0-7.0 (Appendix VI H).

Clarity and colour of solution A solution of 1.0 g in 10 ml of water is clear and colourless. Any opalescence produced is not more pronounced than that of reference suspension II (Appendix IX B); and any colour produced is not more intense than reference solution Y₁ (Appendix IX A, method 1).

Loss on drying When dried to constant weight at 80°C, loses not more than 5.0% of its weight (Appendix VIII L).

Residue on ignition Not more than 0.1% (Appendix VIII N).

Assay Dissolve about 0.2 g, accurately weighed, with 75 ml of water in a 250 ml stoppered conical flask, add 2 ml of 1% sodium bicarbonate solution, mix well. Add 10 ml of chloroform and 8 drops of bromophenol blue IS, titrate with sodium tetraphenylborate (0.02 mol/L) VS shaking vigorously towards the end of titration until the blue colour of the chloroform layer disappears. Each ml of sodium tetraphenylborate (0.02 mol/L) VS is equivalent to 8.289 mg of $C_{22}H_{40}BrNO$.

Category Antiseptic, Disinfectant.

Storage Preserve in tightly closed containers, protected from light.

Preparation Domiphen Bromide Pills

Domiphen Bromide Pills

Domiphen Bromide Pills contain not less than 85.0% and not more than 115.0% of the labelled amount of domiphen bromide ($C_{22}H_{40}BrNO \cdot H_2O$).

Description White to pale yellow pills.

Identification Comply with tests (1), (2) and (4) for Identification described under Domiphen Bromide.

Other requirements Comply with the general requirements for pills (Appendix I H).

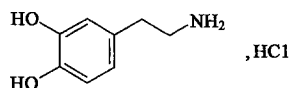
Assay Dissolve 20 pills with a quantity of water in a 50 ml volumetric flask, dilute to volume and mix well. Transfer accurately 20 ml to a 250 ml stoppered conical flask, add 50 ml of water, carry out the method for Assay described under Domiphen Bromide beginning at the words "add 2 ml of 1% sodium bicarbonate solution...". Each ml of sodium tetraphenylborate (0.02 mol/L) VS is equivalent to 8.650 mg of $C_{22}H_{40}BrNO \cdot H_2O$.

Category As described under Domiphen Bromide.

Strength 20 mg

Storage Preserve in tightly closed containers, protected from light.

Dopamine Hydrochloride



$C_8H_{11}NO_2 \cdot HCl$ 189.64

[62-31-7]

Dopamine Hydrochloride is 4-(2-aminoethyl)-1,2-benzenediol hydrochloride. It contains not less than 98.0% of $C_8H_{11}NO_2 \cdot HCl$, calculated on the dried basis.

Description White or almost white lustrous crystals; odourless; taste, slightly bitter; darkens gradually on exposure to light and air.

Freely soluble in water; slightly soluble in dehydrated ethanol; very slightly soluble in chloroform or ether.

Melting range 243-249°C (Appendix VI C).

Identification (1) Dissolve 0.1 g in 5 ml of water, add 20 ml of trinitrophenol TS, mix, a crystalline precipitate is produced on standing. Dry at 105°C after washing with water and small amount of ethanol, it melts at about 200°C with decomposition (Appendix VI C).

(2) Dissolve 10 mg in 1 ml of water, add 1 drop of ferric chloride TS; a deep green colour is produced, which changes to purple on addition of 1% ammonia solution dropwise.

(3) The light absorption of a solution of about 30 µg per ml in 0.5% sulfuric acid solution exhibits maximum at 280 nm (Appendix IV A).

(4) The infrared absorption spectrum (Appendix IV C) is concordant with the reference spectrum of the dopamine hydrochloride (Appendix XVI).

(5) The aqueous solution yields the reactions characteristic of chlorides (Appendix III).

Acidity The solution obtained in Clarity of solution has a pH value of 3.5-5.5 (Appendix VI H).

Clarity and colour of solution A solution of 0.10 g in 10 ml of freshly boiled and cooled water is clear and colourless. Any colour produced is not more intense than reference solution Y₁ (Appendix IX A, method 1).

Loss on drying When dried to constant weight at 105°C, loses not more than 0.5% of its weight (Appendix VIII L).

Residue on ignition Not more than 0.1% (Appendix VIII N).

Assay Dissolve 0.15 g, accurately weighed, in 25 ml of glacial acetic acid by boiling, cool to about 40°C, add 5 ml of mercuric acetate TS, cool, add 1 drop of crystal violet IS. Titrate with perchloric acid (0.1 mol/L) VS until the colour changes to bluish-green. Perform a blank determination and make any necessary correction. Each ml of perchloric acid (0.1 mol/L) VS is equivalent to 18.96 mg of $C_8H_{11}NO_2 \cdot HCl$.

Category Dopamine receptor stimulating agent.

Storage Preserve in tightly closed containers in presence of nitrogen, protected from light.

Preparation Dopamine Hydrochloride Injection

Dopamine Hydrochloride Injection

Dopamine Hydrochloride Injection is a sterile solution of dopamine hydrochloride in Water for Injection. It contains not less than 93.0% and not more than 107.0% of the labelled amount of dopamine hydrochloride ($C_8H_{11}NO_2 \cdot HCl$).

Description A clear, colourless liquid.

Identification Complies with the tests (1), (2), (3) and (5) for Identification described under Dopamine Hydrochloride.

pH value 3.0-4.5 (Appendix VI H).

Other requirements Complies with the general requirements for injections (Appendix I B).

Assay *Reference preparation* Transfer accurately a quantity equivalent to 0.1 g of dopamine hydrochloride CRS to a 100 ml volumetric flask, add sulfuric acid solution (1→350) to volume and shake well.

Test preparation Measure accurately 10 ml to a 100 ml volumetric flask, dilute with sulfuric acid solution (1→350) to volume and mix well.

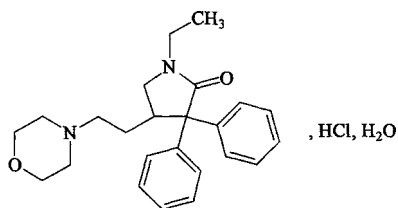
Procedure To 5 ml each of the two solution, accurately measured, in two 100 ml volumetric flasks add 5 ml of freshly prepared ferrous sulfate-tartrate solution (dissolve 1 g of ferrous sulfate, 2 g of sodium potassium tartrate and 0.1 g of sodium bisulfite in water and dilute to 1000 ml), dilute with buffer solution (dissolve 50 g of ammonium acetate in 1000 ml of 20% ethanol and adjust to pH 8.5 with ammonia TS) to volume and mix well. Measure the absorbance at 520 nm (Appendix IV B) and calculate the content of $C_8H_{11}NO_2 \cdot HCl$.

Category As described under Dopamine Hydrochloride.

Strength 2 ml:20 mg

Storage Preserve in well closed containers, protected from light.

Doxapram Hydrochloride



$C_{24}H_{30}N_2O_2 \cdot HCl \cdot H_2O$ 432.99 [7081-53-0]

Doxapram Hydrochloride is 1-ethyl-3,3-diphenyl-4-(2-morpholinoethyl)-2-pyrrolidinone monohydrochloride monohydrate. It contains not less than 98.0% and not more than 100.5% of $C_{24}H_{30}N_2O_2 \cdot HCl$, calculated on the dried basis.

Description A white or almost white crystalline powder, odourless. Sparingly soluble in water, chloroform or ethanol; insoluble in ether.

Melting range 217-221°C (Appendix VI C)

Identification (1) The light absorption of a solution of 400 µg per ml in water exhibits maxima at 252 nm, 258 nm and 264 nm, and minima at 244 nm, 254 nm and 262 nm (Appendix IV A).

(2) The infrared absorption spectrum (Appendix IV C) is concordant with the reference of doxapram hydrochloride (Appendix XVI).

(3) The aqueous solution yields the reactions characteristic of chlorides (Appendix III).

Acidity Dissolve 0.50 g in 50 ml of water, pH 3.5-5.0 (Appendix VI H).

Related substances Carry out the method for thin-layer chromatography (Appendix V B), using silica gel G as the coating substance and a mixture of isopropanol-ammonia (1 mol/L) (15:1) as the mobile phase. Apply separately to the plate 10 µl each of two solutions in methanol containing (1) 60 mg per ml, (2) 0.12 mg per ml of the substance being examined. After developing and removal of the plate, dry in air and spray with diluted potassium iodobismuthate TS. Any spot other than the principal spot, obtained with solution (1) is no more in evidence than the principal spot obtained with solution (2).

Loss on drying When dried at 105°C for 2 hours, loses 3.0%-4.5% of its weight (Appendix VIII L).

Residue on ignition Not more than 0.3% (Appendix VIII N); use 1.0 g.

Heavy metals Carry out the limit test for heavy metals (Appendix VIII H, method 2), using the residue obtained in the test for Residue on ignition; not more than 0.002%.

Arsenic Dissolve 1.0 g in 5 ml of hydrochloric acid and 23 ml of water. Carry out the limit test for arsenic (Appendix VIII J, method 1); not more than 0.0002%.

Assay Dissolve about 0.4 g previously dried at 105°C for 2 hours, accurately weighed, in 20 ml of glacial acetic acid, add 5 ml of mercuric acetate TS and 1 drop of crystal violet IS, titrate with perchloric acid (0.1 mol/L) VS until the colour changes to bluish green. Perform a blank determination and make any necessary correction. Each ml of perchloric acid (0.1 mol/L) VS is equivalent to 41.50 mg

of $C_{24}H_{30}N_2O_2 \cdot HCl$.

Category Central stimulant.

Storage Preserve in tightly closed containers, protected from light.

Preparation Doxapram Hydrochloride Injection

Doxapram Hydrochloride Injection

Doxapram Hydrochloride Injection is a sterile solution of doxapram hydrochloride in Water for Injection. It contains not less than 90.0% and not more than 110.0% of the labelled amount of doxapram hydrochloride ($C_{24}H_{30}N_2O_2 \cdot HCl \cdot H_2O$).

Description A clear, colourless liquid.

Identification (1) The light absorption of the solution obtained in the Assay exhibits maxima at 252 nm, 258 nm and 264 nm, and minima at 244 nm, 254 nm and 262 nm (Appendix IV A).

(2) Yields the reactions characteristic of chlorides (Appendix III).

pH value 3.5-5.5 (Appendix VI H).

Other requirements Complies with the general requirements for injections (Appendix I B).

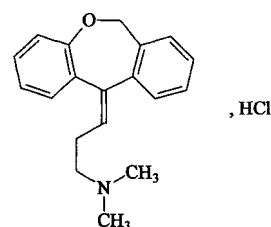
Assay Transfer an accurately measured quantity, equivalent to about 100 mg of doxapram hydrochloride, to a 250 ml volumetric flask, dilute with water to volume and mix well. Measure the absorbance of the resulting solution at 258 nm (Appendix IV A). Repeat the procedure using doxapram hydrochloride CRS instead of the substance being examined. Calculate the content of $C_{24}H_{30}N_2O_2 \cdot HCl \cdot H_2O$.

Category As described under Doxapram Hydrochloride.

Strength 5 ml:100 mg

Storage Preserve in tightly closed containers, protected from light.

Doxepin Hydrochloride



$C_{19}H_{21}NO \cdot HCl$ 315.84

[1229-29-4]

Doxepin Hydrochloride is a mixture of *Z*- and *E*-isomers of 3-dibenz[*b*, *e*]oxepin-11(6*H*)ylidene-*N,N*-dimethyl-1-propanamine hydrochloride. It contains not less than 98.5% of $C_{19}H_{21}NO \cdot HCl$, calculated on the dried basis.

Description A white powder; easily hygroscopic, then its colour gradually turned into slight yellow; taste, slightly sweet with local numbness.

Freely soluble in water; soluble in ethanol or chloroform;

insoluble in benzene.

Melting range 185-191°C (Appendix VI C).

Identification (1) The light absorption of a solution of 0.04 mg per ml in methanolic hydrochloric acid (0.01 mol/L) exhibits a maximum at 297 nm, the absorbance is 0.50-0.55 (Appendix IV A).

(2) The infrared absorption spectrum (Appendix IV C) is concordant with the reference spectrum of doxepin hydrochloride (Appendix XVI).

(3) The aqueous solution yields the reactions characteristic of chlorides (Appendix III).

Acidity Dissolve 0.10 g in 10 ml of water, pH 4.5-6.5 (Appendix VI H).

Z-isomer Carry out the method for gas chromatography (Appendix V E), using a column packed with diatomaceous support coated with 3% of cyanopropylmethyl phenyl methyl silicone fluid (OV-225), maintain the column temperature at 235°C, the number of theoretical plates of the column is not less than 2000, calculated with reference to the peak of Z-doxepin, and the resolution factor between the peaks of Z- and E-doxepin is greater than 1.0.

Internal standard Dissolve a quantity of chlorphenamine maleate in methanol to produce a solution of 5 mg per ml.

Procedure Transfer accurately a quantity equivalent to about 25 mg of doxepin hydrochloride, to a 50 ml volumetric flask, add accurately 5 ml of internal standard solution, and a quantity of methanol to dissolve it, dilute with methanol to volume, mix well and inject 1-3 µl into the column. Repeat the operation, using doxepin hydrochloride CRS instead of the substance being examined. Measure the peak areas of Z- and E-doxepin, the percentage of Z-doxepin is 17.0%-23.0%.

Loss on drying When dried to constant weight at 105°C, loses not more than 1.0% of its weight (Appendix VIII L).

Residue on ignition Not more than 0.1% (Appendix VIII N); use 1.0 g.

Heavy metals Carry out the limit test for heavy metals (Appendix VIII H, method 2), using the residue obtained in the test for Residue on ignition; not more than 0.002%.

Assay Dissolve about 0.2 g, accurately weighed, in 20 ml of glacial acetic acid, add 5 ml of mercuric acetate TS and 1 drop of crystal violet IS, titrate with perchloric acid (0.1 mol/L) VS until the colour changes to bluish green. Perform a blank determination and make any necessary correction. Each ml of perchloric acid (0.1 mol/L) VS is equivalent to 31.58 mg of C₁₉H₂₁NO • HCl.

Category Antidopaminergic.

Storage Preserve in tightly closed containers, protected from light.

Preparation Doxepin Hydrochloride Tablets

Doxepin Hydrochloride Tablets

Doxepin Hydrochloride Tablets contain not less than 90.0% and not more than 110.0% of the labelled amount of doxepin (C₁₉H₂₁NO).

Description Sugar-coated or film coated tablets with white to slightly yellow core.

Identification (1) The light absorption of the solution obtained in the Assay exhibits a maximum at 297 nm (Appendix IV A).

(2) Triturate a quantity of powdered tablets with water and filter. To the filtrate, add drops of silver nitrate TS; a white curdy precipitate is produced.

Dissolution Carry out dissolution test (Appendix X C, method 1), using 900 ml of water as the dissolution medium, adjust the rotational speed of the basket to 100 rpm. Withdraw a quantity of the solution at exact 45 minutes, filter and use the successive filtrate as the test solution. Dissolve a quantity of doxepin hydrochloride CRS, accurately weighed, in water to produce a solution of 30 µg per ml as the reference solution. Measure the absorbance of the resulting solutions at 292 nm (Appendix IV A). Calculate the dissolution of C₁₉H₂₁NO from each tablet; not less than 70% of the labelled amount is dissolved.

Other requirements Comply with the general requirements for tablets (Appendix I A).

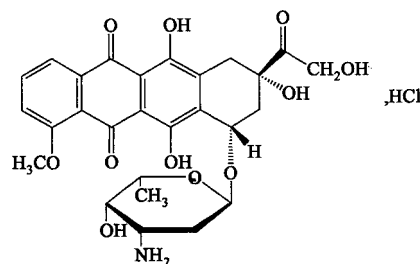
Assay Weigh accurately and powder 20 tablets with coating removed. Transfer accurately a quantity of the powdered tablets equivalent to 25 mg of doxepin to a 100 ml volumetric flask, add 1 ml of hydrochloric acid solution (1 mol/L), shake thoroughly and allow to stand for 10 minutes, add 60 ml of methanol, shake well, dilute with methanol to volume and mix well. Filter and discard the initial filtrate, transfer accurately 10 ml of the successive filtrate to a 50 ml volumetric flask, dilute with methanolic hydrochloric acid solution (0.01 mol/L) to volume and mix well. Measure the absorbance of the resulting solution at 297 nm (Appendix IV A), calculate the content of C₁₉H₂₁NO, taking 150 as the value of A (1%, 1 cm).

Category As described under Doxepin Hydrochloride.

Strength 25 mg (calculated as doxepin)

Storage Preserve in tightly closed containers, protected from light.

Doxorubicin Hydrochloride



C₂₇H₂₉NO₁₁ • HCl 579.99

[25316-40-9]

Doxorubicin Hydrochloride is (8S, 10S)-10-[3-Amino-2, 3, 6-trideoxy-α-L-lyxo-hexopyranosyloxy-8-glycoloyl]-7, 8, 9, 10-tetrahydro-6, 8, 11-trihydroxyl-1-methoxyl-5, 12-naphthacenedione hydrochloride.

It contains not less than 98.0% and not more than 102.0% of Doxorubicin Hydrochloride (C₂₇H₂₉NO₁₁ • HCl), calculated on the anhydrous and residual solvent-free basis.

Description A orange-red crystalline powder, hygroscopic. Soluble in water, slightly soluble in methanol.

Identification (1) The retention time of principal peak of Doxorubicin Hydrochloride in the substance being examined in the chromatogram obtained in the Assay is identical with

that the principal peak of Doxorubicin Hydrochloride CRS in the chromatogram of the reference solution correspondingly.

(2) The infrared absorption spectrum (Appendix VI C) is concordant with the reference spectrum of Doxorubicin Hydrochloride.

(3) To a quantity of the solution of the substance being examined add 5 ml of nitric acid R, add 0.5 ml of water R and heat over a flame for 2 min. Allow to cool and add silver nitrate solution TS. A white precipitate is formed.

Crystallinity Complies with the test for crystallinity (Appendix IX D).

Acidity An aqueous solution of 5 mg per ml, pH 4.5-5.5. (Appendix VI H).

Related substances Carry out the method and use the solution as described under Assay. Adjust the attenuation so that the principal peak height in the chromatogram is about 20%-30% of full scale of chart. Dissolve a quantity of the substance being examined, accurately weighed, in mobile phase to produce solutions of 1.0 mg per ml. Used as the test solutions. Transfer accurately 1 ml to a 100 ml volumetric flask, dilute with the mobile phase to volume and mix well. Used as the reference solution. Inject separately 10 μ l each of the test solution and the reference solution into the column and record the chromatogram for 3.5 times the retention time of the principal peak. Each peak area and the sum of the areas of all peaks other than the principal peak in the chromatogram obtained with the test solution are not greater than 0.5 times (0.5%) and 2 times (2.0%) of area of the principal peak in the chromatogram obtained with the standard solution.

Residual solvent *ethanol, methanol, acetone, and dichloromethane* Dissolve about 0.2 g, accurately weighed, in 5 ml water in a head-sampling bottle. Encapsulate the bottle. Used as the test solution. Weigh accurately, a quantity of methanol, acetone, ethanol and dichloromethane, separately, dissolve with Dimethyl Sulphoxide to produce stock solution individually. Measure accurately a quantity of each stock solution, dilute with water to obtain a mixed solution containing 2 μ g dichloromethane, 20 μ g methanol, 10 μ g acetone and 0.2 mg ethanol per ml. Measure 5 ml accurately in a head-sampling bottle. Encapsulate the bottle. Used as the reference solution.

Carry out the method for Residual solvent (Appendix VIII P). The gas chromatograph is equipped with a flame-ionization detector and a fused-silica capillary column coated with a layer of 6% cyanopropylphenyl/94% dimethylsiloxane or equivalent phase column. Maintain the temperature of the column at 50°C. The injection port is maintained at a temperature of 140°C. The detector is maintained at a temperature of 250°C. Nitrogen or Helium is used as the carrier gas, the flow rate is 5.0 ml per minute. Head-sampling method is used. The head-sampling condition is 90°C for 30 minutes. The injection volume is 1.0 ml. Inject the reference solution into the column and record the chromatogram. The elution order is methanol, ethanol, acetone and dichloromethane. The resolution factor between main peaks complies with the related requirements. Inject separately each of the test solution and the reference solution into the column and record the chromatogram. Calculate the content of methanol, ethanol, acetone and dichloromethane with respect to the peak area of methanol, ethanol, acetone and dichloromethane obtained in the chromatogram by the external standard method respectively. The content of ethanol is not more than 1.0%. The content of methanol, dichloromethane and acetone comply with requirements.

Water Not more than 4.0% (Appendix VIII M, method 1 A).

Bacterial endotoxin Carry out the test for Bacterial endotoxin (Appendix XI E); less than 2.2 EU per mg.

Assay Carry out the method for high performance liquid chromatography (Appendix V D), using a column packed with octadecylsilane bonded silica gel and a mixture of sodium lauryl sulfate solution (weigh about 1.44 g of sodium lauryl sulfate, add 0.68 ml of phosphoric acid, dissolve with 500 ml water)-acetonitrile-methanol(500:500:60) as the mobile phase. The detection wavelength is 254 nm. Dissolve a quantity of doxorubicin hydrochloride CRS and epirubicin hydrochloride CRS in mobile phase to produce a mixed solution containing 50 μ g each of the two substances per ml. Inject 10 μ l of the solution into the column and record the chromatogram. The resolution between doxorubicin and epirubicin is more than 2.0.

Procedure Dissolve a quantity of the substance being examined, accurately weighed, with mobile phase to produce a solution containing 0.1 mg per ml. Inject 10 μ l into the column and record the chromatogram. Repeat the operation, using doxorubicin hydrochloride CRS instead of the substance being examined, calculate the content of doxorubicin hydrochloride ($C_{27}H_{29}NO_{11} \cdot HCl$) with respect to the peak area obtained in the chromatogram by the external standard method.

Category Antitumour.

Storage Preserve in tightly closed containers, stored in a cool place and protected from light.

Preparation Doxorubicin Hydrochloride for Injection.

Doxorubicin Hydrochloride for Injection

Doxorubicin Hydrochloride for Injection is a sterile mixture of Doxorubicin Hydrochloride and suitable amount of Mannitol or other excipient. It contains not less than 90.0% and not more than 115% of the labelled amount of Doxorubicin Hydrochloride ($C_{27}H_{29}NO_{11} \cdot HCl$).

Description A orange-red loosen mass or powder.

Identification Complies with the test (1) and (3) for Identification described under Doxorubicin Hydrochloride.

Related substances Carry out the method and use the solution as described under Doxorubicin Hydrochloride. Each peak area and the sum of the areas of all peaks other than the principal peak in the chromatogram obtained with the test solution are not greater than 1 time (1.0%) and 3 times (3.0%) of area of the principal peak in the chromatogram obtained with the reference solution.

Content uniformity Complies with the test for content uniformity (Appendix X E), the content of Doxorubicin Hydrochloride in each bottle is calculated by Assay.

Acidity Carry out the method for Acidity described under Doxorubicin Hydrochloride.

Water Carry out the method for Water described under Doxorubicin Hydrochloride.

Bacterial endotoxin Carry out the method for Bacterial endotoxin described under Doxorubicin Hydrochloride.

Sterility Dissolve a quantity of the substance being examined in suitable amount of solvent, transfer to at least 500 ml of sterile 0.9% of sodium chloride solution. Complies with the test for sterility (Appendix XI H, membrane filtration

method).

Other requirements Complies with the general requirements for injection (Appendix I B).

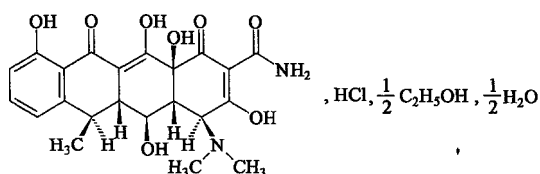
Assay Take 10 packages. Dissolve the substance being examined in each original bottle with mobile phase and dilute to produce a solution containing 0.1 mg per ml. Carry out the Assay described under Doxorubicin Hydrochloride. Calculate the content of Doxorubicin Hydrochloride in each bottle. The average value of these 10 contents is the final result.

Category As described under Doxorubicin Hydrochloride.

Strength Calculated as $C_{27}H_{29}NO_{11} \cdot HCl$
(1) 10 mg (2) 20 mg

Storage Preserve in tightly closed containers, stored in a cool place and protected from light.

Doxycycline Hyclate



$C_{22}H_{24}N_2O_8 \cdot HCl \cdot \frac{1}{2}C_2H_5OH \cdot \frac{1}{2}H_2O$ 512.93
[24390-14-5]

Doxycycline Hyclate is 4-(dimethylamino)-1,4,4a,5,5a,6,11,12a-octahydro-3,5,10,12,12a-pentahydroxy-6-methyl-1,11-dioxo-2-naphthacene-carboxamide monohydrochloride, hemiethanol, hemihydrate. It contains not less than 88.0% and not more than 94.0% of $C_{22}H_{24}N_2O_8$, calculated with reference to the anhydrous, ethanol-free substance.

Description A slightly yellow to yellow crystalline powder; odourless; taste, bitter. Freely soluble in water or methanol; slightly soluble in ethanol or acetone; practically insoluble in chloroform.

Specific optical rotation -105° to -120° measured at $25^\circ C$, in a solution of 10 mg per ml in a mixture of 1 volume of hydrochloric acid solution (9 → 100) and 99 volumes of methanol (Appendix VI E).

Identification (1) The retention time of the principal peak of the substance being examined in the chromatogram obtained in the Assay is correspondent with that of doxycycline CRS in the chromatogram.

(2) The infrared absorption spectrum (Appendix IV C) is concordant with the reference spectrum of Doxycycline (Appendix XVI).

(3) The aqueous solution yields the reactions characteristic of chlorides (Appendix III).

Acidity An aqueous solution of 10 mg per ml, pH 2.0-3.0 (Appendix VI H).

Light absorption The absorbance of a solution of 10 μg per ml in a mixture of 1 volume of hydrochloric acid solution (9 → 100) and 99 volumes of methanol at 349 nm is 0.28-0.31 (Appendix IV A).

Related substances Carry out the method described under

Assay. Dissolve a quantity of the substance being examined, accurately weighed, in 0.01 mol/L hydrochloric acid solution to produce solutions of 0.2 mg per ml as test solution and 4 μg per ml as reference solution. Inject 20 μl of solution (2) into the column, adjust the attenuation so that the principal peak height is 20% of the full scale of the chart. Inject separately 20 μl each of test solution and reference solution, and record the chromatogram for twice the retention time of the principal peak. The peak area of oxytetracycline is not greater than 1/2 of the principal peak area in the chromatogram obtained with reference solution and the peak areas of metacycline and β -doxycycline are not greater than the principal area in the chromatogram obtained with reference solution respectively.

Light absorbing impurities The absorbance of a solution of 10 mg per ml in a mixture of 1 volume of hydrochloric acid solution (9 → 100) and 99 volumes of methanol at 490 nm, is not greater than 0.12 (Appendix IV A).

Ethanol Dilute 0.5 ml of absolute ethanol, accurately measured, with 0.05% (ml/ml) *n*-propanol solution (internal standard solution) to volume in a 100 ml volumetric flask and mix well. Dilute 1.0 ml of the solution, accurately measure, with the internal standard solution to volume in a 10 ml volumetric flask and mix well. Dissolve about 1.0 g, accurately weighed, in internal standard solution, dilute to volume in another 10 ml volumetric flask and mix well. Carry out the method for assay as chromatograph (Appendix V E), using a column packed with porous polymer beads, maintain the column temperature at $135^\circ C$ and the vaporizer and the detector temperature below $150^\circ C$. The resolution factor between the peaks of ethanol and internal standard complies with the related requirement the content of ethanol is 4.3% to 6.0% (g/g).

Water 1.5-3.0% (Appendix VIII M, method 1 A).

Residue on ignition Not more than 0.2% (Appendix VIII N), using 1 g.

Heavy metals Carry out the limit test for heavy metals (Appendix VIII H, method 2), using the residue obtained in the test for Residue on ignition, not more than 0.002%.

Assay Carry out the method for high performance liquid chromatogram (Appendix V D), using a column packed with octadecylsilane bonded silica gel and a mixture of 0.05 mol/L ammonium oxalate solution-dimethylformamide-0.2 mol/L diammonium hydrogen phosphate solution (65:30:5) (adjust pH value to 8.0 ± 0.2 with ammonia TS) as the mobile phase. Maintain the column temperature at $35^\circ C$. Dissolve a mixture of metacycline CRS, oxytetracycline CRS, β -doxycycline CRS and doxycycline CRS, all accurately weighed, in 0.01 mol/L hydrochloric acid solution to produce a solution of 0.08 mg per ml respectively, inject a quantity of the resulting solution into the column. The number of theoretical plates of the column is not less than 1500, calculated with reference to the peak of doxycycline. The resolution factor between the peaks of doxycycline and β -doxycycline complies with the related requirements.

Procedure Dissolve 40 mg, accurately weighed, in 0.01 mol/L hydrochloric acid solution dilute to volume in a 50 ml volumetric flask and mix well. Transfer 5 ml, accurately measured, into another 50 ml volumetric flask, dilute with 0.01 mol/L hydrochloric acid solution to volume and mix well. Inject 20 μl into the column and record the chromatogram. Repeat the operation using doxycycline CRS instead of the substance being examined. Calculate the content of $C_{22}H_{24}N_2O_8$ with respect to the peak area obtained in the chromatogram by the external standard method.

Category Tetracycline antibiotic.

Storage Preserve in tightly closed containers, protected from light.

Preparation (1) Doxycycline Hyclate Capsules
(2) Doxycycline Hyclate Tablets

Doxycycline Hyclate Capsules

Doxycycline Hyclate Capsules contain not less than 90.0% and not more than 110.0% of the labelled amount of Doxycycline ($C_{22}H_{24}N_2O_8$).

Description Capsules containing slightly yellow to yellow powder or granules.

Identification The contents of capsules comply with the tests for Identification described under Doxycycline Hyclate.

Related substances Carry out the method described under Doxycycline Hyclate. Dissolve an accurately weighed quantity of the mixed contents obtained in the test for weight variation of content in 0.01 mol/L hydrochloric acid to produce a solution of 0.2 mg per ml, filter as test solution. Measure a quantity of test solution and dilute with 0.01 mol/L hydrochloric acid to produce a solution of 4 µg per ml as reference solution.

Dissolution Carry out the dissolution test (Appendix X C, method 2), using water as the dissolution medium, adjust the rotational speed of the paddle to 50 rpm. Withdraw a quantity of the solution at exact 45 minutes and filter. Dilute an accurately measured quantity of the successive filtrate with water to produce a solution of 20 µg per ml. Dissolve an accurately weighed quantity of doxycycline hyclate CRS in water to produce a solution of 20 µg per ml. Measure the absorbance of the resulting solutions at 276 nm (Appendix IV A) Calculate the dissolution of $C_{22}H_{24}N_2O_8$ from each tablet, not less than 85% of the labelled amount is dissolved.

Loss on drying When dried the contents of the capsules to constant weight at 105°C, lose not more than 8.5% of their weight (Appendix VIII L).

Other requirements Comply with the general requirements for capsules (Appendix I E).

Assay Dissolve an accurately weighed quantity of the mixed contents equivalent to about 40 mg of doxycycline in the test for weight variation of content in 0.01 mol/L hydrochloric acid solution, dilute to volume in a 50 ml volumetric flask and mix well. Filter, transfer accurately 5 ml of the successive filtrate in another 50 ml volumetric flask and dilute to volume with 0.01 mol/L hydrochloric acid solution. Inject 20 µl into the column. Carry out the Assay described under Doxycycline Hyclate.

Category As described under Doxycycline Hyclate.

Strength 0.1 g (Calculated as $C_{22}H_{24}N_2O_8$)

Storage Preserve in tightly closed containers, stored in a cool and dry place.

Doxycycline Hyclate Tablets

Doxycycline Hyclate Tablets contain not less than 93.0% and not more than 107.0% of the labelled amount of doxycycline ($C_{22}H_{24}N_2O_8$).

Description Pale yellow tablets.

Identification (1) To a quantity of powdered tablets equivalent to about 0.5 mg of doxycycline add 2 ml of sulfuric acid, a yellow colour is produced.

(2) The retention time of the principal peak of the substance being examined in the chromatogram obtained in the Assay is correspondent with that of doxycycline CRS in the chromatogram.

Light absorbing impurities To 5 powdered tablets add a mixture of 1 volume of hydrochloric acid solution (9→100) and 99 volumes of methanol to produce a solution of 10 mg per ml and filter. The absorbance of the successive filtrate at 490 nm is not greater than 0.20 (Appendix IV A).

Related substances Dissolve a quantity of the powdered tablets in 0.01 mol/L hydrochloric acid solution to produce two solutions of 0.2 mg per ml as test solution and 4 µg per ml as reference solution, carry out the method of Related substances described under Doxycycline Hyclate.

Dissolution Carry out the dissolution test (Appendix X C, method 2), using water as the dissolution medium, adjust the rotational speed of the paddle to 50 rpm. Withdraw a quantity of the solution at exact 45 minutes and filter. Dilute a quantity of the successive filtrate with water to produce a solution of 20 µg per ml. Dissolve a quantity of doxycycline Hyclate CRS in water to produce a solution of 20 µg per ml. Measure the absorbance of the resulting solutions at 276 nm (Appendix IV A). Calculate the dissolution of $C_{22}H_{24}N_2O_8$ from each tablet, not less than 85% of the labelled amount is dissolved.

Other requirements Comply with the general requirements for tablets (Appendix I A).

Assay Weigh accurately and powder 10 tablets. Dissolve an accurately weighed quantity, equivalent to about 40 mg of doxycycline, in 0.01 mol/L hydrochloric acid solution, dilute to volume in a 50 ml volumetric flask and mix well. Filter, transfer accurately 5 ml of the successive filtrate to another 50 ml volumetric flask and dilute to volume with 0.01 mol/L hydrochloric acid solution. Inject 20 µl into the column, carry out the Assay described under Doxycycline Hyclate.

Category As described under Doxycycline Hyclate.

Strength Calculated as $C_{22}H_{24}N_2O_8$

(1) 0.05 g (2) 0.1 g

Storage Preserve in tightly closed containers, protected from light.

Dried Calcium Sulfate

$CaSO_4 \cdot \frac{1}{2} H_2O$ 145.15

Dried Calcium Sulfate contains not less than 95.0% of $CaSO_4 \cdot \frac{1}{2} H_2O$.

Description A white fine powder; odourless; tasteless; hygroscopic, forming fine particulates, and the solidifiability is lost.

Slightly soluble in water, insoluble in ethanol, soluble in dilute hydrochloric acid.

Identification Dissolve in dilute hydrochloric acid, the solution yields the reactions characteristic of calcium salts and sulfates (Appendix III).

Fineness of the particles 20 g should pass through No. 5 sieve completely and not less than 80% should pass through No. 6 sieve.

Alkalinity Shake 3.0 g with 10 ml of water, add 1 drop of phenolphthalein IS solution; no pink colour is produced.

Solidification Stir 10 g with 10 ml water thoroughly, a white and compact solid is solidified within 5 minutes. Press the edge of solid with finger; after 3 hours; no chippings are separated.

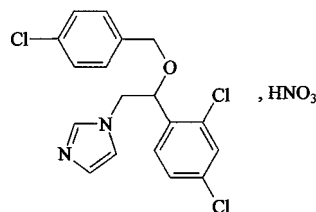
Loss weight on ignition When ignited to constant weight, loses not less than 0.5% and not more than 8.0% of its weight.

Assay Dissolve about 0.15 g accurately weighed in a conical flask with 15 ml of water and 5 ml of dilute hydrochloric acid by heating gently. Cool, add 75 ml of water, 20 ml of sodium hydroxide TS and 0.1 g calcon IS mixture. Titrate with disodium edetate (0.05 mol/L) VS, until the colour turns from violet red to pure blue. Each ml of disodium edetate (0.05 mol/L) VS is equivalent to 7.258 mg of $\text{CaSO}_4 \cdot \frac{1}{2} \text{H}_2\text{O}$.

Category Solidifying agent for orthopaedics.

Storage Preserve in tightly closed containers.

Econazole Nitrate



$\text{C}_{18}\text{H}_{15}\text{Cl}_3\text{N}_2 \cdot \text{HNO}_3$ 444.70

[68979-31-9]

Econazole Nitrate is 1-[2,4-dichloro- β (4-chlorobenzyloxy) phenethyl] imidazole nitrate. It contains not less than 98.5% of $\text{C}_{18}\text{H}_{15}\text{Cl}_3\text{N}_2 \cdot \text{HNO}_3$, calculated on the dried basis.

Description White to slightly yellow crystals or a crystalline powder; odourless.

Freely soluble in methanol; slightly soluble in chloroform; very slightly soluble in water.

Melting range 163-167°C, with decomposition (Appendix VI C).

Identification (1) To about 3 mg add two drops of sulfuric acid and 1 drop of diphenylamine TS, a deep blue colour develops.

(2) The light absorption (Appendix IV A) of the solution of about 0.4 mg per ml in hydrochloric acid solution (0.1 mol/L) and methanol (1:9) exhibits maxima at 265 nm, 272 nm and 280 nm.

(3) The infrared absorption spectrum (Appendix VI C) is concordant with the reference spectrum of econazole nitrate (Appendix XVI).

(4) Weigh about 20 mg and carry out the oxygen flask combustion (Appendix VII C) when the combustion is complete, using 5 ml of solution sodium hydroxy TS as absorbing solution. shake thoroughly. Dilute the resulting solution to 20 ml with water and acidify with dilute nitric acid. This solution yields reactions characteristic of chlorides (Appendix III).

Acidity To 1 g add 50 ml of water, heat for 5 minutes on 70°C water bath. Cool immediately and filter, the pH of filtrate is 3.0-4.5.

Loss on drying When dried to constant weight at 105°C, loses not more than 0.5% of its weight (Appendix VIII L).

Residue on ignition Not more than 0.1%; use 1.0 g. (Appendix VIII N).

Heavy metals Carry out the limit test for heavy metals (Appendix VIII H, method 2), using the residue obtained in the test for Residue on ignition, not more than 0.002%.

Related substances Carry out the method for thin-layer chromatography (Appendix V B), using silica gel G as the coating substance and a mixture of hexane, chloroform, methanol and ammonia (60:30:10:1) as the mobile phase. Apply separately to the plate 25 μl of each of the two solutions in methanol containing (1) 20 mg and (2) 100 μg per ml. After developing and removal of the plate, allow it to dry in a current of air, and expose the plate to iodine vapour. Any secondary spot in the chromatogram obtained with solution (1) is not more intense than the spot in the chromatogram obtained with solution (2).

Assay Dissolve 0.3 g accurately weighed in 30 ml of acetic acid and carry out the potentiometric titration (Appendix VII

A), titrate with perchloric acid (0.1 mol/L) VS. Perform a blank determination and make any necessary correction. Each ml of perchloric acid (0.1 mol/L) VS is equivalent to 44.47 mg of $C_{18}H_{15}Cl_3N_2O \cdot HNO_3$.

Category Antifungal.

Storage Preserve in tightly closed containers.

Preparations (1) Econazole Nitrate Cream
(2) Econazole Nitrate Solutions
(3) Econazole Nitrate Spray
(4) Econazole Nitrate Suppository

Econazole Nitrate Cream

Econazole nitrate cream contains not less than 90.0% and not more than 110.0% of labelled amount of Econazole Nitrate ($C_{18}H_{15}Cl_3N_2O \cdot HNO_3$)

Description A white cream.

Identification Carry out the method for thin-layer chromatography (Appendix V B) using silica gel G as the coating substance and the isopropyl ether as the mobile phase. Apply separately to the plate 5 μ l each following solutions. For solution (1) to about 2 g add 20 ml of methanol, heat on water bath to melt, allow it to cool on ice bath and filter, evaporate the filtrate to dryness and dissolve the residue in 2 ml of methanol. Solution (2) containing 20 mg of econazole nitrate CRS in 2 ml of methanol. After developing and removal of the plate, allow it to dry in a current of air and expose the plate to iodine vapour. The position of principal spot obtained with the solution (1) corresponds to that obtained with solution (2).

Other requirements Complies with the general requirements for cream (Appendix I F).

Assay Dissolve a quantity (equivalent to 40 mg econazole nitrate) accurately weighed, with 40 ml of chloroform in a conical flask with stopper, by shaking, add 20 ml of water and 5 ml of dilute sulfuric acid and 1 ml of mixed indicator of dimethyl yellow-solvent blue IS, shake well and titrate with sodium diethyl sulfosuccinate VS, until the colour of chloroform layer forms from green to red-gray colour. Repeat the operation using a quantity containing 40 mg of econazole nitrate CRS instead of substance being examined. Calculate the content of $C_{18}H_{15}Cl_3N_2O \cdot HNO_3$ accordingly.

Category As described under econazole nitrate.

Strength 10 g \pm 0.1 g

Storage Preserve in tightly closed containers and stored in a cool place.

Econazole Nitrate Solution

Econazole nitrate solution contains not less than 90.0% and not more than 110.0% of labelled amount of econazole nitrate ($C_{18}H_{15}Cl_3N_2O \cdot HNO_3$).

Description A white to pale yellow clear liquid.

Identification Evaporate a quantity of this solution to dryness, the residue complies with tests (1), (2) and (4) for identification described under Econazole Nitrate.

Weight variation of contents Complies with the general requirement of test for weight variation of contents

(Appendix X F).

Assay Shake well 2 ml, accurately measured with 30 ml of chloroform and 20 ml of water in a conical flask with stopper, carry out the Assay described under econazole nitrate cream beginning at the words "add 5 ml of dilute sulfuric acid" and calculate the content of $C_{18}H_{15}Cl_3N_2O \cdot HNO_3$.

Category As described under econazole nitrate.

Strength 1%

Storage Preserve in well closed containers.

Econazole Nitrate Spray

Econazole Nitrate Spray contains not less than 90.0% and not more than 110.0% of labelled amount of Econazole Nitrate ($C_{18}H_{15}Cl_3N_2O \cdot HNO_3$).

Description A colourless to pale yellow and clear liquid, with fragrance.

Identification (1) To 1 ml add 2-3 drops of trinitrophenol TS, a yellowish-white precipitate is produced.
(2) Add 1 ml of diphenylamine TS along the wall of test tube to 2 ml, a blue colour develops between two layers.

Minimum Fill Complies with the general requirement of the test for Minimum fill (Appendix X F).

Assay Dilute a quantity of 15 ml (equivalent to 150 mg of econazole nitrate), accurately measured, to 100 ml with ethanol and shake well, dilute 5 ml of resulting solution to 100 ml with ethanol and shake well. To 5 ml add a mixture of hydrochloric acid solution 0.1 mol/L and methanol (1:9) to 50 ml. Determine the absorbance of the resulting solution at 222 nm and 234 nm (Appendix IV A), using the same solvent as blank. Repeat the operation using econazole nitrate CRS instead of the substance being examined, calculate the difference of the absorbance at $A_{234nm} - A_{222nm}$ respectively. Calculate the content of $C_{18}H_{15}Cl_3N_2O \cdot HNO_3$ accordingly.

Category As described under Econazole Nitrate.

Strength 1%

Storage Preserve in well closed containers.

Econazole Nitrate Suppositories

Econazole nitrate suppositories contains not less than 90.0% and not more than 110.0% of labelled amount of econazole nitrate ($C_{18}H_{15}Cl_3N_2O \cdot HNO_3$).

Description White to slight yellow suppositories.

Identification (1) Dissolve in 15 ml of hexane by warming on water bath, allow it cool in air, discard hexane and wash the residue two times with 10 ml of hexane, Evaporate residual hexane to dryness by heating on water bath. Dissolve 0.1 g of residue in 5 ml of methanol as the test solution. Dissolve about 0.1 g of econazole nitrate CRS in 5 ml of methanol as the reference solution. Carry out the method for thin-layer chromatography using silica gel as the coating substance and as mobile phase. Apply separately to the plate 5 μ l of each two solution. After removal of the plate, allow it to dry in air, and expose the plate to iodine

vapour until a brown spot appears in the chromatogram obtained with.

(2) Comply with tests (1) and (2) for Identification described under econazole nitrate using the residue obtained from identification (1).

Other requirements Comply with the general requirements for suppositories.

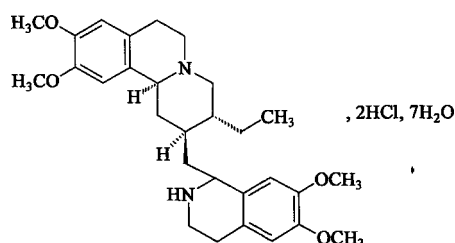
Assay Mix well 10 of suppositories accurately weighed and weigh a quantity (equivalent to 40 mg of Econazole Nitrate), carry out the assay described under Econazole Nitrate Cream.

Category As described under Econazole Nitrate.

Strength (1) 50 mg (2) 150 mg

Storage Preserve in well closed containers and stored in a cool place.

Emetine Hydrochloride



$C_{29}H_{40}N_2O_4 \cdot 2HCl \cdot 7H_2O$ 679.68 [316-42-7]

Emetine Hydrochloride is 6', 7', 10, 11-tetramethoxyemetan dihydrochloride heptahydrate. It contains not less than 98.0% of $C_{29}H_{40}N_2O_4 \cdot 2HCl$, calculated on the dried basis.

Description A white to slightly yellowish crystalline powder; odourless; taste, bitter; deteriorated on exposure to light.

Freely soluble in water, ethanol or chloroform.

Specific optical rotation $+16^\circ$ to $+19^\circ$, in a solution of 50 mg per ml in water (Appendix VI E).

Identification (1) To about 5 mg add 1 ml of ammonium molybdate in sulfuric acid TS, and mix well; a bright-green colour is produced.

(2) The infrared absorption spectrum (Appendix IV C) is concordant with the spectrum of emetine hydrochloride CRS.

(3) Yields the reactions characteristic of chlorides (Appendix III).

Acidity Dissolve 0.10 g in 10 ml of water, add 1 drop of methyl red IS. If the solution becomes pink, it changes to yellow on the addition of 0.5 ml of sodium hydroxide (0.02 mol/L) VS.

Cephaeline Protect the operations from light. Carry out the method for thin-layer chromatography (Appendix V B), using silica gel G as the coating substance and a mixture of chloroform-diethylamine (9:1) as the mobile phase. Apply separately to the plate 10 μ l each of two solutions in methanol containing (1) 10 mg per ml of the substance being examined and (2) 0.2 mg per ml of cephaeline CRS. Develop the chromatogram until the solvent front has moved about 12 cm. Remove the plate, dry in air. Spray the plate with 2.5 mol/L sodium hydroxide solution, and dry at 50°C for 5 minutes. Then spray the plate with diazotized *p*-nitroaniline TS. Any spot in the chromatogram other than the principal spot obtained with solution (1) is not more

intense than the principal spot obtained with solution (2).

Loss on drying When dried to constant weight at 105°C , loses not less than 15% and not more than 19% of its weight (Appendix VIII L).

Residue on ignition Not more than 0.1% (Appendix VIII N).

Assay Dissolve 0.2 g, accurately weighed, in 20 ml of acetic anhydride, add 4 ml of mercuric acetate TS and 1 drop of crystal violet IS. Titrate with perchloric acid (0.1 mol/L) VS until the colour changes to green. Perform a blank determination and make any necessary correction. Each ml of perchloric acid (0.1 mol/L) VS is equivalent to 27.68 mg of $C_{29}H_{40}N_2O_4 \cdot 2HCl$.

Category Amoebacide.

Storage Preserve in tightly closed containers, protected from light.

Preparation Emetine Hydrochloride Injection

Emetine Hydrochloride Injection

Emetine Hydrochloride Injection is a sterile solution of Emetine Hydrochloride in Water for Injection. It contains not less than 95.0% and not more than 105.0% of the labelled amount of $C_{29}H_{40}N_2O_4 \cdot 2HCl \cdot 7H_2O$.

Description A clear, colourless liquid, deteriorated on exposure to light.

Identification Evaporate the injection to dryness, the residue complies with the tests (1), and (3) for Identification described under Emetine Hydrochloride.

pH value 2.6-4.0 (Appendix VI H).

Cephaeline Protect the operations from light. Evaporate 1 ml of the injection on a water bath to dryness by a current of nitrogen. Dissolve the residue in methanol to produce a solution of 10 mg per ml, use this solution as solution (1). Carry out the test for Cephaeline described under Emetine Hydrochloride. Any spot in the chromatogram other than the principal spot obtained with solution (1) is not more intense than the principal spot obtained with solution (2).

Other requirements Complies with the general requirements for injections (Appendix I B).

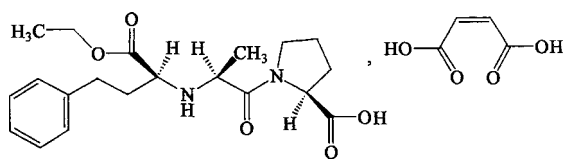
Assay Dilute an accurately measured quantity equivalent to about 0.3 g of emetine hydrochloride to 20 ml with water, add 10 ml of sodium hydroxide TS. Extract with 30 ml of ether followed by several quantities, each of 15 ml, of ether until alkaloids are completely extracted. Wash the combined ether extracts with two 10 ml quantities of water. Extract each washing with the same 20 ml of ether. Combine the two ether extracts. Add 20 ml of hydrochloric acid (0.1 mol/L) VS, measured accurately, shake and extract, allow to separate, retaining the acidic layer. Wash the ether layer with several quantities, each of 20 ml, of water. Combine the washings and acidic layer. Add 1 to 2 drops of methyl red IS, titrate with sodium hydroxide (0.1 mol/L) VS. Each ml hydrochloric acid (0.1 mol/L) VS is equivalent to 33.99 mg of $C_{29}H_{40}N_2O_4 \cdot 2HCl \cdot 7H_2O$.

Category As described under Emetine Hydrochloride.

Strength (1) 1 ml:30 mg (2) 1 ml:60 mg

Storage preserve in well closed containers, protected from light.

Enalapril Maleate



$C_{20}H_{28}N_2O_5 \cdot C_4H_4O_4$ 492.52

Enalapril Maleate is 1-*N*-[(*S*)-1-carboxy-3-phenylpropyl]-*L*-alanyl]-*L*-proline 1'-ethylester, maleate (1 : 1). It contains not less than 98.5% of $C_{20}H_{28}N_2O_5 \cdot C_4H_4O_4$, calculated on the dried basis.

Description A white or almost white crystalline powder; odourless; slightly hygroscopic.

Freely soluble in methanol, sparingly soluble in water, slightly soluble in ethanol or acetone; practically insoluble in chloroform.

Specific optical rotation -41° to -43.5° , in a solution of 50 mg per ml in methanol (Appendix VI E).

Identification (1) To about 20 mg, add 1 ml of sulfuric acid dilute TS and a few drops of potassium permanganate TS, a red colour disappears immediately. (2) The infrared absorption spectrum (Appendix IV C) is concordant with the reference spectrum (Appendix XIII).

Acidity Dissolve 0.1 g in 10 ml of water, pH 2.0-2.8 (Appendix VI H).

Related substances Prepare a solution of 2 mg per ml in the mobile phase as the test solution. Measure accurately a quantity of the test solution, dilute with the mobile phase to produce the reference solution of about 40 μ g per ml. Dissolve separately a quantity of enalapril maleate CRS and enalaprilat CRS, accurately weighed, in water respectively to produce each of solution of 0.1 mg per ml; dissolve a quantity of enalapril diketopiperazine CRS, accurately weighed, in the mobile phase, ultrasonicate to produce a solution of 0.1 mg per ml. Measure accurately a quantity of above three solutions, dilute with water to produce a mixed solution of 0.02 mg per ml containing enalapril maleate, enalaprilat and enalapril diketopiperazine separately. Carry out the method for high performance liquid chromatography (Appendix V D), using a column packed with octasilane bonded silica gel and a mixture of acetonitrile-phosphate BS [0.01 mol/L potassium dihydrogen phosphate solution, adjust to pH 2.2 with phosphoric acid] (25 : 75) as the mobile phase. Detection wavelength is 215 nm. The temperature of the column is maintained at 50°C. Inject 20 μ l of the mixed solution into the column, the number of the theoretical plates of the column is not less than 300, calculated with reference to the peak of enalapril. The tailing factor of the peak of enalapril is not more than 2.0. The resolution factor between the peaks of maleate and enalaprilat complies with related requirements; the resolution factor between the peaks of enalaprilat, enalapril and enalapril diketopiperazine is not less than 4.0. Inject 20 μ l of the reference solution into the column, adjust the attenuation so that the principal peak height in the chromatogram is 15% of the full scale of the chart. Inject separately 20 μ l each of the test solution and the reference solution into the column and record the chromatogram for 3 times the retention time of the peak of enalapril. The sum of the areas of all peaks other than the peak of the principal peak and maleate peak in the

chromatogram obtained with test solution is not greater than the area of the principal peak in the chromatogram obtained with the reference solution.

Acetonitrile Dissolve a quantity of the substance being examined, accurately weighed, in dimethylformamide to produce the test solution of 100 mg per ml. Dissolve a quantity of acetonitrile, accurately weighed, in dimethylformamide to produce the reference solution of 40 μ g per ml. Carry out the method for determination of residual solvents (Appendix VIII P), using a column coated with polyethylene glycol 20000 as the stationary phase, a flame ionization detector is used. Maintain the temperature of the column at 60°C for 2 min, then raise the temperature at a rate of 10°C per minute to 200°C and maintain at 200°C for 5 min; maintain injection port temperature at 200°C and detector temperature at 250°C. The number of the theoretical plates of the column is not less than 10000, calculated with reference to the peak of acetonitrile. Inject separately 1 μ l each of the test solution and the reference solution into the column and record the chromatogram. The content of acetonitrile in test solution complies with related requirement.

Loss on drying When dried in vacuum for 4 hours at 50°C, loses not more than 0.5% of its weight (Appendix VIII L).

Residue on ignition Not more than 0.1% (Appendix VIII N), using 1.0 g.

Heavy metals Carry out the limit test for heavy metals (Appendix VIII H, method 2), using the residue obtained in the test for Residue on ignition; not more than 0.002%.

Assay Weigh accurately about 0.4 g, add 15 ml of glacial acetic acid and 5 ml of anhydrous dioxane (to 500 ml of dioxane, add 10 g of dried 4A molecular sieve and allow to stand for a night), dissolve by warming, add 1 drop of crystal violet IS, titrate with perchloric acid (0.1 mol/L) VS to blue as end point. Perform a blank determination. Each ml of perchloric acid (0.1 mol/L) VS is equivalent to 49.25 mg of $C_{20}H_{28}N_2O_5 \cdot C_4H_4O_4$.

Category Antihypertensive.

Storage Preserve in tightly closed containers, protected from light.

Preparation (1) Enalapril Maleate Tablets
(2) Enalapril Maleate Capsules

Enalapril Maleate Capsules

Enalapril Maleate Capsules contain not less than 90.0% of and not more than 110.0% of the labelled amount of enalapril maleate ($C_{20}H_{28}N_2O_5 \cdot C_4H_4O_4$).

Description Capsules containing white or almost white power.

Identification (1) To a quantity of the contents of the capsules (equivalent to about 20 mg of enalapril maleate), add 2 ml of sulfuric acid dilute TS, stir and filter. Add a few drops of potassium permanganate TS to the filtrate, a red colour disappears immediately.

(2) The retention time of principal peaks of the substance being examined in the chromatogram obtained in the Assay is identical with that of enalapril maleate CRS in the chromatogram of the reference solution.

Content uniformity Comply with the requirements for content uniformity (Appendix X E). Transfer the content of 1 capsule in a 50 ml (for strength 10 mg) or 25 ml (for

strength 5 mg) volumetric flask, wash the shell with water in divided portions, transfer the washings to the same volumetric flask, add a quantity of water, shake to dissolve enalapril maleate, dilute with water to volume, mix well and filter. Carry out the procedure described under Assay, beginning at the words "Inject 20 μ l of the successive filtrate into the column...". Calculate the content of $C_{20}H_{28}N_2O_5 \cdot C_4H_4O_4$.

Dissolution Carry out the dissolution test (Appendix X C, method 1), using 500 ml of water as the dissolution medium, adjust the rotational speed of the basket to 100 rpm. Withdraw the solution after exactly 30 minutes and filter, using the successive filtrate as the test solution. Dissolve a quantity of enalapril maleate CRS, accurately weighed, in water to produce a solution of 20 μ g per ml (for strength 10 mg) or 10 μ g per ml (for strength 5 mg) as the reference solution. Carry out the procedure described under Assay, inject 20 μ l of the above two solutions into the column, and record the chromatogram. Calculate the dissolution of $C_{18}H_{28}N_2O_5 \cdot C_4H_4O_4$ from each capsule. Not less than 75% of the labelled amount is dissolved.

Related substances Weigh accurately a quantity of the powdered contents of capsules, dissolve in the mobile phase to produce a solution containing enalapril maleate of 2 mg per ml as the test solution. Measure accurately a quantity of the solution, dilute with the mobile phase to produce a solution containing enalapril maleate of 0.1 mg per ml as the reference solution. Carry out the procedure described under Assay, Inject 20 μ l of reference solution into the column, adjust the attenuation so that the principal peak height in the chromatogram is 15% of the full scale of the chart. Inject 20 μ l of test solution into the column and record the chromatogram for 3 times the retention time of the principal peak. The sum of the areas of all peaks other than the principal peak and maleate peak in the chromatogram obtained with test solution is not greater than the area of the principal peak in the chromatogram obtained with reference solution.

Other requirements Comply with the general requirements for capsules (Appendix I E).

Assay Carry out the method for high performance liquid chromatography (Appendix V D), using a column packed with octasilane bonded silica gel, and a mixture of acetonitrile-phosphate BS [0.01 mol/L potassium dihydrogen phosphate solution, adjust to pH 2.2 with phosphoric acid] (25 : 75) as the mobile phase. Detection wavelength is 215 nm; the temperature of the column is maintained at 50°C. Dissolve separately a quantity of enalapril maleate CRS and enalaprilat CRS, accurately weighed, in water respectively to produce each of solution of 0.1 mg per ml; dissolve a quantity of enalapril diketopiperazine CRS, accurately weighed, in the mobile phase, ultrasonicate to produce a solution of 0.1 mg per ml. Measure accurately a quantity of above three solutions, dilute with water to produce a mixed solution of 0.02 mg per ml containing enalapril maleate, enalaprilat and enalapril diketopiperazine separately. Inject 20 μ l of the mixed solution into the column, the number of the theoretical plates of the column is not less than 300, calculated with reference to the peak of enalapril. The tailing factor of the peak of enalapril is not more than 2.0. The resolution factor between the peaks of maleate and enalaprilat complies with related requirements; the resolution factor between the peaks of enalaprilat, enalapril and enalapril diketopiperazine is not less than 4.0.

Procedure Weigh accurately the contents of 20 capsules. Triturate an accurately weighed quantity equivalent to about 20 mg of enalapril maleate into a 100 ml volumetric flask,

add a quantity of water, shake to dissolve enalapril maleate, dilute with water to volume, mix well and filter. Inject 20 μ l of the successive filtrate into the column, record the chromatogram. Dissolve a quantity of enalapril maleate CRS, accurately weighed, in water to produce a solution of 0.2 mg per ml, repeat the operation. Calculate the content of $C_{20}H_{28}N_2O_5 \cdot C_4H_4O_4$ with respect to peak area obtained in the chromatogram by external a standard method.

Category As described under Enalapril Maleate.

Strength (1) 5 mg (2) 10 mg

Storage Preserve in tightly closed containers, protected from light.

Enalapril Maleate Tablets

Enalapril Maleate Tablets contain not less than 90% of and not more than 110.0% of the labelled amount of enalapril maleate ($C_{20}H_{28}N_2O_5 \cdot C_4H_4O_4$).

Description White tablets.

Identification (1) To a quantity of powdered tablets (equivalent to about 20 mg of enalapril maleate) add 2 ml of sulfuric acid dilute TS, stir and filter. Add a few drops of potassium permanganate TS to the filtrate, a red colour disappears immediately.

(2) The retention time of the principal peak of the substance being examined in the chromatogram of the test solution is identical with that of enalapril maleate CRS in the chromatogram of the reference solution.

Content uniformity Comply with the requirements for content uniformity (Appendix X E). Place 1 tablet in a 50 ml (10 mg) or 25 ml (5 mg) volumetric flask, add a quantity of water, shake to dissolve enalapril maleate, dilute with water to volume, mix well and filter. Carry out the procedure described under Assay, beginning at the words "Inject 20 μ l of the successive filtrate into the column...". Calculate the content of $C_{18}H_{28}N_2O_5 \cdot C_4H_4O_4$.

Dissolution Carry out the dissolution test (Appendix X C, method 1), using 500 ml of water as the dissolution medium, adjust the rotational speed of the basket to 100 rpm. Withdraw the solution after exactly 30 minutes and filter, using the successive filtrate as the test solution. Dissolve a quantity of enalapril maleate CRS, accurately weighed, in water to produce a solution of 20 μ g per ml (for strength 10 mg) or 10 μ g per ml (for strength 5 mg) as the reference solution. Carry out the procedure described under Assay, inject 20 μ l of the above two solutions into the column, and record the chromatogram. Calculate the dissolution of $C_{18}H_{28}N_2O_5 \cdot C_4H_4O_4$ from each tablet. Not less than 75% of the labeled amount is dissolved.

Related substances Weigh accurately a quantity of the powdered tablets, dissolve in the mobile phase to produce a solution containing enalapril maleate of 2 mg per ml as the test solution. Measure accurately a quantity of the solution, dilute with the mobile phase to produce a solution containing enalapril maleate of 0.1 mg per ml as the reference solution. Carry out the procedure described under Assay, Inject 20 μ l of the reference solution into the column, adjust the attenuation so that the principal peak height in the chromatogram is 15% of the full scale of the chart. Inject 20 μ l of test solution into the column and record the chromatogram for 3 times the retention time of the principal peak. The sum of the areas of all peaks other than the principal peak and maleate peak in the chromatogram obtained with test solution is not greater than the area of the

principal peak in the chromatogram obtained with reference solution.

Other requirements Comply with the general requirements for tablets (Appendix I A).

Assay Carry out the method for high performance liquid chromatography (Appendix V D), using a column packed with octadecylsilane bonded silica gel, and a mixture of acetonitrile-phosphate BS [0.01 mol/L potassium dihydrogen phosphate solution, adjust to pH 2.2 with phosphoric acid] (25 : 75) as the mobile phase. Detection wavelength is 215 nm; the temperature of the column is maintained at 50°C. Dissolve separately a quantity of enalapril maleate CRS and enalaprilat CRS, accurately weighed, in water respectively to produce each of solution of 0.1 mg per ml; dissolve a quantity of enalapril diketopiperazine CRS, accurately weighed, in the mobile phase, ultrasonicate to produce a solution of 0.1 mg per ml. Measure accurately a quantity of above three solutions, dilute with water to produce a mixed solution of 0.02 mg per ml containing enalapril maleate, enalaprilat and enalapril diketopiperazine separately. Inject 20 µl of the mixed solution into the column, the number of the theoretical plates of the column is not less than 300, calculated with reference to the peak of enalapril. The tailing factor of the peak of enalapril is not more than 2.0. The resolution factor between the peaks of maleate and enalaprilat complies with related requirements; the resolution factor between the peaks of enalaprilat, enalapril and enalapril diketopiperazine is not less than 4.0.

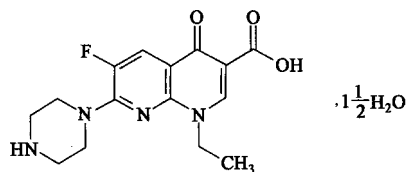
Procedure Weigh accurately 20 tablets. Triturate an accurately weighed quantity equivalent to about 20 mg of enalapril maleate into a 100 ml volumetric flask, add a quantity of water, shake to dissolve enalapril maleate, dilute with water to volume, mix well and filter. Inject 20 µl of the successive filtrate into the column, record the chromatogram. Dissolve a quantity of enalapril maleate CRS, accurately weighed, in water to produce a solution of 20 µg per ml, repeat the operation. Calculate the content of $C_{20}H_{28}N_2O_5 \cdot C_4H_4O_4$ with respect to peak area obtained in the chromatogram by external standard method.

Category As described under Enalapril Maleate.

Strength (1) 5 mg (2) 10 mg

Storage Preserve in tightly closed containers, protected from light.

Enoxacin



$C_{15}H_{17}FN_4O_3 \cdot 1\frac{1}{2}H_2O$ 347.35

Enoxacin is 1-ethyl-6-fluoro-1,4-dihydro-4-oxo-7-(1-piperazinyl)-1,8-naphthyridine-3-carboxylic acid sesquihydrate. It contains not less than 98.5% and not more than 102.0% of $C_{15}H_{17}FN_4O_3$, calculated on the dried basis.

Description An almost white to slightly yellow crystalline powder; odourless; taste, bitter.

Slightly soluble in methanol; very slightly soluble in ethanol; insoluble in water; freely soluble in glacial acetic acid or sodium hydroxide TS.

Melting range 222-227°C, with decomposition (Appendix VI C).

Identification (1) The retention time of principal peaks of the substance being examined in the chromatogram obtained in the Assay is identical with that of enoxacin CRS.

(2) The infrared absorption spectrum (Appendix IV C) is concordant with the reference spectrum of enoxacin (Appendix XVI).

Clarity and colour of solution Dissolve 0.5 g in 10 ml sodium hydroxide TS, the solution is clear and colourless; any opalescence produced is not more pronounced than that of reference suspension I (Appendix IX B); any colour produced is not more intense than that of reference solution Y₄ or YG₄ (Appendix IX A, method 1).

Related substances Dissolve about 50 mg of the substance being examined in 20 ml of 0.1 mol/L hydrochloride solution in a 100 volumetric flask, dilute with mobile phase to volume and mix well (solution 1). Measure accurately a quantity, dilute with mobile phase to produce a solution of 5 µg per ml (solution 2). Carry out the method described under the Assay. Inject 20 µl of solution (2) into the column, adjust the attenuation so that the principal peak height in the chromatogram is 20%-25% of the full scale of the chart. Inject separately 20 µl of above two solutions, and record the chromatogram for twice the retention time of the principal peak. The sum of the areas of all peaks other than the principal peak in the chromatogram obtained with solution (1) is not greater than the area of the principal peak in the chromatogram obtained with solution (2) (1.0%).

Loss on drying When dried to constant weight at 105°C, loses not less than 7.8% and not more than 9.0% (Appendix VIII L).

Residue on ignition Not more than 0.1% (Appendix VIII N), using 1.0 g.

Heavy metals Carry out the limit test for heavy metals (Appendix VIII H, method 2), using the residue obtained in the test for Residue on ignition; not more than 0.002%.

Assay Carry out the method for high performance liquid chromatograph (Appendix V D), using a column packed with octadecylsilane bonded silica gel and a mixture of 0.025 mol/L phosphoric acid solution adjust to pH 3.5 with triethylamine-methanol-acetonitrile (80 : 10 : 10) as the mobile phase. Detection wavelength is 269 nm and the number of the theoretical plates of the column is not less than 2000, calculated with reference to the peak of enoxacin. The resolution factor between the peaks of enoxacin and the neighbour impurity complies with the related requirements.

Procedure Dissolve about 25 mg of the substance being examined, accurately weighed, in 20 ml of 0.1 mol/L hydrochloride solution in a 100 volumetric flask, dilute with mobile phase to volume and mix well. Measure accurately 5 ml of the solution in a 25 ml volumetric flask, dilute with mobile phase to volume and mix well. Inject 20 µl of the solution into the column. Repeat the operation, using enoxacin CRS instead of the substance being examined, calculate the content of $C_{15}H_{17}FN_4O_3$ with respect to the peak area obtained in the chromatogram by the external standard method.

Category Antibiotic.

Storage Preserve in tightly closed containers, stored in a dry place and protected from light.

Preparation (1) Enoxacin Capsules
(2) Enoxacin Eye Drops

- (3) Enoxacin Cream
(4) Enoxacin Tablets

Enoxacin Capsules

Enoxacin Capsules contain not less than 90.0% and not more than 110.0% of the labelled amount of enoxacin ($C_{15}H_{17}FN_4O_3$).

Description Capsules containing white to slightly yellow granules or powder.

Identification (1) The retention time of principal peak of the substance being examined in the chromatogram obtained in the Assay is identical with that of enoxacin CRS.

(2) Dissolve a quantity of the contents in 0.1 mol/L sodium hydroxide solution to produce a solution of 4 µg per ml and filter. The light absorption of the filtrate exhibits two maxima at 266 nm and 346 nm (Appendix IV A).

Dissolution Carry out the dissolution test (Appendix X C, method 1), using 900 ml of diluted hydrochloric acid solution (to 24 ml of dilute hydrochloric acid add water to 1000 ml) as the dissolution medium, adjust the rotational speed of the basket to 100 rpm. Withdraw the solution after exactly 30 minutes and filter. Dilute a quantity of successive filtrate, accurately measured, with the diluted hydrochloric acid solution to produce a solution of about 4 µg per ml. Measure the absorbance of the resulting solution at 266 nm (Appendix IV A). Dissolve a quantity of enoxacin CRS, accurately weighed, in the diluted hydrochloric acid solution to produce a solution of about 4 µg per ml. Measure the absorbance in the same manner. Calculate the dissolution of $C_{15}H_{17}FN_4O_3$ from each capsule. Not less than 80% of the labelled amount is dissolved.

Other requirements Comply with the general requirements for capsules (Appendix I E).

Assay Weigh accurately a quantity of the mixed and finely powdered contents obtained in the test for Weight variation of contents, equivalent to about 25 mg of enoxacin, to a 100 ml volumetric flask, add 20 ml of 0.1 mol/L hydrochloric acid solution, shake for 15 minutes to dissolve enoxacin, dilute with mobile phase to volume, mix well and filter. Measure accurately 5 ml of the successive filtrate to a 25 ml volumetric flask, dilute with mobile phase to volume and mix well. Carry out the method described under Enoxacin, using the resulting solution.

Category As described under Enoxacin.

Strength (1) 0.1 g (2) 0.2 g

Storage Preserve in tightly closed containers, stored in a dry place and protected from light.

Enoxacin Cream

Enoxacin Cream contains not less than 90.0% and not more than 110.0% of the labelled amount of enoxacin ($C_{15}H_{17}FN_4O_3$).

Description A white to pale yellow cream.

Identification (1) The retention time of principal peak of the substance being examined in the chromatogram obtained in the Assay is identical with that of enoxacin CRS.

(2) To a quantity add a quantity of 0.1 mol/L sodium hydroxide solution, heat in a water bath at 50-60°C to produce

a solution of 4 µg per ml. Cool in an ice bath to solidify the matrix, filter. The light absorption of the filtrate exhibits two maxima at 268 nm and 340 nm (Appendix IV A).

Other requirement Complies with the general requirements for cream (Appendix I F).

Assay Weigh accurately a quantity equivalent to about 10 mg of enoxacin to a 50 ml beaker, add about 20 ml of 0.1 mol/L hydrochloric acid solution, stir to dissolve enoxacin. Transfer the solution to a 100 ml volumetric flask, dilute to volume with methanol, mix well and filter. Measure accurately 5 ml of the successive filtrate to a 10 ml volumetric flask, dilute with mobile phase to volume and mix well. Carry out the method described under Enoxacin, using the resulting solution.

Category As described under Enoxacin.

Strength 10 g ± 0.1 g

Storage Preserve in tightly closed containers, stored in a dry and cool place.

Enoxacin Eye Drops

Enoxacin Eye Drops contain not less than 90.0% and not more than 110.0% of the labelled amount of enoxacin ($C_{15}H_{17}FN_4O_3$).

Description A colourless to slightly yellow, clear liquid.

Identification (1) The retention time of principal peaks of the substance being examined in the chromatogram obtained in the Assay is identical with that of enoxacin CRS.

(2) The light absorption of a solution of 4 µg per ml in 0.1 mol/L sodium hydroxide solution exhibits two maxima at 266 nm and 346 nm (Appendix IV A).

pH value 4.5-5.5 (Appendix VI H).

Colour Any colour produced is not more intense than that of reference solution Y₂ or YG₂ (Appendix IX A, method 1).

Other requirements Comply with the general requirements for Eye preparation (Appendix I G).

Assay Dilute an accurately measured quantity of drops with mobile phase to produce a solution of 50 µg of enoxacin per ml, shake well, Carry out the method described under Assay of Enoxacin.

Category As described under Enoxacin.

Strength 8 ml ± 24 mg

Storage Preserve in tightly closed containers, stored in a cool place and protected from light.

Enoxacin Tablets

Enoxacin Tablets contain not less than 93.0% and not more than 107.0% of the labelled amount of enoxacin ($C_{15}H_{17}FN_4O_3$).

Description Almost white or slightly yellow tablets or film coated tablets with almost white or slightly yellow core.

Identification (1) The retention time of principal peaks of the substance being examined in the chromatogram obtained in the Assay is identical with that of enoxacin CRS.

(2) Dissolve a quantity of the powdered tablets in 0.1 mol/L sodium hydroxide solution to produce a solution of 4 µg of

enoxacin per ml and filter. The light absorption of the filtrate exhibits two maxima at 266 nm and 346 nm. (Appendix IV A).

Dissolution Carry out the dissolution test (Appendix X C, method 1), using 900 ml of diluted hydrochloric acid solution (to 24 ml of dilute hydrochloric acid add water to 1000 ml) as the dissolution medium, adjust the rotational speed of the basket to 100 rpm. Withdraw a quantity of the solution after exactly 30 minutes and filter. Dilute a quantity of successive filtrate, accurately measured, with the diluted hydrochloric acid solution to produce a solution of about 4 µg per ml. Measure the absorbance of the resulting solution at 266 nm (Appendix IV A). Dissolve a quantity of enoxacin CRS, accurately weighed, in the diluted hydrochloric acid solution to produce a solution of about 4 µg per ml. Measure the absorbance in the same manner. Calculate the dissolution of $C_{15}H_{17}FN_4O_3$ from each tablet. Not less than 80% of the labelled amount is dissolved.

Other requirements Comply with the general requirements for tablets (Appendix I A).

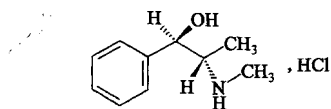
Assay Weigh accurately and powder finely 10 tablets. Weigh accurately a quantity of the powder equivalent to about 25 mg of enoxacin to a 100 ml volumetric flask, add 20 ml of 0.1 mol/L hydrochloric acid solution, shake thoroughly to dissolve enoxacin, dilute to volume with mobile phase and mix well, filter. Measure accurately 5 ml of the successive filtrate to a 25 ml volumetric flask, dilute with mobile phase to volume and mix well. Carry out the method described under Enoxacin, using the resulting solution.

Category As described under Enoxacin.

Strength (1) 0.1 g (2) 0.2 g

Storage Preserve in tightly closed containers, protected from light.

Ephedrine Hydrochloride



$C_{10}H_{15}NO \cdot HCl$ 201.70

[50-98-6]

Ephedrine Hydrochloride is (1R, 2S) -2-methyl-amino-1-phenylpropane-1-ol. It contains not less than 99.0% of $C_{10}H_{15}NO \cdot HCl$, calculated on the dried basis.

Description White needle crystals or a crystalline powder; odorless; taste, bitter.

Freely soluble in water; soluble in ethanol; insoluble in chloroform or ether.

Melting point 217-220°C (Appendix VI C).

Specific optical rotation -33.0° to -35.5°, in an aqueous solution of 50 mg per ml (Appendix VI E).

Identification (1) Dissolve 10 mg in 1 ml of water, add 2 drops of copper sulfate TS and 1 ml of 20% sodium hydroxide solution, a bluish-violet colour is produced. Add 1 ml of ether, shake and allow to stand; a purple colour is produced in the ethereal layer and a blue colour is produced in the aqueous layer.

(2) The infrared absorption spectrum (Appendix IV C) is concordant with the reference spectrum of ephedrine hydrochloride (Appendix XVI).

(3) The aqueous solution yields the reactions characteristic of chlorides (Appendix III).

Clarity of solution A solution of 1.0 g in 20 ml of water is clear.

Acidity or alkalinity Dissolve 1.0 g in 20 ml of water, add 1 drop of methyl red IS; not more than 0.10 ml of either sulfuric acid (0.01 mol/L) VS or sodium hydroxide (0.02 mol/L) VS is required to change the colour of the solution.

Sulfate Carry out the limit test for sulfates (Appendix VIII B), using 1.0 g. Any opalescence produced is not more intense than that of a reference using 1.0 ml of potassium sulfate standard solution (0.010%).

Loss on drying When dried to constant weight at 105°C, loses not more than 0.5% of its weight (Appendix VIII L).

Residue on ignition Not more than 0.1% (Appendix VIII N).

Heavy metals Dissolve 1.0 g in 23 ml of water, add 2 ml of sodium acetate BS (pH 3.5). Carry out the limit test for heavy metals (Appendix VIII H, method 1); not more than 0.002%.

Assay Dissolve 0.15 g, accurately weighed, in 10 ml of glacial acetic acid by warming, add 4 ml of mercuric acetate TS and 1 drop of crystal violet IS, titrate with perchloric acid (0.1 mol/L) VS until the colour changes to emerald green. Perform a blank determination and make any necessary correction. Each ml of perchloric acid (0.1 mol/L) VS is equivalent to 20.17 mg of $C_{10}H_{15}NO \cdot HCl$.

Category β_2 Adrenergic drug.

Storage Preserve in tightly closed containers.

Preparation (1) Ephedrine Hydrochloride Injection
(2) Ephedrine Hydrochloride Nasal Drops

Ephedrine Hydrochloride Injection

Ephedrine Hydrochloride Injection is a sterile solution of ephedrine hydrochloride in Water for Injection. It contains not less than 95.0% and not more than 105.0% of the labelled amount of ephedrine hydrochloride ($C_{10}H_{15}NO \cdot HCl$).

Description A colourless, clear liquid.

Identification Complies with the tests for Identification (1) and (3) described under Ephedrine Hydrochloride.

pH value 4.5-6.5 (Appendix VI H).

Other requirements Complies with the general requirements for injections (Appendix I B).

Assay Measure accurately a quantity equivalent to about 0.15 g of ephedrine hydrochloride. Evaporate it to dryness on a water bath, dry at 105°C for 1 hour and cool to room temperature. Dissolve the residue in 10 ml of glacial acetic acid, add 5 ml of mercuric acetate TS, 2 ml of acetic anhydride and 1 drop of crystal violet IS, titrate with perchloric acid (0.1 mol/L) VS to an emerald green colour. Perform a blank determination and make any necessary correction. Each ml of perchloric acid (0.1 mol/L) VS is equivalent to 20.17 mg of $C_{10}H_{15}NO \cdot HCl$.

Category As described under Ephedrine Hydrochloride.

Strength 1 ml:30 mg

Storage Preserve in well closed containers, protected from light.

Ephedrine Hydrochloride Nasal Drops

Ephedrine Hydrochloride Nasal Drops contain not less than 90.0% and not more than 110.0% of the labelled amount of Ephedrine Hydrochloride ($C_{10}H_{15}NO \cdot HCl$).

Description A clear, colourless liquid.

Identification Comply with the tests for Identification described under Ephedrine Hydrochloride.

pH value pH 5.0-7.0 (Appendix VI H).

Other requirements Comply with the general requirements for nasal preparations (Appendix I R).

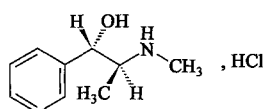
Assay Measure accurately 2 ml, equivalent to about 20 mg of Ephedrine Hydrochloride, into a 100 ml volumetric flask, dilute with water to volume and mix well, use this solution as test solution. Dissolve an accurately weighed quantity of ephedrine hydrochloride CRS, in water to produce solution containing about 0.2 mg of ephedrine hydrochloride CRS per ml as a reference solution. Measure accurately 1 ml of each of the above two solutions separately into two test tubes, add 1 ml of ninhydrine solution (dissolve 0.4 g of ninhydrine in 2 ml of ethanol, dilute with water to 20 ml, add a 1% solution of sodium carbonate to adjust to pH 7.8-7.9. This solution should be freshly prepared), heat on a water bath for 10 minutes, cool rapidly, add 7 ml of water and mix well. All the solutions to be added above should be measured accurately. Measure the absorbance of the solutions at 570 nm at once (Appendix IV), calculate the content of $C_{10}H_{15}NO \cdot HCl$.

Category As described under Ephedrine Hydrochloride.

Strength 1%

Storage Preserve in tightly closed containers, protected from light.

Pseudoephedrine Hydrochloride



$C_{10}H_{15}NO \cdot HCl$ 201.70

[345-78-8]

Pseudoephedrine Hydrochloride is $S-(R^*, R^*)$ - α -[1-(methylamino) ethyl]-benzenemethanol hydrochloride. It contains not less than 99.0% of $C_{10}H_{15}NO \cdot HCl$, calculated on the dried basis.

Description A white, crystalline powder; odourless; taste, bitter.

Very soluble in water; freely soluble in ethanol; slightly soluble in chloroform.

Melting point 183-186°C (Appendix VI C).

Specific optical rotation +61.0° to +62.5°, in a solution of 50 mg per ml in water (Appendix VI E).

Identification (1) The light absorption of a solution of 0.5 mg per ml in water exhibits maxima at 251 nm, 257 nm and 263 nm (Appendix IV A).

(2) The infrared absorption spectrum (Appendix IV C) is

concordant with the reference spectrum of pseudoephedrine hydrochloride (Appendix XI).

(3) The aqueous solution yields reactions characteristic of chlorides (Appendix III).

Acidity or alkalinity Dissolve 0.2 g in 10 ml of water, add 1 drop of methyl red IS; not more than 0.10 ml of sodium hydroxide (0.02 mol/L) VS or hydrochloric acid (0.02 mol/L) VS is required to change the colour of the solution.

Clarity and colour of solution A solution of 1 g in 20 ml of water is colourless and clear or almost no opalescence; any opalescence produced is not more pronounced than that of reference suspension I (Appendix IX B).

Related substances Carry out the method for high performance liquid chromatography (Appendix V D), using a column packed with phenylsilane bonded silica gel and a mixture of 1.16% ammonium acetate solution-methanol (94:6, adjust with acetic acid to pH of 4.0) as the mobile phase. Detection wavelength is at 257 nm, and the number of theoretical plates of the column is not less than 2000, calculated with reference to the peak of pseudoephedrine and the resolution factor of the two peaks is not less than 2.0. Dissolve a quantity in the mobile phase to produce the solution of the substance being examined containing (1) 2 mg per ml. Measure accurately a quantity of solution (1), dilute with mobile phase to produce the solution (2) 0.01 mg per ml. Dissolve 10 mg of ephedrine hydrochloride CRS with 5 ml of solution (1) in a 100 ml volumetric flask and dilute with the mobile phase to the volume, mix well, as solution (3). Inject 20 μ l of solution (3) into the column, accurately measured, adjust the attenuation so that the two principal peak height in the chromatogram is not less than 50% of the full scale of the chart. Inject separately 20 μ l each of the solution (1) and (2), accurately measured, into the column and record the chromatogram for twice the retention time of the pseudoephedrine peak. The peak area of single impurity is not greater than the principal peak area of the solution (2). The sum of peak areas of all impurities is not greater than twice of the principal peak area of the solution (2) (any peak area less than 10% of the principal peak area obtained with solution (2) can be omitted).

Loss on drying When dried to constant weight at 105°C, loses not more than 0.5% of its weight (Appendix VIII L).

Residue on ignition Not more than 0.1% (Appendix VIII N).

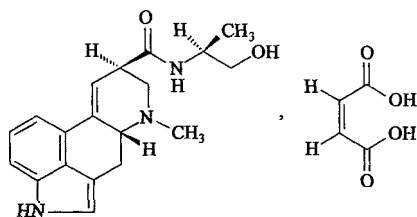
Heavy metals Dissolve 1.0 g in 23 ml of water, add 2 ml of acetate BS (pH 3.5). Carry out the limit test for heavy metals (Appendix VIII H, method 1); not more than 0.002%.

Assay Dissolve about 0.3 g, accurately weighed, in 10 ml of glacial acetic acid on warming, add 5 ml of mercuric acetate TS and 1 drop of crystal violet IS, titrate with perchloric acid (0.1 mol/L) VS until the colour changes to bluish green. Perform a blank determination and make any necessary correction. Each ml of perchloric acid (0.1 mol/L) VS is equivalent to 20.17 mg of $C_{10}H_{15}NO \cdot HCl$.

Category β_2 adrenergic receptor stimulant.

Storage Preserve in tightly closed containers, protected from light.

Ergometrine Maleate



$C_{19}H_{23}N_3O_2 \cdot C_4H_4O_4$ 441.48

[129-51-1]

Ergometrine Maleate is 6-methylergoline *N*-[(*S*)-2-hydroxy-1-methylethyl]-9,10-didehydro-8 β -carboxamide maleate (1:1) (salt). It contains not less than 98.0% of $C_{19}H_{23}N_3O_2 \cdot C_4H_4O_4$, calculated on the dried basis.

Description A white or almost white crystalline powder; odourless; slightly hygroscopic; deteriorated on exposure to light.

Sparingly soluble in water; slightly soluble in ethanol; insoluble in chloroform or ether.

Specific optical rotation +53° to +56°, in a solution of 10 mg per ml in water (Appendix VI E).

Identification (1) The aqueous solution exhibits a blue fluorescence.

(2) Dissolve about 1 mg in 1 ml of water, add 2 ml of *p*-dimethylaminobenzaldehyde TS; a deep blue colour is produced in 5 minutes.

(3) The infrared absorption spectrum (Appendix IV C) is concordant with the reference spectrum of ergometrine maleate (Appendix XVI).

Related substances Carry out the method for thin-layer chromatography (Appendix V B), using silica gel G as the coating substance and a mixture of chloroform-methanol-water (25:8:1) as the mobile phase. Apply separately to the plate 10 μ l each of three solutions in ethanol-concentrated ammonia solution (9:1) containing (1) 5 mg per ml, (2) 0.2 mg per ml of the substance being examined and (3) 5 mg per ml of ergometrine maleate CRS. After developing and removal of the plate, dry in air and examine under ultraviolet light (365 nm). The principal spot and the

... y p ... g ...
(1) correspond to those of solution (3) in position; only the principal spot is present in the chromatogram obtained with solution (2).

Loss on drying When dried to constant weight over phosphorous pentoxide, loses not more than 2.0% of its weight (Appendix VIII L).

Assay Dissolve about 60 mg, accurately weighed, in 20 ml of glacial acetic acid, add 1 drop of crystal violet IS, titrate with perchloric acid (0.05 mol/L) VS until a bluish-green colour is obtained. Perform a blank determination and make any necessary correction. Each ml of perchloric acid (0.05 mol/L) VS is equivalent to 22.07 mg of $C_{19}H_{23}N_3O_2 \cdot C_4H_4O_4$.

Category Uterine stimulant.

Storage Preserve in tightly closed containers, stored in a cool place, protected from light.

Preparation Ergometrine Maleate Injection

Ergometrine Maleate Injection

Ergometrine Maleate Injection is a sterile solution of ergometrine maleate in Water for Injection. It contains not less than 90.0% and not more than 110.0% of the labelled amount of ergometrine maleate ($C_{19}H_{23}N_3O_2 \cdot C_4H_4O_4$).

Description A clear, colourless or almost colourless liquid with weak blue fluorescence.

Identification To a quantity equivalent to about 0.5 mg of ergometrine maleate, add 2 ml of *p*-dimethylaminobenzaldehyde TS, a deep blue colour is produced in 5 minutes.

pH value 3.0-5.0 (Appendix VI H).

Other requirements Complies with the general requirements for injections (Appendix I B).

Assay Reference preparation Dissolve about 15 mg of ergometrine maleate CRS, accurately weighed, in 1% tartaric acid solution in a 250 ml volumetric flask, and dilute to volume, mix well.

Test preparation Transfer an accurately measured quantity equivalent to 1.5 mg of ergometrine maleate to a 25 ml volumetric flask, add water to volume and mix well.

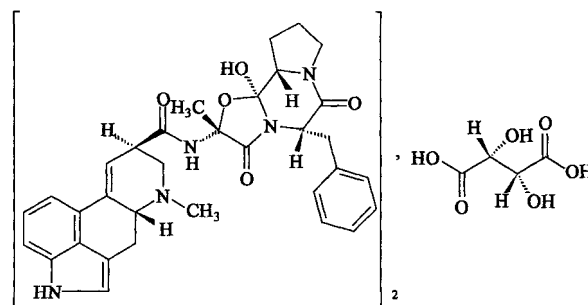
Procedure Transfer separately 1 ml each of the reference preparation and the test preparation accurately measured, to two graduated test tubes with stopper. To each test tube add accurately 1 ml of 1% tartaric acid solution and 4 ml of *p*-dimethylaminobenzaldehyde TS, mix well, allow to stand for 5 minutes and measure the absorbance at 550 nm (Appendix IV A). Calculate the content of $C_{19}H_{23}N_3O_2 \cdot C_4H_4O_4$.

Category As described under Ergometrine Maleate.

Strength (1) 1 ml:0.2 mg (2) 1 ml:0.5 mg

Storage Preserve in well closed containers, protected from light, and store in a cool place.

Ergotamine Tartrate



$(C_{33}H_{35}N_5O_5)_2 \cdot C_4H_6O_6$ 1313.43

[379-79-3]

Ergotamine Tartrate is [*R*-(*R*^{*}, *R*^{*})]-2'-methyl-5'- α -(phenylmethyl)-12'-hydroxyergotaman-3', 6', 18-trione tartrate, in the crystalline form, it may contain two molecular equivalents of methanol. It contains not less than 97.0% and not more than 103.0% of $(C_{33}H_{35}N_5O_5)_2 \cdot C_4H_6O_6$, calculated on the dried basis.

Description Colourless crystals or a almost white, crystalline powder; odourless. Slightly soluble in ethanol; freely soluble in tartaric acid solution.

Specific optical rotation Carry out the procedure within an hour, protected from light. To 0.30 g add 0.5 g of sodium bicarbonate and 25 ml of water. Shake with ethanol-free chloroform (wash chloroform thoroughly with water) for 7 times, using 10 ml for the first time and 6 ml for each of the succeeding times. Combine the chloroform extracts, filter and make up to 50.0 ml. Measure the optical rotation of this solution (Appendix VI E). Measure accurately 25 ml of this solution, remove chloroform by a current of nitrogen. Dissolve the residue in 20 ml of glacial acetic acid, add 1 drop of crystal violet IS, titrate with perchloric acid (0.05 mol/L) VS until a bluish-green colour is produced. Perform a blank determination and make any necessary correction. Calculate the content of ergotamine in the solution, each ml of perchloric acid (0.05 mol/L) VS is equivalent to 29.08 mg of ergotamine. The specific optical rotation is -154° to -165° , calculated on the basis of ergotamine.

Identification (1) To about 30 mg add 15 mg of tartaric acid, dissolve the mixture in 6 ml of water with shaking. Heat 0.1 ml of the solution in a water bath at 80°C with 1 ml of glacial acetic acid, 1 drop of ferric chloride TS and 1 ml of phosphoric acid, a bluish-violet colour is produced.

(2) To a small quantity on a slide, add 1 drop of concentrated hydrogen peroxide solution, 0.1 ml of dilute acetic acid and 0.2 ml of potassium acetate TS, a colourless crystalline precipitate is observed under a microscope.

(3) The infrared absorption spectrum (Appendix IV C) is concordant with the reference spectrum of ergotamine Tartrate (Appendix XVI).

Acidity Dissolve 20 mg in 8 ml of water, the pH value is 4.0-6.0 (Appendix VI H).

Clarity and colour of solution To 30 mg add 15 mg of tartaric acid, dissolve the mixture, in 6 ml of water with shaking, the solution is clear, any colour produced is not more intensely than that of reference solution Y_3 (Appendix IX A, method 1).

Chloride To 25 mg add 15 mg of tartaric acid, dissolve the mixture in 25 ml of water with shaking. Carry out the limit test for chlorides (Appendix VIII A), any opalescence produced is not more intensely than that of a reference using 0.5 ml of sodium chloride standard solution (0.02%).

Loss on drying When dried to constant weight in vacuum at 95°C , loses not more than 6.0% of its weight (Appendix VIII L), using about 0.2 g.

Assay Reference preparation Dissolve about 10 mg of ergometrine maleate CRS, accurately weighed, in 1% tartaric acid solution in a 200 ml volumetric flask, and dilute to volume, mix well.

Test preparation Weigh accurately 10 mg of the substance being examined, in a 200 ml volumetric flask, dissolve in 1% tartaric acid solution, dilute to volume and mix well.

Procedure Transfer separately 5 ml each of the two preparations, accurately measured, to two stoppered test tubes. To each test tube, add 10 ml of *p*-dimethylamino-benzaldehyde TS, accurately measured, and allow to stand in a dark place for 30 minutes. Measure the absorbance of the two solutions at 550 nm (Appendix IV A). Calculate the content of ergotamine tartrate, each mg of ergometrine maleate is equivalent to 1.488 mg of $(C_{33}H_{35}N_5O_5)_2 \cdot C_4H_6O_6$.

Category Antimigrainic agent.

Storage Preserve in tightly closed containers, protected from light and stored in a cold place.

Preparation Ergotamine and Caffeine Tablets

Ergotamine and Caffeine Tablets

Ergotamine and Caffeine Tablets contain not less than 0.85 mg and not more than 1.15 mg of ergotamine tartrate $[(C_{33}H_{35}N_5O_5)_2 \cdot C_4H_6O_6]$, and not less than 90.0 mg and not more than 110.0 mg of anhydrous caffeine ($C_8H_{10}N_4O_2$) in each tablet.

Formula	Ergotamine Tartrate	1 g
	Caffeine, anhydrous	100 g
	To make	1000 tablets

Description Sugar coated or two-layer tablets; the inner layer which contains ergotamine tartrate may be coloured with pigments; the outer layer which contains caffeine is white.

Identification (1) Shake 1 powdered tablet (sugar coating removed) with 5 ml of glacial acetic acid and 5 ml of ethyl acetate, filter. To 1 ml of the filtrate, add slowly 1 ml of sulfuric acid, a violet ring is produced, which disappears on shaking, the solution becomes violet-blue.

(2) To one tenth of a powdered tablet with sugar coating removed in a porcelain dish, add 1 ml of hydrochloric acid and 0.1 g of potassium chlorate, evaporate on a water bath to dryness. Place the inverted dish over another porcelain dish holding a few drops of ammonia TS, the colour of the residue becomes violet which disappears on the addition of a few drops of sodium hydroxide TS.

Other requirements Comply with the general requirements for tablets (Appendix I A), except that the double tablets disintegrate within 30 minutes.

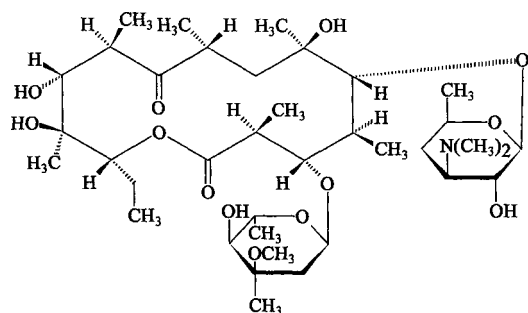
Assay Ergotamine tartrate Weigh accurately and powder 20 tablets with sugar coating removed. Triturate an accurately weighed quantity of the powder equivalent to about 5 mg of ergotamine tartrate with 2 ml of dilute ethanol in a mortar for 5 minutes, transfer with 50 ml of 1% tartaric acid solution in portions to a 100 ml volumetric flask, shake for 30 minutes. Add 1% tartaric acid solution to volume, mix well and filter. Carry out the Assay described under Ergotamine Tartrate, using the filtrate as the test preparation.

Caffeine Measure accurately 20 ml of the above test solution into a 100 ml volumetric flask, add 20 ml of water and 10 ml of dilute sulfuric acid, add accurately 50 ml of iodine (0.1 mol/L) VS, dilute with water to volume and mix well, allow to stand in a dark place for 15 minutes. Filter with a dry filter paper, titrate 50 ml of the successive filtrate, accurately measured, with sodium thiosulfate (0.1 mol/L) VS, add 2 ml of starch IS towards the end of titration, continue the titration until the blue colour disappears. Perform a blank determination and make any necessary correction. Each ml of iodine (0.1 mol/L) VS is equivalent to 4.855 mg of $C_8H_{10}N_4O_2$.

Category As described under Ergotamine tartrate.

Storage Preserve in tightly closed containers, protected from light and stored in a cool place.

Erythromycin



$C_{37}H_{67}NO_{13}$ 733.94

[114-07-8]

Erythromycin has a potency of not less than 920 Erythromycin Units per mg, calculated on the anhydrous basis.

Description White or almost white crystals or a powder; odourless; taste, bitter; hygroscopic. Freely soluble in methanol, ethanol or acetone, very slightly soluble in water.

Specific optical rotation -71° to -78° , in a solution of 20 mg per ml in dehydrated ethanol (Appendix VI E).

Identification (1) The retention times of the principal peak of erythromycin in the substance being examined in the chromatogram obtained in the test for Erythromycin A is identical with that of the principal peak of Erythromycin CRS in the chromatogram of the reference solution correspondingly.

(2) The infrared absorption spectrum (Appendix IV C) is concordant with the reference spectrum of erythromycin (Appendix VI). If the spectra obtained show differences, dissolve a quantity of the substance to be examined and of the reference separately in chloroform, evaporate to dryness on a water bath and dry over phosphorous pentoxide. Carry out the test again, it complies with the requirement disregard any band in the region from 1980 to 2050 cm^{-1} .

Alkalinity Shake 0.1 g with 150 ml of water, pH 8.0-10.5 (Appendix VI H).

Erythromycin A Carry out the method for high performance liquid chromatography (Appendix V D), using a column packed with octadecylsilane bonded silica gel and a mixture of 0.2 mol/L ammonium phosphate solution BS (to 1.15 g of ammonium dihydrogen phosphate add 50 ml of water, adjust the pH value to 6.5 by triethylamine)-0.2 mol/L tetramethylammonium hydroxide solution (to 14.6 ml of 25% tetramethylammonium hydroxide add 100 ml of water, adjust the pH value to 6.5 by phosphoric acid, dilute with water to 200 ml)-acetonitrile-water (5:20:30:45) as the mobile phase. Detection wavelength is 215 nm. Weigh accurately 10 mg of Erythromycin CRS in 10 ml volumetric flasks, add 5 ml of methanol and dilute with phosphate BS (20 ml of phosphate buffer solution pH 7.0, adjust the pH value to 3.5 by phosphoric acid) to volume, allow to stand for 30 minutes. Inject 20 μl of the resulting solution into the column and record the chromatogram. The retention times of the four principal peaks are in this order: erythromycin C, erythromycin A, erythromycin B and erythromycin A enol ether. The resolution factor between the peaks of erythromycin A and erythromycin A enol ether (the retention time is about 3.5 times of erythromycin A) is not less than 14.0. The tailing factor of the peak of

erythromycin A is not more than 2.5.

Procedure Dissolve an accurately weighed quantity of the substance to be examined and of the reference separately in 5 ml of methanol, dilute with a mixture of phosphate buffer solution (pH 7.0)-methanol (15:1) to produce a solution of 4 mg per ml as the test solution and reference solution separately. Inject 20 μl of the two solutions into the column and record the chromatogram. Calculate the content of Erythromycin A with respect to the peak area obtained in the chromatogram by the external method, not less than 88.0% of erythromycin A on the anhydrous basis.

Erythromycin B, C and Related Substance Dissolve an accurately weighed quantity in a mixture of phosphate buffer solution (pH 7.0)-methanol (15:1) to produce a solution of 4 mg per ml as the test solution. Transfer 5 ml of the test solution measure accurately in a 100 ml volumetric flask, dilute with the above solution to volume, mix well as the reference solution. Carry out method as described under Erythromycin A components. Inject 20 μl of the reference solution into the column, adjust the attenuation so that the principal peak height in the chromatogram is 20% of the full scale of the chart. Inject 20 μl of the test solution and the reference solution separately into the column and record the chromatogram for 4 times the retention time of the principal peak. Multiply the peak areas of erythromycin B and erythromycin C by the correction factor (the correction factor of erythromycin A, erythromycin B and erythromycin C is 1.0, 0.7 and 1.0 respectively), the peak areas of erythromycin B and erythromycin C are not greater than the area of the principal peak in the chromatogram obtained with the reference solution respectively (5%). The multiplied peak area of erythromycin A enol ether (the correction factor of erythromycin A enol ether is 0.09) is not greater than 3/5 times the area of the principal peak in the chromatogram obtained with the reference solution (3%); each peak area is not greater than 3/5 times the area of the principal peak in the chromatogram obtained with the reference solution (3%); the sum of the areas of all the other secondary peaks are not greater than the area of the principal peak in the chromatogram obtained with the reference solution (5%) (disregard any peaks not more than 0.01 times of the area of the principal peak in the chromatogram obtained with the test solution).

Residue on ignition Not more than 0.2% (Appendix VIII N).

Thiocyanate Dissolve about 0.1 g, accurately weighed, in 20 ml of methanol in a 50 ml amber-coloured volumetric flask, add 1 ml of ferric chloride TS, dilute with methanol to volume, mix well as the test solution. Dissolve two portions of 0.1 g of potassium thiocyanate, previously dried at 105°C for 1 hour, accurately weighed, in two 50 ml volumetric flask separately, add 20 ml of methanol, dilute with methanol to volume, mix well, transfer separately 5 ml to another 50 ml volumetric flasks, dilute with methanol to volume, mix well, transfer separately 5 ml to another 50 ml amber-coloured volumetric flasks, add 1 ml of ferric chloride TS, dilute with methanol to volume, mix well, as the reference solution. Transfer 1 ml of ferric chloride TS to 50 ml amber-coloured volumetric flasks, dilute with methanol to volume, mix well as the blank solution. Measure the absorbance at 492 nm (Appendix IV A) (the test solution, two reference solutions and the blank solution must be determined in 30 minutes). The test is not valid unless the ratio of the mass and absorbances of the two reference solutions is not less than 0.985 and not more than 1.015. The content of thiocyanate in erythromycin is not more than 0.3%. Relative molecular mass of the thiocyanate moiety is 58.08, relative molecular mass of potassium thiocyanate

is 97.18.

Water Not more than 6.0% (Appendix VIII M, method 1). Dissolve 0.2 g in 10% imidazole solution in anhydrous methanol.

Assay Dissolve an accurately weighed quantity in a few ml of ethanol, dilute with sterile water to produce a solution of about 1000 Units per ml. Carry out the microbiological assay of antibiotics (Appendix XI A). The fiducial limit is not more than 7%. 1000 Erythromycin Units are equivalent to 1 mg of $C_{37}H_{67}NO_{13}$.

Category Macrolide antibiotic.

Storage Preserve in tightly closed containers, stored in a dry place.

Preparation (1) Erythromycin Enteric-coated Tablets
(2) Erythromycin Eye Ointment
(3) Erythromycin Ointment

Erythromycin Enteric-coated Tablets

Erythromycin Enteric-coated Tablets contain not less than 90.0% and not more than 110.0% of the labelled potency of erythromycin ($C_{37}H_{67}NO_{13}$).

Description Enteric-coated tablets with white or almost white cores.

Identification (1) The retention time of the peak of erythromycin A in the substance being examined in the chromatogram obtained in the test for Erythromycin A is identical with that of the peak of Erythromycin CRS in the chromatogram of the reference solution.

(2) Carry out the method for thin-layer chromatography (Appendix V B) using silica gel G as the coating substance and a mixture of chloroform-methanol (85:15) as mobile phase. Apply separately to the plate 10 μ l each of two solutions in methanol containing (1) 2.5 mg per ml of the substance being examined and (2) 2.5 mg per ml of erythromycin CRS respectively. After developing and removal of the plate, dry in air, spray with ethanol-p-methoxybenzaldehyde-sulfuric acid (90:5:5), heat at 100°C for several minutes until the black to purple in colour of the spots are developed. The colour and position of the two principal spots in the chromatogram obtained with the test solution correspond to the principal spot obtained with reference solutions.

(1) or (2) may be used alternative.

Dissolution Carry out the method for dissolution test (Appendix X D method 2 (1) and X C, method 1) using hydrochloric acid solution (9 \rightarrow 1000) as the dissolution medium initially, adjust the rotational speed to 100 rpm. Any enteric-coated tablets shows no cracking, disintegrating or softening after exactly 2 hours. Then using phosphate BS (pH 6.8) as the solvent, withdraw 10 ml of the solution after exactly 45 minutes and filter. Dilute a quantity of the successive filtrate, accurately measured, with phosphate BS (pH 6.8) to produce a solution containing about 55 μ g of erythromycin per ml. Triturate 10 tablets a quantity of erythromycin (about one tablets average weigh) Dissolve in phosphate BS (pH 6.8) to produce a solution containing about 55 μ g of erythromycin per ml. Add 5 ml of sulfuric acid solution (75 \rightarrow 100) to 5 ml of each of above two solution, mix well, allow them to stand for 30-40 minutes. Measure the absorbance of the resulting solution at 482 nm (Appendix IV A). Calculate the dissolution of $C_{37}H_{67}NO_{13}$ from each tablet. Not less than 85% of the labelled amount is dissolved.

Erythromycin A Weigh and powder 20 tablets with enteric sugar coating removed. Dissolve a quantity of the powdered tablets equivalent to about 0.1 g of erythromycin in 5 ml of methanol, dilute with a mixture of phosphate buffer solution (pH 7.0)-methanol (15:1) to produce a solution of 4 mg per ml as the test solution. Carry out the method as described under Erythromycin. Calculate the content of Erythromycin A on the labeled amount, not less than 83.5% of erythromycin A is found.

Other requirements Comply with the general requirements for tablets (Appendix I A).

Assay Triturate 4 tablets with ethanol (using 25 ml of ethanol for about 0.25 g of Erythromycin) in several portions to dissolve erythromycin. Dilute with water to produce a solution of about 1000 Units per ml and mix well. Allow it to stand, measure accurately a quantity of the supernatant liquid and carry out the Assay described under Erythromycin.

Category As described under Erythromycin.

Strength (1) 0.125 g (125000 Units)
(2) 0.25 g (250000 Units)

Storage Preserve in tightly closed containers, stored in a dry place.

Erythromycin Eye Ointment

Erythromycin Eye Ointment contains not less than 90.0% and not more than 110.0% of the labelled potency of erythromycin ($C_{37}H_{67}NO_{13}$).

Description A white to yellow ointment.

Identification To about 0.5 g add 5 ml of sulfuric acid solution (0.1 mol/L), heat and stir on a water bath to dissolve erythromycin. Allow it to cool. To the aqueous layer add 2 ml of sulfuric acid, mix slowly, a brown colour is produced.

Other requirements Complies with the general requirements for Eye preparations (Appendix I G).

Assay Dissolve an accurately weighed quantity equivalent to about 10 mg of erythromycin, in 20 ml of petroleum ether in a separator, extract with 4 quantities each of 25 ml of phosphate BS (pH 7.8-8.0) and dilute the combined extracts to 100 ml with phosphate BS (pH 7.8-8.0). Carry out the Assay described under Erythromycin.

Category As described under Erythromycin.

Strength 0.5%

Storage Preserve in well closed containers, stored in a cool and dry place.

Erythromycin Ointment

Erythromycin ointment contains not less than 90.0% and not more than 110.0% of the labelled amount of erythromycin ($C_{37}H_{67}NO_{13}$).

Description A white to yellow ointment.

Identification To about 0.5 g add 5 ml of sulfuric acid solution (0.1 mol/L), heat and stir well in a water bath. Allow it to cool, to the water layer add 2 ml of sulfuric acid, mix gently, a brown colour is produced.

Other requirements Complies with the general requirements for ointments (Appendix I F).

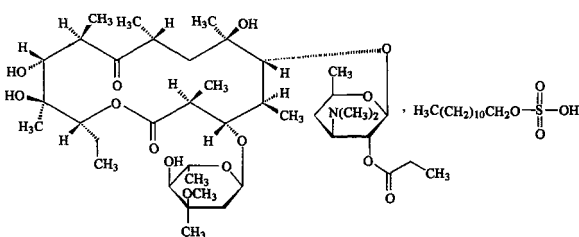
Assay Dissolve as completely as possible an accurately weighed quantity equivalent to about 10 mg of erythromycin in 20 ml of petroleum ether in a separator, extract with 4 quantities of 25 ml each of phosphate BS (pH 7.8-8.0) and dilute the combined extracts to 100 ml with phosphate BS (pH 7.8-8.0), carry out the assay described under Erythromycin.

Category As described under Erythromycin.

Strength 1%

Storage Preserve in well closed containers, stored in a cool and dry place.

Erythromycin Estolate



$C_{40}H_{71}NO_{14} \cdot C_{12}H_{26}O_4S$ 1056.40 [3521-62-8]

Erythromycin Estolate is erythromycin propionate dodecyl sulfate. It has a potency of not less than 610 Erythromycin Units per mg, calculated on the anhydrous basis.

Description A white crystalline powder; odourless; tasteless or almost tasteless. Freely soluble in ethanol or chloroform, practically insoluble in water.

Melting range 132-138°C, regulating the rise of temperature at a rate of 2.5-3.0°C per minute after dried over phosphorous pentoxide (Appendix VI C).

Identification (1) Dissolve 5 mg in 2 ml of acetone and add 2 ml of hydrochloric acid; an orange-yellow colour is produced then gradually changes to purplish-red. Add 2 ml of chloroform and shake, the chloroform layer becomes blue colour.

(2) The infrared absorption spectrum (Appendix IV C) is concordant with the reference spectrum of erythromycin estolate (Appendix XVI).

Acidity or alkalinity A supernatant liquid of 40 mg per ml in water, pH 5.0-7.2 (Appendix VI H)

Free erythromycin Carry out the method for thin layer chromatography (Appendix V B), using silica gel G as coating substance and a mixture of methanol-chloroform (85:15) as the mobile phase. Elute the plate with methanol and allow it to dry in air before use. Apply separately to the plate 1 μ l each of two solutions in methanol containing (1) 10.0 mg per ml of the substance being examined and (2) 0.3 mg per ml of erythromycin RS. After developing and removal of the plate, dry in air and spray with a solution containing 0.18 ml of 10% xanthidrol in methanol and 100 ml of a mixture of hydrochloric acid-glacial acetic acid (92.5:7.5), heat at 105°C for several minutes until the purple spots develop. The erythromycin spot in the chromatogram obtained with solution (1) is not more intense than the principal spot obtained with solution (2).

Water Not more than 4.0% (Appendix VIII M, method 1 A), using a quantity in a 10% imidazole solution in anhydrous methanol.

Assay Dissolve an accurately weighed quantity equivalent to about 50 mg of erythromycin in 50 ml ethanol in a 100 ml volumetric flask and dilute to volume with phosphate BS (pH 7.8). Mix well and warm the solution on water bath at 37°C for 6 hours to hydrolyze the solution completely. Dissolve about 25 mg of erythromycin RS, accurately weighed, in 25 ml ethanol in a 50 ml volumetric flask and dilute to volume with phosphate BS (pH 7.8) and mix well. Carry out the Microbiological Assay of Antibiotics described under Erythromycin (Appendix XI A).

Category macrolide antibiotic.

Storage Preserve in tightly closed containers, protected from light.

Preparation (1) Erythromycin Estolate Capsules
(2) Erythromycin Estolate Granules
(3) Erythromycin Estolate Tablets

Erythromycin Estolate Capsules

Erythromycin Estolate Capsules contain not less than 90.0% and not more than 110.0% of the average amount of erythromycin ($C_{37}H_{67}NO_{13}$).

Identification Triturate a quantity of the powdered contents equivalent to 0.1 g of erythromycin estolate with 5 ml of chloroform, filter and evaporate the filtrate to dryness. The residue complies with the tests for Identification described under Erythromycin Estolate.

Dissolution Carry out the dissolution test (Appendix X C, method 2), using 900 ml of 0.2% sodium dodecylsulfate solution in hydrochloric acid solution (9 \rightarrow 1000) as the dissolution medium, adjust the rotational speed to 75 rpm [50 mg, carry out the dissolution test (Appendix X C, method 3), using 250 ml of 0.2% sodium dodecylsulfate solution in hydrochloric acid solution (9 \rightarrow 1000) as the solvent, adjust the rotational speed to 50 rpm]. Withdraw the solution after exactly 45 minutes and filter, as the test solution. Dissolve a quantity, equivalent to about the average weight of one capsule obtained in the test for weight variation of contents, in ethanol (dissolve 25 mg of erythromycin in 5 ml ethanol according to the labelled amount) and dilute to produce a solution of 138 μ g of erythromycin per ml with a 0.2% solution of sodium dodecylsulfate in hydrochloric acid solution (9 \rightarrow 1000) according to the labelled amount, and filter, the successive filtrate as the reference solution. Measure accurately 2 ml each of the two solutions separately, add 5 ml of sulfuric acid solution (75 \rightarrow 100), mix well, allow it to stand for 30 minutes and cool. Measure the absorbances of the resulting solutions at 482 nm (Appendix IV A), calculate the dissolution of $C_{37}H_{67}NO_{13}$ from each capsule. Not less than 70% of the labelled amount is dissolved.

Water Not more than 5.0% (Appendix VIII A, method 1A), using about 0.2 g of the contents of the capsules in a 10% imidazole solution in anhydrous methanol.

Other requirements Comply with the general requirements for capsules (Appendix I E).

Assay Dissolve an accurately weighed quantity equivalent to 0.125 g of erythromycin obtained in the test for weight variation of contents in 125 ml ethanol in a 250 ml volumetric flask and dilute to volume with phosphate BS (pH 7.8).

Mix well and warm the solution on water bath at 37°C for 6 hours to hydrolyze the solution completely. Measure accurately a quantity of the supernatant and carry out the Assay described under Erythromycin Estolate.

Category As described under Erythromycin Estolate.

Strength Calculated as erythromycin
(1) 50 mg (50000 Units)
(2) 125 mg (125000 Units)

Storage Preserve in tightly closed containers, protected from light.

Erythromycin Estolate Granules

Erythromycin Estolate Granules contain not less than 90.0% and not more than 110.0% of the labelled amount of erythromycin ($C_{37}H_{67}NO_{13}$).

Description Suspensible granules, odour fragrant; taste, sweet.

Identification Shake a quantity of the powdered granules equivalent to about 20 mg of erythromycin estolate in a centrifuge tube with a quantity of water to produce a homogeneous suspension, centrifuge and discard the supernatant and wash the precipitate with water for 3 times. The precipitate dried in a desiccator over phosphorous pentoxide complies with test (1) for Identification described under Erythromycin Estolate.

Acidity or Alkalinity A suspension of 3.3 g in 10 ml of water, pH 5.0-7.0 (Appendix VI H).

Water Not more than 2.0% (Appendix VIII A, method 1A), using 0.2 g in a 10% imidazole solution in anhydrous methanol.

Other requirements Comply with the general requirements for Granules (Appendix I N).

Assay Dissolve an accurately weighed quantity equivalent to 0.125 g of erythromycin estolate in the test or weight variation of contents in 125 ml ethanol in a 250 ml volumetric flask and dilute to volume with phosphate BS (pH 7.8). Mix well and warm the solution on water bath at 37°C for 6 hours to hydrolyze the solution completely. Measure accurately a quantity of the supernatant and carry out the Assay described under Erythromycin Estolate.

Category As described under Erythromycin Estolate.

Strength (1) 75 mg (75000 Units)
(2) 250 mg (25000 Units)
(calculated as erythromycin)

Storage Preserve in tightly closed containers, protected from light.

Erythromycin Estolate Tablets

Erythromycin Estolate Tablets contain not less than 90.0% and not more than 110.0% of the labelled potency of erythromycin ($C_{37}H_{67}NO_{13}$).

Description White tablets.

Identification To 1 powdered tablet add 5 ml of chloroform, triturate and filter. The residue obtained after evaporation of the filtrate complies with the tests for Identification described under Erythromycin Estolate.

Dissolution Carry out the dissolution test (Appendix X C, method 2), using 900 ml of 0.2% sodium dodecylsulfate solution in hydrochloric acid solution (9→1000) as the dissolution medium, adjust the rotational speed to 75 rpm. Withdraw the solution after exactly 45 minutes and filter, as the test solution. Dissolve a quantity of 10 powdered tablets equivalent to about the average weight of one tablet in ethanol (dissolve 25 mg of erythromycin in 5 ml ethanol according to the labelled amount). Dilute to produce a solution of 138 µg of erythromycin per ml with a 0.2% sodium dodecylsulfate solution in hydrochloric acid solution (9→1000) according to the labelled amount and filter, the successive filtrate as the reference solution. Measure accurately 2 ml each of the two solutions separately, add 5 ml of sulfuric acid solution (75→100), mix well, allow it to stand for 30 minutes and cool. Measure the absorbances of the resulting solutions at 482 nm (Appendix IV A), calculate the dissolution of $C_{37}H_{67}NO_{13}$ from each tablet. Not less than 70% of the labelled amount is dissolved.

Other requirements Comply with the general requirements for tablets (Appendix I A).

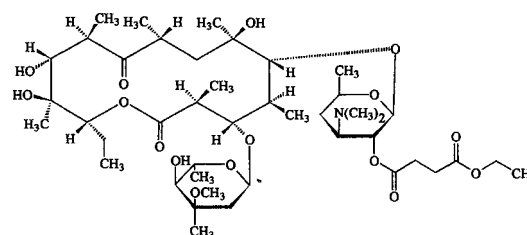
Assay Weigh and powder 10 tablets. Dissolve an accurately weighed quantity equivalent to about 0.125 g erythromycin in 125 ml ethanol and dilute to volume in a 250 ml volumetric flask with phosphate BS (pH 7.8). Mix well and warm the solution on water bath at 37°C for 6 hours to hydrolyze the solution completely. Measure accurately a quantity of the supernatant liquid and carry out the Assay described under Erythromycin Estolate.

Category As described under Erythromycin Estolate.

Strength 0.125 g (125000 Units) Calculated as erythromycin

Storage Preserve in tightly closed containers, protected from light.

Erythromycin Ethylsuccinate



$C_{43}H_{75}NO_{16}$ 862.07

[41342-53-4]

Erythromycin Ethylsuccinate is ethylsuccinate of erythromycin. It contains not less than 765 erythromycin Units per mg, calculated on the anhydrous basis.

Description A white or crystalline powder; odourless; tasteless. Freely soluble in dehydrated ethanol, acetone or chloroform; sparingly soluble in ether; practically insoluble in water.

Identification (1) To about 5 mg add 3-5 drops each of a saturated methanolic solution of hydroxylamine hydrochloride and sodium hydroxide, heat on a water bath until bubbles are evolved, cool, acidify with hydrochloric acid solution (4.5→100), add 0.5 ml of ferric chloride TS; a reddish violet colour is produced.

(2) Carry out the method described under Related substances, applying separately to the plate 10 µl of each of two solutions in acetone containing (1) 4 mg of the

substance being examined per ml and (2) 4 mg of erythromycin ethylsuccinate (RS) per ml. The colour and position of the principal spot in the chromatogram obtained with solution (1) correspond to the principal spot obtained with solution (2).

(3) The infrared absorption spectrum (Appendix IV C) is concordant with the reference spectrum of erythromycin ethylsuccinate (Appendix XVI).

Acidity or alkalinity A supernatant liquid of 10 mg per ml in water, pH 6.0-8.5 (Appendix VI H).

Related substances Carry out the method for thin-layer chromatography (Appendix V B), using silica gel G as the coating substance and a mixture of chloroform-ethanol-15% ammonium acetate solution (85:15:1), pH 7.0 adjust to with ammonia solution before use, as the mobile phase. Apply separately to the plate 10 μ l of each of two solutions in acetone containing (1) 4.0 mg per ml of the substance being examined and (2) 0.2 mg per ml of erythromycin RS. After developing and removal of the plate, dry in air, spray with a solution containing 0.5 ml of anisaldehyde, 10 ml of glacial acetic acid, 85 ml of methanol and 5 ml of sulfuric acid, heat at 110°C until the spots develop. Any spot in the chromatogram other than the principal spot obtained with solution (1) is not more intense than the principal spot obtained with solution (2).

Water Dissolve a quantity in 100 g/L imidazole solution in anhydrous methanol, carry out the method for determination of water (Appendix VIII M, method 1A); not more than 3.0%.

Residue on ignition Not more than 0.5% (Appendix VIII N).

Assay Dissolve an accurately weighed quantity in ethanol (using 4 ml of ethanol for 10 mg of Erythromycin Ethylsuccinate), dilute with phosphate BS (pH 7.8) to produce a solution of about 500 Units per ml, to stand for 16 hours in air or to stand at 40°C for 6 hours. Dissolve about 25 mg of Erythromycin RS, accurately weighed, add 12.5 ml of ethanol, dilute with phosphate BS (pH 7.8) to produce a solution of about 500 Units per ml. Carry out the microbiological assay of antibiotics described under Erythromycin (Appendix XI A). 1000 Erythromycin Units are equivalent to 1 mg $C_{37}H_{67}NO_{13}$.

Category Macrolide antibiotic.

Storage Preserve in tightly closed containers, stored in a dry place.

Preparation (1) Erythromycin Ethylsuccinate Capsules
(2) Erythromycin Ethylsuccinate Granules
(3) Erythromycin Ethylsuccinate Dispersible Tablets
(4) Erythromycin Ethylsuccinate Tablets

Erythromycin Ethylsuccinate Capsules

Erythromycin Ethylsuccinate Capsules contain not less than 90.0% and not more than 110.0% of the labelled amount of Erythromycin Ethylsuccinate, calculated with reference to Erythromycin ($C_{37}H_{67}NO_{13}$).

Description Capsules containing white granules or powder.

Identification (1) Comply with test (1) for Identification described under Erythromycin Ethylsuccinate, using a quantity of the contents of the capsules equivalent to 5 mg of

Erythromycin Ethylsuccinate.

(2) Dissolve a quantity of the contents of the capsules in acetone to produce a solution containing 4 mg of Erythromycin Ethylsuccinate per ml and filter, using the filtrate as a test solution. The test solution complies with test (2) for Identification described under Erythromycin Ethylsuccinate.

Dissolution Carry out the dissolution test (Appendix X C, method 2) using 0.1 mol/L hydrochloric acid solution as the dissolution medium, adjust the rotational speed of the paddle to 50 rpm. Withdraw a quantity of the solution after exactly 30 minutes and filter, use the successive filtrate as a test solution. Triturate the contents of 10 capsules, dissolve an accurately weighed quantity equivalent to about the average weight of one capsule in ethanol (using 5 ml of ethanol for 10 mg of Erythromycin), dilute with 0.1 mol/L hydrochloric acid solution to produce a solution containing 0.1 mg of Erythromycin per ml, filter, use the successive filtrate as a reference solution. Measure accurately 5 ml of the above two solutions in two 25 ml volume flasks, respectively. To each add 5 ml of 0.1 mol/L hydrochloride solution and 10 ml of sulfuric acid solution (75→100), mix well and allow to stand for 30 minutes, dilute with 0.1 mol/L hydrochloric acid solution to volume, mix well. Measure the absorbances of the resulting solutions at 482 nm (Appendix IV A). Calculate the dissolution of $C_{37}H_{67}NO_{13}$ from each capsule. Not less than 80% of the labelled amount is dissolved.

Water Dissolve a quantity in 100 g/L imidazole solution in anhydrous methanol, carry out the method for determination of water (Appendix VIII M, method 1 A); not more than 3.0%.

Other requirements comply with the general requirements for capsules (Appendix I E).

Assay Weigh accurately and powder 10 tablets. Triturate an accurately weighed quantity of the powder equivalent to about 0.1 g of Erythromycin with 50 ml of ethanol in portions to dissolve Erythromycin Ethylsuccinate, dilute with phosphate BS (pH 7.8) to produce a solution of about 500 Units per ml, mix well and allow to stand for 16 hour in air or to stand at 40°C for 6 hours. Measure accurately a quantity of the supernatant liquid and carry out the microbiological assay of antibiotics described under Erythromycin (Appendix XI A).

Category As described under Erythromycin Ethylsuccinate.

Strength 0.1 g (100000 Units) (Calculated as $C_{37}H_{67}NO_{13}$)

Storage Preserve in tightly closed containers, stored in a dry place.

Erythromycin Ethylsuccinate Dispersible Tablets

Erythromycin Ethylsuccinate Dispersible Tablets contain not less than 90.0% and not more than 110.0% of the labelled amount of Erythromycin Ethylsuccinate, calculated with reference to Erythromycin ($C_{37}H_{67}NO_{13}$).

Description White tablets.

Identification (1) Comply with test (1) for Identification described under Erythromycin Ethylsuccinate, using a quantity of powdered tablets equivalent to 5 mg of Erythromycin Ethylsuccinate.

(2) Dissolve a quantity of powdered tablets in acetone to produce a solution containing 4 mg of Erythromycin Ethylsuccinate per ml and filter, use the successive filtrate as a test solution. The test solution complies with test (2) for Identification described under Erythromycin Ethylsuccinate.

Dissolution Carry out the dissolution test (Appendix X C, method 2) 0.1 mol/L using hydrochloric acid solution as the dissolution medium, adjust the rotational speed of the paddle to 50 rpm. Withdraw a quantity of the solution after exactly 15 minutes and filter, use the successive filtrate as a test solution. Triturate 10 tablets and dissolve an accurately weighed quantity equivalent to about the average weight of one tablet in ethanol (using 5 ml of ethanol for 10 mg of Erythromycin), dilute with 0.1 mol/L hydrochloric acid solution to produce a solution containing 0.1 mg of Erythromycin per ml, filter, use the filtrate as a reference solution. Measure accurately 5 ml of the above two solutions in two 25 ml volume flasks, respectively. To each add 5 ml of 0.1 mol/L hydrochloride solution and 10 ml of sulfuric acid solution (75→100), mix well and allow to stand for 30 minutes, dilute the filtrate with hydrochloric acid solution (0.1 mol/L) to volume, mix well. Measure the absorbances of the resulting solutions at 482 nm (Appendix IV A). Calculate the dissolution of $C_{37}H_{67}NO_{13}$ from each tablets. Not less than 80% of the labelled amount is dissolved.

Other requirements comply with the general requirements for tablets (Appendix I A).

Assay Weigh accurately and powder 10 tablets. Triturate an accurately weighed quantity of the powder equivalent to about 0.1 g of Erythromycin with 50 ml of ethanol in portions to dissolve Erythromycin Ethylsuccinate, dilute with phosphate BS (pH 7.8) to produce a solution of about 500 Units per ml, mix well and allow to stand for 16 hour in air or to stand at 40°C for 6 hour. Measure accurately a quantity of the supernatant liquid and carry out the microbiological assay of antibiotics described under Erythromycin (Appendix XI A).

Category As described under Erythromycin Ethylsuccinate.

Strength Calculated as $C_{37}H_{67}NO_{13}$
 (1) 0.1 g (100000 Units)
 (2) 0.125 g (125000 Units)

Storage Preserve in tightly closed containers, stored in a dry place.

Erythromycin Ethylsuccinate Granules

Erythromycin Ethylsuccinate Granules contain not less than 90.0% and not more than 110.0% of the labelled amount of Erythromycin Ethylsuccinate, calculated with reference to Erythromycin ($C_{37}H_{67}NO_{13}$).

Description Soluble granules; taste sweet, aromatic.

Identification (1) A quantity of powdered granules equivalent to 5 mg of Erythromycin Ethylsuccinate complies with test (1) for Identification described under Erythromycin Ethylsuccinate

(2) Dissolve a quantity of powered granules in acetone to produce a solution containing 4 mg of Erythromycin Ethylsuccinate per ml and filter, use the successive filtrate as a test solution. The test solution complies with test (2) for Identification described under Erythromycin Ethylsuccinate.

Acidity or alkalinity To a quantity of the substance being examined add water to produce a suspension of 40 mg per ml, the pH value of the supernatant liquid is 7.0-9.0

(Appendix VI H).

Other requirements Comply with the general requirements for granules (Appendix I N).

Assay Triturate 5 containers of powdered granules equivalent to about 50 mg of Erythromycin with 25 ml of ethanol in portions to dissolve Erythromycin Ethylsuccinate, dilute with phosphate BS (pH 7.8) to produce a solution of about 500 Units per ml, mix well and allow to stand for 16 hours in air or to stand at 40°C for 6 hours. Measure accurately a quantity of the supernatant liquid and carry out the Microbiological Assay of Antibiotic (Appendix XI A).

Category As described under Erythromycin Ethylsuccinate.

Strength Calculated as $C_{37}H_{67}NO_{13}$
 (1) 0.05 g (50000 Units)
 (2) 0.1 g (100000 Units)
 (3) 0.125 g (125000 Units)
 (4) 0.25 g (250000 Units)

Storage Preserved in tightly closed containers, stored in a dry place and protected from light.

Erythromycin Ethylsuccinate Tablets

Erythromycin Ethylsuccinate Tablets contain not less than 90.0% and not more than 110.0% of the labelled amount of Erythromycin Ethylsuccinate, calculated with reference to Erythromycin ($C_{37}H_{67}NO_{13}$).

Description White tablets.

Identification (1) Comply with test (1) for Identification described under Erythromycin Ethylsuccinate, using a quantity of powdered tablets equivalent to 5 mg of erythromycin ethylsuccinate.

(2) Dissolve a quantity of powered granules in acetone to produce a solution containing 4 mg of Erythromycin Ethylsuccinate per ml and filter, use the successive filtrate as a test solution. The test solution complies with test (2) for Identification described under Erythromycin Ethylsuccinate.

Dissolution Carry out the dissolution test (Appendix X C, method 2) using 0.1 mol/L hydrochloric acid solution as the dissolution medium, adjust the rotational speed of the paddle to 50 rpm. Withdraw a quantity of the solution after exactly 30 minutes and filter. Dilute the successive filtrate with 0.1 mol/L hydrochloric acid solution to produce a solution containing 0.1 mg of Erythromycin per ml as a test solution. Triturate 10 tablets and dissolve an accurately weighed quantity equivalent to about the average weight of one tablet in ethanol (using 5 ml of ethanol for 10 mg of Erythromycin), dilute with 0.1 mol/L hydrochloric acid solution to produce a solution containing 0.1 mg of Erythromycin per ml, filter, use the successive filtrate as a reference solution. Measure accurately 5 ml of the above two solutions in two 25 ml volume flasks, respectively. To each flask add 5 ml of 0.1 mol/L hydrochloride solution and 10 ml of sulfuric acid solution (75→100), mix well and allow to stand for 30 minutes, dilute with 0.1 mol/L hydrochloric acid solution to volume, mix well. Measure the absorbance of the resulting solutions at 482 nm (Appendix IV A). Calculate the dissolution of $C_{37}H_{67}NO_{13}$ from each tablet. Not less than 80% of the labelled amount is dissolved.

Other requirements Comply with the general requirements for tablets (Appendix I A).

Assay Weigh accurately and powder 10 tablets. Triturate

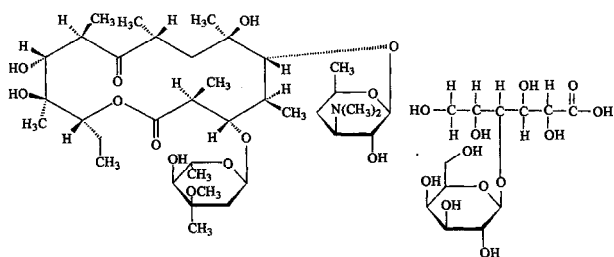
an accurately weighed quantity of the powder equivalent to about 0.1 g of erythromycin with 40 ml of ethanol in portions to dissolve erythromycin ethylsuccinate, dilute with phosphate BS (pH 7.8) to produce a solution of about 500 Units per ml, mix well and allow to stand for 16 hours in air or to stand at 40°C for 6 hours. Measure accurately a quantity of the supernatant liquid and carry out the Microbiological Assay of Antibiotics described under erythromycin (Appendix XI A).

Category As described under Erythromycin Ethylsuccinate.

Strength Calculated as $C_{37}H_{67}NO_{13}$
 (1) 0.1 g (100000 Units)
 (2) 0.125 g (125000 Units)
 (3) 0.25 g (250000 Units).

Storage Preserve in tightly closed containers, stored in a dry place.

Erythromycin Lactobionate



$C_{37}H_{67}NO_{13} \cdot C_{12}H_{22}O_{12}$ 1092.24 [3847-29-8]

Erythromycin Lactobionate is erythromycin lactobionate (1:1). It has a potency of not less than 610 Erythromycin Units per mg, calculated on the dried basis.

Description White or almost white crystals or a crystalline powder; odourless; taste, bitter. Freely soluble in water or ethanol, slightly soluble in acetone or chloroform, insoluble in ether.

Identification The infrared absorption spectrum (Appendix IV C) is concordant with the reference spectrum of erythromycin lactobionate (Appendix XVI). If the absorption band at $1750-1680\text{ cm}^{-1}$ is not concordant with the reference spectrum, dissolve a quantity in dehydrated ethanol, evaporate to dryness on a water bath and dry in a vacuum desiccator. Carry out the test again, it complies with the requirement.

Acidity or alkalinity Dissolve 0.85 g in 10 ml of water, pH 6.0-7.5 (Appendix VI H).

Clarity and colour of solution Dissolve 5 portions each of 0.85 g in 10 ml of water respectively, the solutions are clear and colourless; any opalescence produced is not more pronounced than that of reference suspension I (Appendix IX B); any colour produced is not more intense than that of reference solution Y₁ (Appendix IX A, method 1).

Related substances Carry out the method for thin-layer chromatography (Appendix V B) using silica gel G and kieselguhr G (mix 1 g each of silica gel G and kieselguhr G, triturate with 8 ml of water in two portions) as the coating substance and ethyl acetate saturated with concentrated ammonia solution (shake 10 volumes of ethyl acetate with 1 volume of concentrated ammonia solution in a separator, allow it to stand, decant the ammonia saturated ethyl acetate

layer into chromatographic chamber, let the vapour to saturate the chamber for at least 4 hours) as mobile phase. Spread the coating substance over a 10 cm × 20 cm glass plate, dry in air and activate at 105°C for 1-2 hours. Apply separately to the plate 5 μl each of two solutions in ethanol containing (1) 20 mg of the substance being examined (Calculated with reference to erythromycin) per ml and (2) 1.5 mg of the erythromycin RS per ml. After developing and removal of the plate, dry in air and spray with a solution containing 1 g of cerium sulfate and 2.5 g of sodium molybdate in 100 ml of 10% sulfuric acid solution, heat at 105°C for several minutes until blue spots are developed. Any spot, other than the principal spot (the spot of lactobionic acid remaining in the origin) in the chromatogram, obtained with solution (1) is not more intense than the principal spot obtained with solution (2).

Loss on drying When dried to constant weight at 105°C, loses not more than 4.0% of its weight (Appendix VIII L).

Bacterial endotoxin Carry out the test for bacterial endotoxin (Appendix XI E); not more than 1 EU each 1000 units of erythromycin ethylsuccinate.

Sterility Complies with the test for sterility (Appendix XI), g portions each containing the maximum dose of the preparation being examined, and to each portion add sterile water to produce a solution of 30000 Units per ml.

Assay Dissolve an accurately weighed quantity in sterile water to produce a solution of 1000 Units per ml and carry out the Microbiological Assay of Antibiotics described under Erythromycin. The fiducial limit is not more than 7%.

Category Macrolide antibiotic.

Storage Preserve in hermetically sealed containers, stored in a dry place.

Preparation Erythromycin Lactobionate for Injection

Erythromycin Lactobionate for Injection

Erythromycin Lactobionate for Injection is a sterile crystal or powder, or sterile lyophilized substance. It has a potency of not less than 610 Erythromycin Units per mg, calculated on the dried basis; it contains not less than 93.0% and not more than 107.0% of the labelled potency of erythromycin ($C_{37}H_{67}NO_{13}$), calculated on the basis of the average weight of contents.

Description White or almost white crystals or a powder, or loose masses.

Identification Complies with the tests for Identification described under Erythromycin Lactobionate.

Clarity and colour of solution To each of 5 containers, add water to produce solutions containing 50 mg of erythromycin per ml. The solutions are clear and colourless; any opalescence produced is not more pronounced than that of reference suspension I (Appendix IX B); any colour produced is not more intense than that of reference solution Y₁ (Appendix IX A, method 1).

Related substances Complies with the test for Related substances described under Erythromycin Lactobionate.

Loss on drying When dried to constant weight at 105°C,

loses not more than 5.0% of its weight (Appendix VIII L).

Acidity or alkalinity, Bacterial endotoxin, Sterility Complies with the corresponding requirement described under Erythromycin Lactobionate.

Other requirements Complies with the general requirements for injections (Appendix I B).

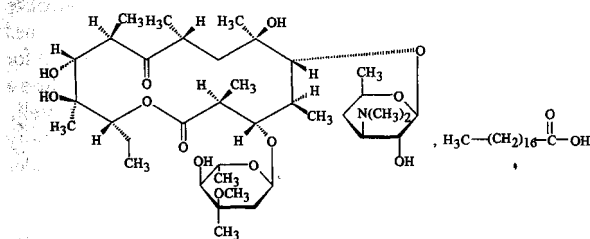
Assay Carry out the Assay described under Erythromycin Lactobionate, using the mixed contents obtained in the test for weight variation of contents.

Category As described under Erythromycin Lactobionate.

Strength (1) 0.25 g (250000 Units)
(2) 0.3 g (300000 Units)

Storage Preserve in well closed containers, stored in a dry place.

Erythromycin Stearate



$C_{37}H_{67}NO_{13} \cdot C_{18}H_{36}O_2$ 1018.42

[643-22-1]

Erythromycin Stearate is a mixture of the stearic acid salt of erythromycin and excess amount of stearic acid. It has a potency of not less than 550 Erythromycin Units per mg, calculated on the anhydrous basis.

Description A white or almost white crystalline powder; odourless; taste, bitter.

Soluble in methanol, ethanol or chloroform; slightly soluble in acetone; practically insoluble in water.

Identification (1) Dissolve 3 mg in 2 ml of acetone and add 2 ml of hydrochloric acid; an orange yellow colour is produced which gradually changes to purplish-red. Add 2 ml of chloroform and shake, the chloroform layer becomes blue.

(2) To 0.1 g add 5 ml of hydrochloric acid solution (2 mol/L) and 10 ml of water, gently heat to boiling when oily pearls float on the surface, allow it to cool, to the fatty layer add 3 ml of sodium hydroxide solution (0.1 mol/L), heat to boil, allow it to cool, a white gel is formed. Add 10 ml of boiling water to dissolve the gel (heat if necessary), shake to form foams. To 1 ml of the solution add 3-4 drops of a 10% solution of calcium chloride, while heating and shaking a granular precipitate is produced, which is insoluble in hydrochloric acid.

(3) The infra red absorption spectrum (Appendix IV C) is concordant with the reference spectrum of Erythromycin Stearate (Appendix XVI).

Free stearic acid Dissolve 0.4 g, accurately weighed, in 50 ml of ethanol previously neutralized to phenolphthalein IS with sodium hydroxide VS (0.1 mol/L), add 1-2 drops of phenolphthalein IS and titrate with sodium hydroxide VS (0.1 mol/L) until the colour changes to pink. Calculate the volume (ml) of sodium hydroxide VS (0.1 mol/L) required for each g of substance being examined and subtract

the volume (ml) of perchloric acid VS (0.1 mol/L) required for each g of the substance being examined in the test for Erythromycin stearate, each ml of the difference is equivalent to 28.45 mg of $C_{18}H_{36}O_2$. The content of stearic acid is not more than 14.0%, calculated on the anhydrous basis.

Erythromycin stearate Dissolve 0.5 g, accurately weighed in 30 ml of chloroform, shake thoroughly, filter, extract the residue with 3 portions each of 25 ml of chloroform, filter the extracts, wash the filter paper with chloroform, evaporate the combined filtrates and washings on a water bath to about 30 ml, add 50 ml of anhydrous glacial acetic acid previously neutralized with perchloric acid VS (0.1 mol/L), using crystal violet IS as indicator, titrate with perchloric acid VS (0.1 mol/L) until the colour changes to bluish-green. Each ml of perchloric acid VS (0.1 mol/L) is equivalent to 101.8 mg of $C_{37}H_{67}NO_{13} \cdot C_{18}H_{36}O_2$. The content of erythromycin stearate is not less than 77.0%, calculated on the anhydrous basis.

Sodium stearate Carry out the method for residue on ignition (Appendix VIII N), using 2.0 g. Each g of the residue is equivalent to 4.317 g of $C_{18}H_{35}NaO_2$; not more than 6.0%.

Free stearic acid, Erythromycin stearate and sodium stearate Not less than 98.0% and not more than 103.0%, calculated by adding together the percentage of free stearic acid, erythromycin stearate and sodium stearate determined as described above, and on the anhydrous basis.

Related substances Carry out the method for thin layer chromatography (Appendix V B), using silica gel G and K_2CO_3 -silica gel G (1:1) as the coating substance and a freshly prepared ethyl acetate solution saturated with concentrated ammonia solution [shake 10 volume of ethyl acetate with 1 volume of concentrated ammonia solution in a separator, allow it to stand, and transfer the ethyl acetate layer into a chromatographic chamber for not less than 4 hours.] as the mobile phase. Spread the coating substance over a 10 cm \times 20 cm glass plate, dry it at room temperature and activate at 105°C for 1-2 hours. Apply separately to the plate 5 μ l each of two solutions in ethanol containing (1) 20 mg of the substance being examined per ml, calculated as erythromycin, and (2) 1.5 mg of the erythromycin RS per ml. After developing and removal of the plate, dry it in air and spray with a solution (containing 1 g of cerium sulfate and 2.5 g of sodium molybdate, in 100 ml of 10% sulfuric acid), heat at 105°C for several minutes until blue spots are developed. Any spot, other than the principal spot in the chromatogram obtained with the solution (1) is not more intense than the principal spot obtained with solution (2).

Water Not more than 4.0% (Appendix VIII M method 1A), dissolving a quantity equivalent to about 0.2 g of erythromycin in a 10% imidazole solution in anhydrous methanol.

Assay Dissolve an accurately weighed quantity in ethanol to produce a solution of 1000 Units per ml, stand for 2 hours. Dissolve an accurately weighed quantity of Erythromycin RS in ethanol to produce a solution of 1000 Units per ml. Carry out the microbiological assay of antibiotics (Appendix XI A), 1000 erythromycin Units are equivalent to 1 mg of $C_{37}H_{67}NO_{13}$. The fiducial limits is not more than 7%.

Category Macrolide antibiotic.

Storage Preserve in tightly closed containers, protected from light.

Preparation (1) Erythromycin Stearate Capsules
(2) Erythromycin Stearate Granules
(3) Erythromycin Stearate Tablets

Erythromycin Stearate Capsules

Erythromycin Stearate Capsules contain not less than 90.0% and not more than 110.0% of the labelled amount of erythromycin ($C_{37}H_{67}NO_{13}$).

Identification The contents of capsules comply with test (1) and (2) for Identification described under Erythromycin Stearate.

Related substances Carry out the method for Related Substances described under Erythromycin Stearate, using the contents of capsules.

Water Not more than 4.0%, (Appendix VIII M method 1 A) dissolving a quantity of the contents of capsules, equivalent to about 0.2 g of erythromycin, in a 10% imidazole solution in anhydrous methanol.

Dissolution Carry out the dissolution test (Appendix X C, method 1), using hydrochloric acid solution (9→1000) as the dissolution medium, adjust the rotational speed of the basket to 100 rpm. Withdraw a quantity of the solution after exactly 45 minutes and filter. Dilute a quantity of the successive filtrate with the dissolution medium to produce a solution of 55 µg of erythromycin per ml (solution 1). Dissolve an accurately weighed quantity, equivalent to about the average weight in each capsule of the mixed contents in the test for weight variation of contents, in the dissolution medium and dilute to volume in a 1000 ml volumetric flask. Filter, dilute an accurately measured quantity of the successive filtrate with the dissolution medium to produce a solution of 55 µg of erythromycin per ml (solution 2). Measure the absorbance of the resulting two solutions at 482 nm (Appendix IV A) respectively and calculate the dissolution of $C_{37}H_{67}NO_{13}$ from each capsule. Not less than 75% is dissolved.

Other requirements Comply with the general requirements for capsules (Appendix I E).

Assay Dissolve an accurately weighed quantity, equivalent to about 0.1 g of erythromycin of mixed contents obtained from test for weight variation of contents, in ethanol and dilute to produce a solution of 1000 Units per ml, mix well, allow it to stand for 2 hours, measure accurately a quantity of the supernatant and carry out the assay described under Erythromycin Stearate.

Category As described under Erythromycin Stearate.

Strength Calculated as $C_{37}H_{67}NO_{13}$
(1) 0.1 g (100000 Units)
(2) 0.125 g (120000 Units)

Storage Preserve in tightly closed containers, protected from light and stored in a dry place.

Erythromycin Stearate Granules

Erythromycin Stearate Granules contain not less than 90.0% and not more than 110.0% of the labelled amount of erythromycin ($C_{37}H_{67}NO_{13}$).

Description Suspensible granules; odour fragrant; taste, sweet.

Identification (1) To a quantity of the powdered granules equivalent to about 3 mg of erythromycin add 3 ml of acetone, filter, add 2 ml of hydrochloric acid to the filtrate,

an orange yellow colour is produced, which gradually changes to violet red. Add 2 ml of chloroform and shake, the chloroform layer becomes violet.

(2) To 3 g add a quantity of water in a centrifuge tube, shake thoroughly, centrifuge and wash the precipitate with a quantity of water for 3 times. To precipitate add 3.5 ml of dilute hydrochloric acid and 10 ml of water, mix well, gently heat to boil, when oily pearls float on the surface, allow it to cool, to the fatty layer add 3 ml of a 0.4% solution of sodium hydroxide, heat to boil, allow it to cool, a white gel is formed, which forms foams on shaking with 10 ml of boiling water. To 1 ml of the solution add 3-4 drops of calcium chloride TS, a granular precipitate is produced, which is insoluble in hydrochloric acid.

Acidity or alkalinity A suspension of 0.1 mg per ml in water, pH 6.0-9.0 (Appendix VI H).

Loss on drying when dried to constant weight at 105°C, loses not more than 2.0% of its weight (Appendix VIII L).

Other requirements Comply with the general requirements for granules (Appendix I N).

Assay Dissolve an accurately weighed quantity equivalent to about 0.1 g of erythromycin, of mixed contents obtained from test for weight variation of contents or from the test for minimum packing amount, in ethanol and dilute to produce a solution of 1000 Units per ml with sterile water, mix well, allow it to stand for 2 hours, measure accurately a quantity of the supernatant and carry out the Assay described under Erythromycin Stearate.

Category As described under Erythromycin Stearate.

Strength 50 mg (50000 Units), calculated as $C_{37}H_{67}NO_{13}$

Storage Preserve in tightly closed containers, protected from light and stored in a dry place.

Erythromycin Stearate Tablets

Erythromycin Stearate Tablets contain not less than 90.0% and not more than 110.0% of the labelled amount of erythromycin ($C_{37}H_{67}NO_{13}$).

Description Sugar coated or film coated tablets, with white or almost white core.

Identification (1) Comply with test (1) for Identification described under Erythromycin Stearate, using a quantity of powdered tablets.

(2) Triturate a quantity of the powdered tablets with 10 ml of chloroform, filter, evaporate the filtrate to dryness on a water bath, the residue complies with test (2) for Identification described under Erythromycin Stearate.

Related substances To an accurately weighed quantity of powdered tablets add ethanol to produce a solution of 20 mg per ml (calculated as erythromycin), filter, using the filtrate as the solution of the substance being examined, and carry out the procedure for Related Substances described under Erythromycin Stearate, beginning at the words "To an accurately weighed quantity of erythromycin RS...".

Dissolution Carry out the dissolution test (Appendix X C, method 1), using hydrochloric acid solution (9→1000) as the dissolution medium, adjust the rotational speed of the basket to 100 rpm. Withdraw a quantity of the solution after exactly 45 minutes and filter. Dilute a quantity of the successive filtrate with the dissolution medium to produce a solution of 55 µg of erythromycin per ml (solution 1). Weigh accurately and powder 10 tablets, dissolve a quantity

of the powder equivalent to about the average weight in the dissolution medium and dilute to volume in a 1000 ml volumetric flask. Filter, dilute the successive filtrate with the dissolution medium to produce a solution of 55 μg of erythromycin per ml (solution 2). Mix 5 ml of two solutions with 5 ml of sulfuric acid solution (75 \rightarrow 100) respectively. After exactly 45 minutes, measure the absorbance of the resulting two solutions at 482 nm (Appendix IV A) respectively and calculate the dissolution of $\text{C}_{37}\text{H}_{67}\text{NO}_{13}$ from each tablet. Not less than 75% is dissolved.

Other requirements Comply with the general requirements for tablets (Appendix I A).

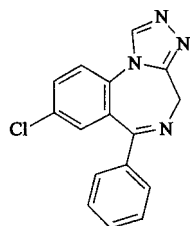
Assay Weigh accurately and powder 4 tablets. Triturate with ethanol in several portions to dissolve erythromycin stearate and dilute with ethanol to produce a solution of 1000 Units per ml and mix well. Allow it to stand for 2 hours, measure accurately a quantity of the supernatant liquid and carry out the assay described under Erythromycin Stearate.

Category As described under Erythromycin Stearate.

Strength Calculated as $\text{C}_{37}\text{H}_{67}\text{NO}_{13}$
 (1) 0.05 g (50000 Units)
 (2) 0.125 g (125000 Units)
 (3) 0.25 g (250000 Units)

Storage Preserve in tightly closed containers, protected from light and stored in a dry place.

Estazolam



$\text{C}_{16}\text{H}_{11}\text{ClN}_4$ 294.7 [29975-16-4]

Estazolam is 6-phenyl-8-chloro-4H-[1,2,4] triazolo-[4,3- α][1,4] benzodiazepine. It contains not less than 98.5% of $\text{C}_{16}\text{H}_{11}\text{ClN}_4$, calculated on the dried basis.

Description A white or almost white crystalline powder; odourless; taste, slightly bitter. Freely soluble in acetic anhydride or chloroform; soluble in methanol; sparingly soluble in ethyl acetate or ethanol; practically insoluble in water.

Melting point 229-232°C (Appendix VI C).

Specific absorbance Dilute an accurately weighed quantity with hydrochloric acid solution (9 \rightarrow 1000) to produce a solution of 10 μg per ml. Measure the absorbance at 271 nm, the value of A (1%, 1 cm) is 349-367 (Appendix IV A).

Identification (1) To about 10 mg add 15 ml of hydrochloric acid solution (1 \rightarrow 2), boil gently for 15 minutes, cool. The solution yields the reaction characteristic of primary aromatic amines (Appendix III).

(2) Dissolve 1 mg in 1-2 drops of dilute sulfuric acid TS. Examine under ultraviolet light (365 nm), a sky blue fluorescence is produced.

(3) The infrared absorption spectrum (Appendix IV C) is concordant with the reference spectrum of estazolam

(Appendix XVI).

Chloride To 1.0 g add 50 ml of water, shake for 10 minutes and filter. Carry out the limit test for chlorides (Appendix VIII A), using 25 ml of the filtrate. Any opalescence produced is not more intense than that of a reference using 7.0 ml of sodium chloride standard solution (0.014%).

Related substances Carry out the method for high performance liquid chromatography (Appendix V D), using a column packed with octadecylsilane bonded silica gel and a mixture of methanol-water (65:35) as the mobile phase. Detection wavelength is at 223 nm, and the number of theoretical plates of the column is not less than 2000, calculated with reference to the peak of estazolam. Dissolve a quantity in mobile phase to produce the solution of the substance being examined containing 0.2 mg per ml as test solution, mix well. Measure accurately a quantity of test solution, dilute with mobile phase as the reference solution containing 2 μg per ml. Inject 20 μl of the reference solution into the column, accurately measured, adjust the attenuation so that the principal peak height in the chromatogram is 20%-25% of the full scale of the chart. Inject separately 20 μl each of the test and reference solutions, both accurately measured, into the column and record the chromatogram for 3 times the retention time of the principal peak. The sum of peak areas other than the principal peak is not greater than 1/2 of area of the principal peak area of the reference solution.

Loss on drying When dried at 105°C to constant weight, loses not more than 0.5% of its weight (Appendix VIII L).

Residue on ignition Not more than 0.1% (Appendix VIII N).

Assay Dissolve about 0.1 g of the substance in 50 ml of acetic anhydride, add 2 drops of crystal violet IS. Titrate with perchloric acid (0.1 mol/L) VS until the colour changes to yellow. Perform a blank determination and make any necessary correction. Each ml of perchloric acid (0.1 mol/L) VS is equivalent to 14.7 mg of $\text{C}_{16}\text{H}_{11}\text{ClN}_4$.

Category Antianxiety agent.

Storage Preserve in tightly closed containers.

Preparation (1) Estazolam Tablets
 (2) Estazolam Injection

Estazolam Injection

Estazolam Injection is a sterile solution of estazolam containing suitable solubilizers. It contains not less than 90.0% and not more than 110.0% of the labelled amount of estazolam ($\text{C}_{16}\text{H}_{11}\text{ClN}_4$).

Description A clear, colourless liquid.

Identification (1) To a quantity equivalent about 1 mg of estazolam add 2 drops of diluted sulfuric acid TS. Examine under ultraviolet light (365 nm), a sky blue fluorescence is produced.

(2) The retention time of principal peak in the substance being examined in the chromatogram obtained in the Assay is identical with that the principal peak in the chromatogram of the reference solution.

pH value 5.6-7.0 (Appendix VI H).

Related substances Carry out the method for high performance liquid chromatography (Appendix V D), using a column packed with octadecylsilane bonded silica gel and a

Procedure Dissolve about 25 mg of estradiol benzoate CRS, accurately weighed, in methanol in a 25 ml volumetric flask by gentle warming, cool, dilute with methanol to volume, mix well, as the reference solution. Transfer 5 ml each of the reference solution and the internal standard solution, accurately measured, in a 25 ml volumetric flask, dilute with methanol to volume, mix well, inject 10 μ l of the resulting solution into column. Repeat the operation using the substance being examined instead of estradiol benzoate CRS, calculate the content of $C_{25}H_{28}O_3$.

Category Estrogen.

Storage Preserve in tightly closed containers, protected from light.

Preparation Estradiol Benzoate Injection

Estradiol Benzoate Injection

Estradiol Benzoate Injection is a sterile solution of estradiol benzoate in oil. It contains not less than 90.0% and not more than 110.0% of the labelled amount of estradiol benzoate ($C_{25}H_{28}O_3$).

Description A pale yellow clear oily liquid.

Identification Shake a quantity equivalent to about 1 mg of estradiol benzoate with 10 ml of dehydrated ethanol, allow to stand in an ice bath until separated into layers. Centrifuge the upper ethanolic layer, and use the supernatant liquid as the test preparation. Prepare a solution containing 0.1 mg of estradiol benzoate CRS per ml in dehydrated ethanol as the reference preparation. Carry out the method for thin-layer chromatography (Appendix V B), using silica gel G as the coating substance and a mixture of benzene-ether-glacial acetic acid (50 : 30 : 5) as the mobile phase. Apply separately to the plate 10 μ l each of the two solutions. After developing and removal of the plate, dry in air and spray with sulfuric acid-dehydrated ethanol (1:1), heat at 105°C for 10-20 minutes, cool, examine under ultraviolet light (365 nm). The colour and position of the principal spot in the chromatogram obtained with the test preparation corresponds to the principal spot obtained with the reference preparation.

Other requirements Complies with the general requirements for injections (Appendix I B).

Assay Carry out the method for high performance liquid chromatography (Appendix V D), using a column packed with octadecylsilane bonded silica gel and a mixture of methanol-water (80 : 20) as the mobile phase. Detection wavelength is 230 nm and the number of the theoretical plates of the column is not less than 2000.

Procedure Transfer a quantity, measured accurately, equivalent to about 2 mg of estradiol benzoate, to a 100 ml volumetric flask, add a quantity of absolute ethanol and shake thoroughly. After the solution is clear, dilute with absolute ethanol to volume and mix well. Inject 20 μ l into the column and record the chromatogram. Dissolve a quantity of estradiol benzoate CRS, accurately weighed, in absolute ethanol and dilute to produce a solution of 20 μ g per ml. Repeat the operation using the resulting solution. Calculate the content of $C_{25}H_{28}O_3$ with respect to the peak area obtained in the chromatogram by the external standard method.

Category As described under Estradiol Benzoate.

Strength (1) 1 ml:1 mg (2) 1 ml:2 mg

Storage Preserve in well closed containers, protected from light.

Estradiol Sustained-release Patches

Estradiol Sustained-release Patches contain not less than 85.0% and not more than 115.0% of the labelled amount of estradiol ($C_{18}H_{24}O_2$).

Description The patches consist of an outer covering which supports a preparation which contains the active substance and adhesive matrix. The patches are covered by a protective liner, which is transparent or creamy coloured.

Identification (1) To one patch with protective liner removed, add a quantity of acetone, shake to dissolve estradiol. Evaporate on a water bath to remove acetone, dissolve the residue in 2 ml of sulfuric acid, a yellowish-green fluorescence is produced; add 3 drops of ferric chloride TS, the colour changes to green, then changes to red on diluting with water.

(2) To one patch with protective liner removed, add 10 ml of methanol, shake to dissolve estradiol, use the supernatant liquid as the test solution. Prepare a reference solution of 0.25 mg of estradiol CRS per ml in methanol. Carry out the method for thin-layer chromatography (Appendix V B), using silica gel G as the coating substance and a mixture of toluene-acetone (4:1) as the mobile phase. Apply separately to the plate 20 μ l each of above two solutions. After developing and removal of the plate, dry it in air, spray with sulfuric acid-ethanol (1:1), heat at 105°C for 5 minutes. The colour and position of the principal spot in the chromatogram obtained with the test solution correspond to the principal spot obtained with the reference solution.

(3) The retention time of the principal peak of the test solution is identical with that of the reference solution in the Assay.

Content uniformity Comply with the requirements for Content uniformity (Appendix X E). Carry out the method for high performance liquid chromatography (Appendix V D), using a column packed with octadecylsilane bonded silica gel and a mixture of methanol-water (75:25) as the mobile phase. Detection wavelength is 280 nm and the number of theoretical plate of the column is not less than 2000, calculated with reference to the peak of estradiol. Transfer one patch with protective liner removed in a 100 ml volumetric flask, soak the patch in 5 ml of ethyl acetate for 30 minutes, place the volumetric flask in an ultrasonic bath for 15 minutes to dissolve estradiol, cool to room temperature, dilute with methanol to volume, mix well and filter, using the successive filtrate as the test solution. Dissolve an accurately weighed quantity of estradiol CRS in methanol to produce a reference solution of about 25 μ g per ml. Inject 20 μ l each of the resulting solutions separately into the column and record the chromatogram. Calculate the content of $C_{18}H_{24}O_2$ with respect to the peak area obtained in the chromatogram by the external standard method. The limit is $\pm 20\%$.

Drug Release Carry out the method for drug release test (Appendix X D, method 3), using 1000 ml of 1% polyglycol 400 solution as the dissolution medium and adjust the rotational speed of the paddle to 30 rpm. Withdraw the whole solution at exact 24,72,120 and 168 hours respectively, filter and supply 1000 ml of the dissolution medium accordingly in the vessel immediately, use the successive filtrate as test solutions. Transfer about 12.5 mg

of estradiol CRS, accurately weighed, in a 100 ml volumetric flask, add a quantity of methanol to dissolve estradiol, and dilute it with methanol to volume. Measure accurately a quantity of the resulting solution, dilute with the dissolution medium to produce a reference solution of about 0.5 μg per ml. Carry out the method for high performance liquid chromatography as described under Content uniformity. Calculate the content of $\text{C}_{18}\text{H}_{24}\text{O}_2$ dissolved from each patch at 24, 72, 120 and 168 hours separately. The dissolution of estradiol complies with the requirement; the quantity dissolved of each patch is not less than 20%-50%, 40%-70%, 60%-80% and over 70% of the labelled amount of $\text{C}_{18}\text{H}_{24}\text{O}_2$ at 24, 72, 120 and 168 hours respectively.

Test for heat resistance Heat 2 patches with protective liner removed at 120°C for 30 minutes, allow to cool; the back of the out covering does not change to yellow, and the release surface maintain adhesion by touching with fingers.

Other requirements Comply with the general requirements for patches (Appendix I V).

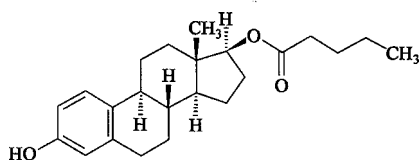
Assay Calculate the average of 10 patches results obtained under the test for Content uniformity.

Category As described under Estradiol.

Strength 2.5 mg (4.0 cm × 2.6 cm)

Storage Preserve in tightly closed containers, stored in a cool place.

Estradiol Valerate



$\text{C}_{23}\text{H}_{32}\text{O}_3$ 356.51

[979-32-8]

Estradiol Valerate is estro 1,3,5 (10)-triene-3,17 β -diol-17-pentanoate. It contains not less than 96.0% and not more than 103.0% of $\text{C}_{23}\text{H}_{32}\text{O}_3$, calculated on the dried basis.

Description A white crystalline powder; odourless. Freely soluble in ethanol, acetone or chloroform; slightly soluble in vegetable oil; practically insoluble in water.

Melting range 145-150°C (Appendix VI C).

Specific optical rotation +41° to +47° measured at 25°C, in a solution of 10 mg per ml in dioxane (Appendix VI E).

Identification (1) The retention time of principal peak of the substance being examined is identical with that of principal peak of the reference solution in the chromatogram obtained in the Assay.

(2) The infrared absorption spectrum (Appendix IV C) is concordant with the reference spectrum of estradiol valerate (Appendix XVI).

Related substances Carry out the method as described under Assay. Dissolve a quantity of the substance being examined in methanol to produce a solution (1) of about 4 mg per ml. Measure accurately 2 ml of solution (1) into a 100 ml volumetric flask and dilute with methanol to volume, shake well as solution (2). Inject 10 μl of solution (2) into the column. Adjust the attenuation so that the principal peak

height in the chromatogram is about full scale of the chart. Then inject separately 10 μl of solution (1) and (2) into the column, and record the chromatogram for twice of the retention time of the principal peak. If there are any other peaks except the principal peaks in the chromatogram of solution (1), the area of any one is not greater than 1/2 of the area of the principal peak of solution (2), the sum of the areas of all peaks other than the principal peak is not greater than 3/4 of the area of the principal peak of solution (2).

Loss on drying When dried to constant weight at 105°C, loses not more than 0.5% of its weight (Appendix VIII L).

Assay Carry out the method for high performance liquid chromatography (Appendix V D), using a column packed with octadecylsilane bonded silica gel and a mixture of methanol-water (85:15) as the mobile phase. Detection wavelength is 218 nm and the number of the theoretical plates of the column is not less than 3000, calculated with reference to estradiol valerate. The resolution factor between the peaks of estradiol valerate and internal standard complies with the related requirements.

Internal standard solution Dissolve a quantity of megestrol acetate, accurately weighed, in methanol to produce a solution of about 0.4 mg per ml.

Procedure Dissolve a quantity of estradiol valerate CRS, accurately weighed, in methanol to produce a solution of about 8 mg per ml as reference solution. Transfer 2 ml each of the reference solution and the internal standard solution, both accurately measured, in a 10 ml volumetric flask, dilute with methanol to volume, mix well, inject 5 μl of the resulting solution into the column. Repeat the operation, using the substance being examined instead of estradiol valerate CRS, calculate the content of $\text{C}_{23}\text{H}_{32}\text{O}_3$.

Category Estrogen.

Storage Preserve in tightly closed containers, protected from light.

Preparation Estradiol Valerate Injection

Estradiol Valerate Injection

Estradiol Valerate Injection is a sterile solution of estradiol valerate in oil. It contains not less than 90.0% and not more than 110.0% of the labelled amount of estradiol valerate ($\text{C}_{23}\text{H}_{32}\text{O}_3$).

Description A pale yellow clear oily liquid.

Identification (1) Shake a quantity equivalent to about 5 mg of estradiol valerate with 2.5 ml of methanol for 10 minutes and centrifuge, use the methanol solution as the test solution. Dissolve a quantity of estradiol valerate CRS with methanol to produce a solution of 2 mg per ml. Carry out the method for thin-layer chromatography (Appendix V B), using silica gel G as the coating substance and a mixture of benzene-ether-glacial acetic acid (50:30:0.5) as the mobile phase. Apply separately to the plate 5 μl each of the two solutions mentioned above. After developing and removal of the plate, dry in air and then at 105°C for 10 minutes, cool and spray with sulfuric acid-dehydrated ethanol (1:1), heat at 105°C for 10 minutes, cool and examine immediately. The position of the principal spot in the chromatogram obtained with the test solution is identical with that of the principal spot obtained with the reference solution.

(2) The retention time of principal peak of the substance being examined is identical with that of principal peak of the reference solution in the chromatogram obtained in the

Assay.

(1) or (2) may be used alternatively.

Other requirements Comply with the general requirements for injections (Appendix I B).

Assay Carry out the method for high performance liquid chromatography (Appendix V D), using a column packed with octadecylsilane bonded silica gel and a mixture of methanol-water (85 : 15) as mobile phase. Detection wavelength is 281 nm and the number of the theoretical plates of the column is not less than 3000, calculated with reference to the peaks of estradiol valerate. The resolution factor between the peaks of estradiol valerate and internal standard complies with the related requirements.

Internal Standard Solution Dissolve a quantity of testosterone propionate in methanol to produce a solution of about 5 mg per ml.

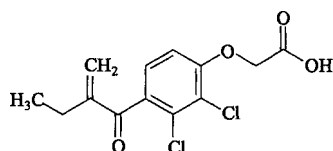
Procedure Transfer an accurately measured quantity of the injection equivalent to about 10 mg of estradiol valerate to a stoppered centrifugal tube with a "to contain" pipet, wash the interior of the pipet with several portions of ether, combine the washings to the same tube, evaporate the ether on a warm water bath. Extract the injection with 5, 5, 5, 3 ml of methanol, respectively, in each extraction shake 10 minutes and centrifuge. Transfer the methanol solutions to a 25 ml volumetric flask with a dropper, combine the methanolic extracts, add 5 ml of internal standard solution and dilute with methanol to volume, mix well, as the test solution, inject 20 μ l into the column. Dissolve an accurately weighed quantity of estradiol valerate CRS in methanol to produce a solution of 2 mg per ml. Measure accurately, 5 ml each of the solution and the internal standard solution in a 25 ml volumetric flask, dilute with methanol to volume, mix well, as the reference solution, inject the reference solution into the column in the same manner, calculate the content of $C_{23}H_{32}O_3$.

Category As described under Estradiol Valerate.

Strength (1) 1 ml:5 mg (2) 1 ml:10 mg

Storage Preserve in well closed containers, protected from light.

Etacrynic Acid



$C_{13}H_{12}Cl_2O_4$ 303.14

[58-54-8]

Etacrynic Acid is [4-(2-methylene-1-oxobutyl) phenoxy-2,3-dichloro] acetic acid. It contains not less than 98.0% of $C_{13}H_{12}Cl_2O_4$, calculated on the dried basis.

Description A white crystalline powder; odourless; taste, slightly bitter and astringent.

Freely soluble in ethanol or ether; practically insoluble in water; freely soluble in glacial acetic acid.

Melting range 121-125°C (Appendix VI C).

Identification (1) Heat about 30 mg with 2 ml of sodium hydroxide TS in a water bath for 5 minutes, cool, add 0.25 ml of sulfuric acid solution (1 \rightarrow 2) and 0.5 ml of 10% sodium chromotopate solution, then add 2 ml of sulfuric

acid cautiously; a deep violet colour is produced.

(2) The light absorption of a solution of 50 μ g per ml in hydrochloric acid-methanol (1:1000) exhibits a maximum at 270 nm; the absorbance is about 0.58 (Appendix IV A).

(3) The infrared absorption spectrum (Appendix IV C) is concordant with the reference spectrum of etacrynic acid (Appendix XVI).

(4) Mix about 20 mg with 0.10 g of anhydrous sodium carbonate and ignite, cool; dissolve the residue in 10 ml of water with heating and filter. The filtrate yields the reaction characteristic of chlorides (Appendix III).

Benzene extractive Dissolve 1.0 g in 50 ml of 8% sodium sulfite solution with shaking. Allow to stand for 20 minutes, add 5 ml of hydrochloric acid and mix well. Extract with three portions of 15 ml of benzene, shaking for 2 minutes each time. Transfer the benzene layer to a centrifuge tube and centrifuge if necessary. Then transfer the combined benzene extracts to a tared evaporating dish, evaporate on a water bath to dryness and dry the residue at 60°C under reduced pressure for 2 hours. The residue weighs not more than 20 mg.

Loss on drying When dried in vacuum over phosphorous pentoxide to constant weight, loses not more than 0.5% of its weight (Appendix VIII L).

Residue on ignition Not more than 0.1% (Appendix VIII N); use 1.0 g.

Heavy metals Carry out the limit test for heavy metals (Appendix VIII H, method 2), using the residue obtained in the test for Residue on ignition; not more than 0.002%.

Assay Dissolve about 0.15 g, accurately weighed, in 40 ml of glacial acetic acid in an iodine flask. Add accurately 25 ml of bromine (0.05 mol/L) VS and 3 ml of hydrochloric acid, immediately stopper the flask, mix well and allow to stand in dark for 1 hour. Add 10 ml of potassium iodide TS, immediately stopper the flask, mix well, add 100 ml of water. Titrate with sodium thiosulfate (0.1 mol/L) VS, add 2 ml of starch IS towards the end-point, continue the titration until the blue colour disappears. Perform a blank determination and make any necessary correction. Each ml of bromine (0.05 mol/L) VS is equivalent to 15.16 mg of $C_{13}H_{12}Cl_2O_4$.

Category Diuretic.

Storage Preserve in tightly closed containers, protected from light.

Preparation Etacrynic Acid Tablets

Etacrynic Acid Tablets

Etacrynic Acid Tablets contain not less than 90.0% and not more than 110.0% of the labelled amount of etacrynic acid ($C_{13}H_{12}Cl_2O_4$).

Description White tablets.

Identification Mix a quantity of the powdered tablets equivalent to about 0.1 g of etacrynic acid with 10 ml of ethanol, stir to dissolve etacrynic acid, filter, evaporate the filtrate to dryness on a water bath. The residue complies with (1), (2) and (4) tests for Identification described under Etacrynic Acid.

Dissolution Carry out dissolution test (Appendix X C, method 2) using 900 ml of phosphate buffer solution (to 13.6 g of potassium dihydrogen phosphate add 95 ml of 0.1 mol/L sodium hydroxide solution, and adjust to pH 8.0

with 0.1 mol/L sodium hydroxide solution and dilute with water to 1000 ml) as the dissolution medium, adjust the rotational speed of the paddle to 50 rpm. Withdraw a quantity of the solution after exactly 45 minutes and filter. Measure the absorbance of the successive filtrate at 277 nm (Appendix IV A). Dissolve a quantity of etacrynic acid CRS, accurately weighed, in above dissolution medium and dilute to produce a solution of 30 µg per ml. Measure the absorbance in the same manner. Calculate the dissolution of $C_{13}H_{12}Cl_2O_4$ from each tablet. Not less than 75% of the labelled amount is dissolved.

Other requirements Comply with the general requirements for tablets (Appendix I A).

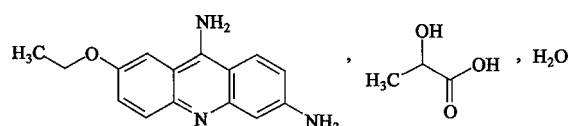
Assay Weight accurately and powder 20 tablets. Transfer an accurately weighed quantity of the powdered tablets equivalent to about 0.15 g of etacrynic acid to a separator, add 25 ml of 0.1 mol/L hydrochloric acid solution and shake thoroughly. Extract with three portions of 50 ml each of dichloromethane, filter the combined extracts into a 250 ml iodine flask, evaporated to dryness on a water bath. Carry out the Assay described under Etacrynic Acid, beginning at the words "dissolve in 40 ml of glacial acetic acid". Each ml of bromine (0.1 mol/L) VS is equivalent to 15.16 mg of $C_{13}H_{12}Cl_2O_4$.

Category As described under Etacrynic Acid.

Strength 25 mg

Storage Preserve in tightly closed containers, protected from light.

Ethacridine Lactate



$C_{15}H_{15}N_3O \cdot C_3H_6O_3 \cdot H_2O$ 361.40 [1837-57-6]

Ethacridine lactate is α -ethoxyacridine-6,9-diamino lactate monohydrate. It contains not less than 99.0% of $C_{15}H_{15}N_3O \cdot C_3H_6O_3$, calculated on the dried basis.

Description A yellow crystalline powder; odourless; taste, bitter. Freely soluble in hot water; soluble in boiling dehydrated ethanol; sparingly soluble in water; slightly soluble in ethanol; insoluble in ether.

Identification (1) Dissolve about 0.1 g in 10 ml of water, add sodium hydroxide TS to make alkaline, a yellow precipitate is produced. Filter, add 2 ml of sulfuric acid solution (0.5 mol/L) and a few drops of potassium permanganate TS, a purple colour is produced which disappears on heating.

(2) Dissolve 50 mg in 5 ml of water, acidify with dilute hydrochloric acid, add 1 ml of sodium nitrite TS, a cherry red colour is produced.

(3) To the aqueous solution (1→2000) add a few drops of iodine TS, a deep bluish-green precipitate is produced which disappears on addition of ethanol.

(4) The aqueous solution (1→40000) exhibits yellowish green fluorescence at the transmission light.

Acidity Dissolve 0.1 g in 100 ml of water, pH 6.0-7.0 (Appendix VI H).

Clarity and colour of solution A solution of 0.20 g in 10 ml of freshly boiled and cooled to 50°C water is clear. Any colour produced by 5 ml of this solution diluted to 10 ml with water is not more intense than that of reference solution (9.5 ml of 1% trinitrophenol solution, add 0.22 ml of ferric chloride CS (Appendix XVI B) and 0.28 ml of water, mix well).

Chloride Dissolve 1 g in 80 ml of water by heating on water bath and cool. Add 10 ml of sodium hydroxide TS, dilute with water to 100 ml, shake and mix well. Allow to stand for 30 minutes and filter. Measure 20 ml of successive filtrate, add 7 ml of dilute nitric acid and 1 ml of silver nitrate TS, dilute with water to 50 ml. Carry out the limit test for chloride (Appendix VIII A). Any opalescence produced is not more pronounced than that of a reference solution using 5 ml of sodium chloride standard solution (0.025%).

Sulfate To 20 ml of above filtrate, add 4.5 ml of water and 1.5 ml of dilute hydrochloric acid. Carry out the limit test for sulfate (Appendix VIII B). Any opalescence produced is not more pronounced than that of a reference solution using 10 ml of potassium sulfate standard solution (0.5%).

Loss on drying When dried to constant weight at 105°C, loses not more than 5.5% of its weight (Appendix VIII L).

Residue on ignition Not more than 0.1% (Appendix VIII N); use 1.0 g.

Heavy metals Carry out the limit test for heavy metals (Appendix VIII H, method 2), using the residue obtained in the test for Residue on ignition; not more than 0.003%.

Assay To about 0.3 g accurately weighed, in a 100 ml volumetric flask, add 25 ml of water, 20 ml of sodium acetate TS and 1.25 ml of dilute hydrochloric acid, then add accurately 50 ml of potassium dichromate (0.01667 mol/L) V in water to volume. Allow to stand for 1 hour with frequently shaking and filter. Measure accurately 50 ml of the successive filtrate in a conical flask with stopper, add 30 ml of dilute sulfuric acid and 6 ml of potassium iodide TS, stopper the flask immediately, mix well and allow to stand in dark place for 5 minutes. Add 50 ml of water, titrate with sodium thiosulfate (0.1 mol/L) VS towards the end of titration. Add 3 ml of starch IS, continue to titrate until blue colour disappears and a bright green colour is produced. Perform a blank determination and make any necessary correction. Each ml of potassium dichromate (0.01667 mol/L) VS is equivalent to 11.45 mg $C_{15}H_{15}N_3O \cdot C_3H_6O_3$.

Category Antiseptics-Disinfectant.

Storage Preserve in tightly closed containers.

Preparation (1) Ethacridine Lactate Injection
(2) Ethacridine Lactate Solution

Ethacridine Lactate Injection

Ethacridine Lactate Injection is a sterile solution of Ethacridine Lactate in water for injection. It contains not less than 93.0% and not more than 107.0% of the labelled amount of Ethacridine Lactate ($C_{15}H_{15}N_3O \cdot C_3H_6O_3$).

Description A clear, yellow liquid.

Identification (1) To 2 ml of the test solution, acidify with dilute hydrochloric acid, add 1 ml of sodium nitrite TS, a cherry red colour is produced.

(2) To 4 ml of the test solution, add sodium hydroxide TS

to make alkaline, a yellow precipitate is produced. Filter, add 2 ml of sulfuric acid solution (3→100) and a few drops of potassium permanganate TS, a purple colour is produced which disappears on heating.

(3) The light absorption of a solution of 5 µg per ml in water exhibits maxima at 206 nm, 260 nm and 362 nm (Appendix IV A).

pH value 5.5-7.5 (Appendix VI H).

Colour of solution Any colour produced by 4 ml of the test solution diluted to 10 ml with water is not more intense than that of the reference solution (9.5 ml of 1% trinitrophenol solution, add 0.22 ml of ferric chloride CS and 0.28 ml of water, mix well).

Other requirements Comply with the general requirements for injections (Appendix I B).

Assay To 10 ml of the injection, accurately measured, in a 100 ml volumetric flask, add 25 ml of water, 20 ml of sodium acetate TS and 1.25 ml of dilute hydrochloric acid, then add accurately 50 ml of potassium dichromate (0.0167 mol/L) VS and water to volume. Allow to stand for 1 hour with frequently shaking, filter, discards 20 ml of the initial filtrate. Measure accurately 50 ml of the successive filtrate in a conical flask with stopper, add 30 ml of dilute sulfuric acid and 6 ml of potassium iodide TS, stopper the flask immediately, mix well and allow to stand in dark place for 5 minutes. Add 50 ml of water, titrate with sodium thiosulfate (0.1 mol/L) VS towards the end of titration. Add 3 ml of starch IS, continue to titrate until blue colour disappears and a bright green colour is produced. Perform a blank determination and make any necessary correction. Each ml of potassium dichromate (0.01667 mol/L) VS is equivalent to 11.45 mg of $C_{15}H_{15}N_3O \cdot C_3H_6O_3$.

Category As described under Ethacridine Lactate.

Strength 2 ml:50 mg

Storage Preserve in well closed container, protected from light.

Ethacridine Lactate Solution

Ethacridine Lactate Solution is a solution of ethacridine lactate in water. It contains not less than 93.0% and not more than 107.0% of the labelled amount of ethacridine lactate ($C_{15}H_{15}N_3O \cdot C_3H_6O_3$).

Description A clear yellow liquid.

Identification (1) Acidify about 10 ml with dilute hydrochloric acid, add 1 ml of sodium nitrite TS, a cherry-red colour is produced.

(2) Alkalize about 10 ml with sodium hydroxide TS, a yellow precipitate is formed and filter. Add 2 ml of sulfuric acid solution (3→100) and a few drops of potassium permanganate TS to the filtrate, a violet-red colour is produced and disappears on heating.

pH value 5.0-7.5 (Appendix VI H).

Minimum Fill Complies with the test for Minimum Fill (Appendix X F).

Assay Measure accurately 50 ml into a 100 ml volumetric flask, add 15 ml of water, 20 ml of sodium acetate TS and 1.25 ml of dilute hydrochloric acid, add accurately 10 ml of potassium dichromate (0.01667 mol/L) VS, dilute with water to volume, shake thoroughly, allow to stand for an hour, shake frequently and filter. Measure accurately 50 ml

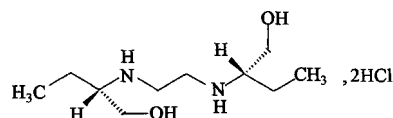
of successive filtrate into an iodine flask, add 30 ml of dilute sulfuric acid and 6 ml of potassium iodide TS, stopper immediately and mix well. Allow to stand in a dark place for 5 minutes. Add 50 ml of water and titrate with sodium thiosulfate (0.025 mol/L) VS until the end point is nearly reached, add 3 ml of starch IS and continue to titrate until the colour turns from blue to brilliant green. Perform a blank determination and make any necessary correction. Each ml of sodium thiosulfate (0.025 mol/L) VS is equivalent to 11.45 mg of $C_{15}H_{15}N_3O \cdot C_3H_6O_3$.

Category As described under Ethacridine Lactate.

Strength 0.1%

Storage Preserve in tightly closed containers, protected from light.

Ethambutol Hydrochloride



$C_{10}H_{24}N_2O_2 \cdot 2HCl$ 277.23

[1070-11-7]

Ethambutol Hydrochloride is (+) 2,2'-(ethylene-diimino)-di-1-butanol dihydrochloride. It contains not less than 98.5% of $C_{10}H_{24}N_2O_2 \cdot 2HCl$, calculated on the dried basis.

Description A white, crystalline powder; odourless or almost odourless; slightly hygroscopic.

Very soluble in water; sparingly soluble in ethanol; very slightly soluble in chloroform; practically insoluble in ether.

Melting range 199-204°C, with decomposition (Appendix VI C).

Specific optical rotation +6.0° to +7.0°, in a solution of about 0.10 g per ml in water, measured at 25°C (Appendix VI E).

Identification (1) Dissolve about 20 mg in 2 ml of water, add 2-3 drops of cupric sulfate TS, mix well, then add 2-3 drops of sodium hydroxide TS, a deep blue colour is produced.

(2) The infrared absorption spectrum (Appendix IV C) is concordant with the reference spectrum of ethambutol hydrochloride (Appendix XVI).

(3) The aqueous solution yields the reactions characteristic of chlorides (Appendix III).

(+) 2-Aminobutanol Carry out the method for thin layer chromatography (Appendix V B), using silica gel G as the coating substance and a mixture of ethyl acetate-glacial acetic acid-hydrochloric acid-water (11:7:1:1) as the mobile phase. Apply separately to the plate 5 µl each of two solutions in methanol containing (1) 20 mg per ml of the substance being examined, (2) 0.20 mg per ml of (+) 2-aminobutanol CRS. After developing and removal of the plate, dry in air and then at 105°C for 30 minutes. Allow to cool and spray with ninhydrin TS, dry again at 105°C for 30 minutes. Any spot other than the principal spot in the chromatogram obtained with solution (1) is not more intense than that of the principal spot obtained with solution (2) (1.0%).

Loss on drying When dried to constant weight at 105°C, loses not more than 0.5% of its weight (Appendix VIII L).

Residue on ignition Not more than 0.1% (Appendix VIII N).

Heavy metals Dissolve 1.0 g in 2 ml of acetate BS (pH 3.5) and sufficient water to produce 25 ml, carry out the limit test for heavy metals (Appendix VIII H, method 1); not more than 0.001%.

Assay Dissolve about 0.1 g, accurately weighed, in 20 ml of glacial acetic acid, add 5 ml of mercury acetate TS and 1 drop of crystal violet IS. Titrate with perchloric acid (0.1 mol/L) VS until the solution becomes bluish-green. Perform a blank determination and make any necessary correction. Each ml of perchloric acid (0.1 mol/L) VS is equivalent to 13.86 mg of $C_{10}H_{24}N_2O_2 \cdot 2HCl$.

Category Tuberculostatic agent.

Storage Preserve in tightly closed containers, protected from light.

Preparation (1) Ethambutol Hydrochloride Tablets
(2) Ethambutol Hydrochloride Capsules

Ethambutol Hydrochloride Capsules

Ethambutol Hydrochloride Capsules contain not less than 90.0% and not more than 110.0% of the labelled amount of ethambutol hydrochloride ($C_{10}H_{24}N_2O_2 \cdot 2HCl$).

Description Capsules containing white crystalline powder.

Identification (1) Dissolve about 20 mg of contents of the capsules in 2 ml of water, add 2-3 drops of cupric sulfate TS, mix well, then add 2-3 drops of sodium hydroxide TS, a deep blue colour is produced.

(2) The aqueous solution of contents of the capsules yields the reactions characteristic of chlorides (Appendix III).

Other requirements Comply with the general requirements for capsules (Appendix I E).

Assay Dissolve an accurately weighed quantity of the mixed contents obtained in the test for weight variation for contents equivalent to about 0.1 g of ethambutol hydrochloride in 20 ml of glacial acetic acid, add 5 ml of mercury acetate TS and 1 drop of crystal violet IS. Titrate with perchloric acid (0.1 mol/L) VS until the solution becomes bluish-green. Perform a blank determination and make any necessary correction. Each ml of perchloric acid (0.1 mol/L) VS is equivalent to 13.86 mg of $C_{10}H_{24}N_2O_2 \cdot 2HCl$.

Category As described under Ethambutol Hydrochloride.

Strength 0.25 g

Storage Preserve in tightly closed containers, stored in a dry place and protected from light.

Ethambutol Hydrochloride Tablets

Ethambutol Hydrochloride Tablets contain not less than 93.0% and not more than 107.0% of the labelled amount of ethambutol hydrochloride ($C_{10}H_{24}N_2O_2 \cdot 2HCl$).

Description White or film coated tablets with white core.

Identification To a quantity of the powdered tablets equivalent to about 0.1 g of ethambutol hydrochloride add 10 ml of water, shake to dissolve ethambutol hydrochloride and

filter. The filtrate complies with tests (1) and (3) for Identification described under Ethambutol Hydrochloride.

Dissolution Comply with the dissolution test (Appendix X C, method 1), using 900 ml of water as dissolution medium, adjust the rotational speed of the basket to 100 rpm. Withdraw 5 ml of the solution after exactly 45 minutes and filter. discard the initial filtrate measure accurately 2 ml of the successive filtrate in a 10 ml volumetric flask and dilute with water to volume, mix well. Measure accurately 2 ml of the solution, add 10 ml of bromocresol green solution [dissolve 0.2 g of bromocresol green in 30 ml of water and 6.5 ml of sodium hydroxide (0.1 mol/L) VS, add 19.0 g of sodium dihydrogen phosphate and 2.5 g of sodium hydrogen phosphate, dilute with water to produce 500 ml, mix well, adjust to pH 4.6 ± 0.1 with hydrochloric acid (0.1 mol/L) VS, mix well] and extract with exactly 20 ml of chloroform. Separate the clear chloroform layer and measure the absorbance at 420 nm (Appendix IV A). Measure accurately 2 ml of ethambutol hydrochloride CRS solution (each ml contains 50.0 μ g of ethambutol hydrochloride CRS), proceed as described above, beginning at the words "add 10 ml of bromocresol green solution...". Calculate the dissolution of $C_{10}H_{24}N_2O_2 \cdot 2HCl$ from each tablet. Not less than 75% of the labelled amount is dissolved.

Other requirements Comply with the general requirements for tablets (Appendix I A).

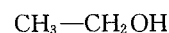
Assay Weigh accurately and powder finely 10 tablets. Weigh accurately a quantity of the powder equivalent to about 0.1 g of ethambutol hydrochloride to a separator, add 10 ml of a 8% solution of sodium hydroxide and 2 g of sodium chloride. Extract with 5 quantities, each of 25 ml, of chloroform, shake for about 5 minutes, filter the chloroform extracts through a layer of anhydrous sodium sulfate in a funnel and wash the filter with 25 ml of chloroform. Evaporate the combined washings and extracts of chloroform at 70°C in a water bath and cool. Add 75 ml of glacial acetic acid and 1 drop of crystal violet IS. Titrate with perchloric acid (0.1 mol/L) VS until the solution becomes bluish-green. Perform a blank determination and make any necessary correction. Each ml of perchloric acid (0.1 mol/L) VS is equivalent to 13.86 mg of $C_{10}H_{24}N_2O_2 \cdot 2HCl$.

Category As described under Ethambutol Hydrochloride.

Strength 0.25 g

Storage Preserve in tightly closed containers, protected from light.

Ethanol



C_2H_6O 46.07

[64-17-5]

Description A colourless and clear liquid; odour, slightly characteristic; taste, burning; readily volatile and inflammable, burns with a blue flame; boils at about 78°C. Miscible with water, glycerol, chloroform or ether.

Relative density Not more than 0.8129 (Appendix VI A) equivalent to not less than 95.0% (ml/ml) of C_2H_6O .

Identification To 1 ml add 5 ml of water and 1 ml of sodium hydroxide TS, add dropwise 2 ml of iodine TS slowly; an odour of iodoform is yielded and a yellow precipitate is formed.

Acidity To 10 ml add 25 ml of water and 2 drops of

phenolphthalein IS, mix well, add dropwise sodium hydroxide (0.02 mol/L) VS until the solution becomes slightly red; add 25 ml of the substance being examined, add 10 ml of water and 2 drops of phenolphthalein IS, mix well, and add 0.5 ml of sodium hydroxide (0.02 mol/L) VS; a slightly red colour is produced.

Water insoluble substances Mix with an equal volume of water, the solution is clear, allow to stand at 10°C for 30 minutes, the solution maintains clear.

Fusel oil Mix 10 ml with 5 ml of water and 1 ml of 1-cerol, drop on a piece of filter paper slowly and allow the ethanol to evaporate at room temperature; no abnormal odour is perceptible.

Methanol Dilute 5.0 ml with water to produce 100 ml and mix well. To 1.0 ml of the solution add 0.2 ml of phosphoric acid solution (1 → 10) and 0.25 ml of 5% potassium permanganate solution. Allow it to stand at 30–35°C for 15 minutes, add 10% sodium metabisulfite solution until the solution becomes colourless, add slowly 5 ml of precooled sulfuric acid solution (3 → 4) with cooling in an ice bath. Add 0.1 ml of freshly prepared 1% chromotropic acid solution and heat in a water bath for 20 minutes. Any colour produced is not more intense than that of a reference solution prepared in the same manner, using 1.0 ml of methanol standard solution (to 20 mg, accurately weighed, of methanol add water to produce 200 ml) (0.20%).

Readily oxidizable substances Transfer 20 ml to a 50 ml stoppered cylinder washed successively with hydrochloric acid, water and the substance being examined. Cool to 15°C, add 0.10 ml of potassium permanganate (0.02 mol/L) VS, stopper and mix well. Allow it to stand at 15°C for 10 minutes; the pink colour does not disappear completely.

Acetone and isopropanol To 1.0 ml of alcohol add 1.0 ml of water, 1.0 ml of saturated disodium hydrogen phosphate solution and 3.0 ml of saturated potassium permanganate solution, mix well and allow to stand in a water bath at 45–50°C until the colour of potassium permanganate disappears. Add 3.0 ml 10% sodium hydroxide solution, mix well, filter with a sintered glass filter. Add 1.0 ml of freshly prepared 1% furfural solution to the filtrate and allow to stand for 10 minutes. Add 3.0 ml of hydrochloric acid to 1.0 ml of the solution and examine within 3 minutes. Any pink colour produced is not more intense than that of a reference preparation (Mix 1.0 ml of saturated disodium hydrogen phosphate solution with 3.0 ml of 10% sodium hydroxide solution, 0.8 ml of 0.001% acetone solution and 1.0 ml of 1% furfural solution, dilute with water to produce 10 ml, and allow to stand for 10 minutes. To 1.0 ml of the resulting solution add 3.0 ml of hydrochloric acid) (0.0008%).

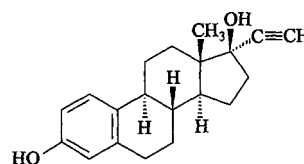
Pentanol or non-volatile readily carbonizable substances Evaporate 25 ml on a water bath to about 0.05 ml, add a few drops of 95% sulfuric acid; no red or brown colour is produced.

Non-volatile matter Transfer 40 ml to an evaporating dish previously dried to constant weight at 105°C, evaporate on a water bath to dryness, dry at 105°C for 2 hours; the residue is not more than 1 mg.

Category Solvent and antiseptic-disinfectant agent.

Storage Preserve in tightly closed containers, protected from light.

Ethinylestradiol



$C_{20}H_{24}O_2$ 296.41

[57-63-6]

Ethinylestradiol is 19-nor-17 α -pregna-1,3,5 (10)-trien-20-yne-3,17-diol. It contains not less than 97.0% and not more than 103.0% of $C_{20}H_{24}O_2$, calculated on the dried basis.

Description A white or almost white crystalline powder; odourless.

Freely soluble in ethanol, propanol or ether; soluble in chloroform; insoluble in water.

Melting range 180–186°C (Appendix VI C).

Specific optical rotation -26° to -31° , in a solution of 10 mg per ml in pyridine (Appendix VI E).

Identification (1) Dissolve 2 mg in 2 ml of sulfuric acid, the solution is coloured orange red with a yellowish-green fluorescence; pour the solution into 4 ml of water, a rose red flocculent precipitate is produced.

(2) Dissolve 10 mg in 1 ml of ethanol, add 5–6 drops of silver nitrate TS, a white precipitate is produced.

(3) The retention time of principal peak of the substance being examined is identical with that of principal peak of the reference solution in the chromatogram obtained in Assay.

(4) The infrared absorption spectrum (Appendix IV C) is concordant with the reference spectrum of ethinylestradiol (Appendix XVI).

Related substances Carry out the method as described under Assay. Dissolve a quantity of the substance being examined in absolute ethanol to produce a solution (1) of about 8 mg per ml. Measure accurately 2 ml of solution (1) into a 100 ml volumetric flask and dilute with absolute ethanol to the volume, shake well as solution (2). Inject 10 μ l of solution (2) into the column. Adjust the attenuation so that the principal peak height in the chromatogram is about full scale of the chart. Then inject separately 10 μ l of solutions (1) and (2) into the column and record the chromatogram for twice of the retention time of the principal peak. Not more than 4 peaks other than the principal peak in the chromatogram obtained with solution (1), each peak area is not greater than 1/2 of area of the principal peak of solution (2), the sum of the areas of all peaks other than the principal peak is not greater than 3/4 of area of the principal peak area of solution (2).

Loss on drying When dried to constant weight at 105°C, loses not more than 0.5% of its weight (Appendix VIII L).

Assay Carry out the method for high performance liquid chromatography (Appendix V D), using a column packed with octadecylsilane bonded silica gel and a mixture of methanol-water (70 : 30) as the mobile phase. Detection wavelength is 281 nm and the number of theoretical plates of the column is not less than 1000, calculated with reference to the peak of ethinylestradiol. The resolution factor between the peaks of ethinylestradiol and internal standard solution complies with the related requirements.

Internal standard solution Dissolve about 20 mg of

megestrol acetate, accurately weighed, in dehydrated ethanol in a 10 ml volumetric flask and dilute to volume, mix well.

Procedure Dissolve about 40 mg of ethinylestradiol CRS, accurately weighed, in dehydrated ethanol in a 5 ml volumetric flask and dilute to volume, mix well as the reference solution. Transfer 2 ml each of the reference solution and internal standard solution, both accurately measured, into a 10 ml volumetric flask, dilute with methanol to volume, mix well, inject 10 μ l of the resulting solution into the column. Repeat the operation using a quantity of the substance being examined instead of ethinylestradiol CRS, calculate the content of $C_{20}H_{24}O_2$.

Category Estrogen.

Storage Preserve in tightly closed container, protected from light.

Preparation Ethinylestradiol Tablets

Ethinylestradiol Tablets

Ethinylestradiol Tablets contain not less than 80.0% and not more than 120.0% of the labelled amount of ethinylestradiol ($C_{20}H_{24}O_2$).

Description Sugar coated tablets with white or almost white core.

Identification (1) Triturate tablets equivalent to about 20 μ g of ethinylestradiol and triturate with 5 ml of dehydrated ethanol for a few minutes, filter, evaporate the filtrate to dryness in a water bath, add 1 ml of sulfuric acid dropwise; an orange red colour is produced.

(2) The retention time of principal peak of the substance being examined is identical with that of principal peak of the reference solution in the chromatogram obtained in Assay.

Content uniformity Comply with the requirements for content uniformity (Appendix X E) except the limit is $\pm 20\%$. Take 1 tablet into a cube with plug (for strength 5 μ g, 20 μ g and 50 μ g) or a 100 ml volumetric flask (for strength 500 μ g) with 1 ml (for strength 5 μ g), 4 ml (for strength 20 μ g), 10 ml (for strength 50 μ g) or a quantity (for strength 500 μ g) of mobile phase, after 30 minutes of ultrasonic processing to make ethinylestradiol dissolve, then cool to room temperature, dilute to the volume with mobile phase, mix well and centrifugate, take the supernate as the test solution. Carry out the method described under the Assay, calculate the content of $C_{22}H_{29}FO_5$.

Other requirements Comply with the general requirements for tablets (Appendix I A).

Assay Carry out the method for high performance liquid chromatography (Appendix V D), using a column packed with octadecylsilane bonded silica gel and a mixture of methanol-water (70 : 30) as the mobile phase. Detective wavelength is 220 nm. The number of theoretical plates of the column, calculated with reference the peak of ethinylestradiol, is not less than 4000 and The resolution factor between the peaks of ethinylestradiol and adjacent peaks should comply with the requirement.

Procedure Weigh accurately and powder 20 tablets. To a quantity, weighed accurately, equivalent to about 50 μ g of ethinylestradiol in a cube with plug, add 10 ml of mobile phase, sonicate for 30 minutes until ethinylestradiol is dissolved. Shake well and centrifugate, take the supernate as the test solution. Inject 20 μ l into the column and record the chromatogram. Dissolve a quantity of ethinylestradiol CRS, accurately weighed, in mobile phase and dilute with

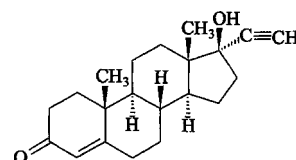
mobile phase to produce a solution of about 5 μ g per ml, repeat the operations of the test solution, calculate the content of $C_{20}H_{24}O_2$ with respect to the peak area obtained in the chromatogram by the external standard method.

Category As described under Ethinylestradiol.

Strength (1) 5 μ g (2) 20 μ g (3) 50 μ g (4) 500 μ g

Storage Preserve in tightly closed containers, protected from light.

Ethisterone



$C_{21}H_{28}O_2$ 312.45

[434-03-7]

Ethisterone is 17-Ethynyl-17 α -hydroxyandrost-4-en-3-one. It contains not less than 97.0% and not more than 103.0% of $C_{21}H_{28}O_2$, calculated on the dried basis.

Description A white or almost white crystalline powder; odourless or almost odourless.

Slightly soluble in pyridine, sparingly soluble in chloroform practically insoluble in water.

Specific optical rotation +28 to +33, in a solution of 10 mg per ml in pyridine (Appendix VI E).

Identification (1) To about 2 mg add 4 ml of dehydrated ethanol-sulfuric acid (1:1), heat in water bath to dissolve, a red solution is produced showing bright red fluorescence under ultra violet light (365 nm).

(2) To about 2 mg add 2 ml of ethanol, 1 ml of ethanolic solution of 1% 2,6-ditertial butyl benzoic acid and 2 ml of sodium hydroxide TS, heat in a water bath for 30 minutes, allow to cool, a deep blue colour is produced.

(3) To about 2 mg add 2 ml of ethanol in a clean test tube and then 1 ml of ammoniated silver nitrate TS, heat in a water bath, a silver mirror is formed on the inner surface of the tube.

(4) The infrared absorption spectrum (Appendix IV C) is concordant with the reference spectrum of ethisterone.

Related substances Carry out the method for thin layer chromatography (Appendix V B), using silica gel G as the coating material and chloroform-methanol (95:5) as mobile phase. Weigh accurately a quantity to prepare a solution of about 10 mg per ml of chloroform-methanol (3:1) as the test solution and a reference solution of 50 μ g per ml. Apply 10 μ l each of the two solutions to the same plate separately. After developing and removal of the plate, dry in air, spray with sulfuric acid-ethanol (2:8), heat for 5 minutes at 120°C, observe under ultra violet light (365 nm). The intensity of the fluorescence of any secondary spots of the test solution in the chromatogram is not more intense than that of the principal spot of the reference solution.

Loss on drying When dried for 4 hours at 105°C, loses not more than 0.5% of its weight (Appendix VIII L).

Assay Carry out the method for spectrophotometry (Appendix IV A), using a solution of about 10 mg per ml of dehydrated ethanol. Measure the absorbance at 240 nm, calculate the content of $C_{21}H_{28}O_2$, taking the value of A

(1%, 1 cm) as 520.

Category Progesteroid.

Storage Preserve in tightly closed containers, protected from light.

Preparation Ethisterone Tablets

Ethisterone Tablets

Ethisterone Tablets contain not less than 90.0% and not more than 110.0% of the labelled amount of Ethisterone ($C_{21}H_{28}O_2$).

Description White tablets.

Identification (1) Dissolve about 10 mg of the extract obtained in Assay in 1 ml of ethanol, add 5-6 drops of silver nitrate TS, a white precipitate is formed.

(2) Dissolve a quantity of extract obtained in the Assay in dehydrate ethanol to prepare a solution of about 10 μ g per ml. Measure the absorbance of the solution (Appendix IV A), it exhibits a maximum at 240 nm with the value of A (1%, 1 cm) in the range of 0.50-0.54.

Other requirements Comply with the general requirements for tablets (Appendix I A).

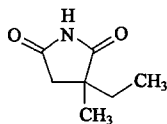
Assay Weigh and powder 20 tablets. Weigh accurately a quantity equivalent to about 50 mg of norethisterone in a separator, extract 4 times with petroleum ether. Discard the extract and remove all the petroleum ether in the separator. Extract again with 60 ml of chloroform in portions for 4 times. Transfer the extract to a tared conical flask, evaporate to remove chloroform to nearly dryness. Dry the residue at 105°C for 2 hours. Allow to cool, weigh and calculate the content of $C_{21}H_{28}O_2$.

Category As described under Ethisterone.

Strength (1) 5 mg (2) 10 mg (3) 25 mg

Storage Preserved in tightly closed containers, protected from light.

Ethosuximide



$C_7H_{11}NO_2$ 141.17

[77-67-8]

Ethosuximide is 2-ethyl-2-methylsuccinimide. It contains not less than 98.0% of $C_7H_{11}NO_2$, calculated on the anhydrous basis.

Description A white or pale yellow waxy solid; almost odourless; taste, slightly bitter; hygroscopic. Very soluble in ethanol or chloroform; freely soluble in water.

Melting range 43-47°C (use liquid paraffin as the heating liquid) (Appendix VI C).

Identification (1) To about 20 mg add 2 ml of sodium hydroxide TS, boil gently, the vapour produced turns moistened red litmus paper to blue.

(2) Heat 0.1 g with 0.2 g of resorcinol and 2 drops of sulfuric acid at about 140°C for 5 minutes, add 5 ml of water and make alkaline with 20% sodium hydroxide solution. Add a few drops of the solution into 5 ml of water; a yellowish-green fluorescence is produced.

(3) The infrared absorption spectrum (Appendix IV C) is concordant with the reference spectrum of ethosuximide (Appendix XVI) (If necessary, treat the sample with dehydrated ethanol).

Acidity Dissolve 0.10 g in 10 ml of water, pH 3.0-4.5 (Appendix VI H).

Cyanide Comply with the limit test for cyanides, using 0.5 g (Appendix VIII F, method 1).

Water Carry out the determination of water, not more than 1.0% (Appendix VIII M, method 1A).

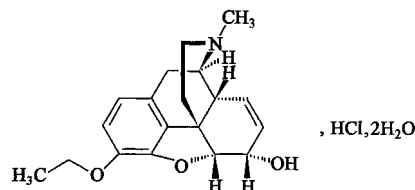
Residue on ignition Not more than 0.1% (Appendix VIII N).

Assay Dissolve about 0.2 g, accurately weighed, in 30 ml of dimethylformamide, add 2 drops of azo violet IS, titrate with sodium methoxide (0.1 mol/L) VS in a current of nitrogen until the solution becomes blue. Perform a blank determination and make any necessary correction. Each ml of sodium methoxide (0.1 mol/L) VS is equivalent to 14.12 mg of $C_7H_{11}NO_2$.

Category Anti-epileptic agent.

Storage Preserve in tightly closed containers.

Ethylmorphine Hydrochloride



$C_{19}H_{23}NO_3 \cdot HCl \cdot 2H_2O$ 385.89

[125-30-4]

Ethylmorphine Hydrochloride is 17-methyl-3-ethoxy-4, 5 α -epoxy-7, 8-didehydromorphinan-6 α -ol hydrochloride dihydrate. It contains not less than 98.5% of $C_{19}H_{23}NO_3 \cdot HCl$, calculated on the dried basis.

Description A white to pale yellow, crystalline powder; odourless.

Soluble in water or ethanol; slightly soluble in chloroform or ether.

Melting point 120-123°C, with decomposition (Appendix VI C).

Identification (1) Dissolve about 10 mg in 10 ml of sulfuric acid, add 1 drop of ferric chloride TS and heat on a water bath; a green colour is produced, turning gradually to deep purple-blue and subsequently to deep red on adding 1 drop of nitric acid.

(2) Dissolve about 20 mg in 1 ml of water, add 5 drops of ammonia TS and shake; a white turbidity is produced gradually (distinction from codeine).

(3) The infrared absorption spectrum (Appendix IV C) is concordant with the reference spectrum of ethylmorphine Hydrochloride (Appendix XVI).

(4) The aqueous solution yields the reactions characteristic of chlorides (Appendix III).

Acidity Dissolve 0.50 g in 15 ml of water, add 1 drop of methyl red IS, the red colour produced becomes yellow on the addition of 0.30 ml of sodium hydroxide (0.02 mol/L) VS.

Clarity and colour of solution Dissolve 0.20 g in 10 ml of freshly boiled and cooled water any opalescence produced is not more pronounced than that of reference suspension I (Appendix IX B); any colour produced is not more intense than that of the reference solution Y₂ (Appendix IX A, method 1).

Ammonium Dissolve 0.25 g in 5 ml of water, add 5 ml of sodium hydroxide TS and heat in a water bath, the vapour evolved does not turn moistened red litmus paper to blue.

Morphine Dissolve 0.10 g in 5 ml of hydrochloric acid solution (9→1000), add 2 ml of sodium nitrite TS, mix well and allow to stand for 15 minutes, then add 3 ml of ammonia TS, mix well, any yellowish-brown colour produced is not more intense than that of a reference solution prepared in a similar manner using 5.0 ml of a morphine solution [dissolve 2.0 mg of anhydrous morphine in hydrochloric acid solution (9→1000) to produce 100 ml] (0.1%).

Loss on drying When dried at 50–60°C for 4 hours and then at 105°C to constant weight, loses not more than 10.0% of its weight (Appendix VIII L), use 0.5 g.

Residue on ignition Not more than 0.15% (Appendix VIII N).

Assay Dissolve about 0.3 g, accurately weighed, in 10 ml of glacial acetic acid and 6 ml of mercury acetate TS, add 1 drop of crystal violet IS. Titrate with perchloric acid (0.1 mol/L) VS until the solution becomes green. Perform a blank determination and make any necessary correction. Each ml of perchloric acid (0.1 mol/L) VS is equivalent to 34.99 mg of C₁₉H₂₃NO₃ · HCl.

Category Local stimulant (ophthalmic).

Storage Preserve in tightly closed containers.

Etifenin and Stannous Chloride for Injection

Etifenin and Stannous Chloride is a sterile, lyophilized mixture of Etifenin (C₁₆H₂₂N₂O₅) and Stannous chloride (SnCl₂ · 2H₂O). It contains not less than 85.0% and not more than 110.0% of the labelled amount of Etifenin.

Description A white lyophilized powder. Freely soluble in water.

Identification (1) Dissolve the contents of 1 container in water, add 1 drop of copper sulfate TS, shake well and add a few drops of sodium hydroxide TS; a brilliant green colour is produced.

(2) Apply 1 drop of the aqueous solution to a strip of ammonium phosphomolybdate TP; a blue colour is produced.

Clarity and colour of solution Dissolve the content of 1 container in 5 ml of Sodium Chloride Injection, the solution is clear and colourless.

Stannite Dissolve the contents of 5 containers in 3 ml of 1 mol/L hydrochloric acid solution saturated with nitrogen respectively. Carry out the method for potentiometric titration (Appendix VII A) under nitrogen current, titrate

with potassium iodate (0.01667 mol/L) VS. Not less than 0.07 ml of potassium iodate (0.01667 mol/L) VS is consumed for each container. If one of the containers fails to comply with the requirements, repeat the test on 5 additional containers and all of them should comply with the requirements.

Acidity The pH value of the solution obtained in the test for clarity and colour of solution is 3.8–4.8 (Appendix VI H).

Bacterial endotoxin Dissolve a quantity of the content in BET water (5 ml of BET water for each container), and dilute to more than 30 times of its original volume. Carry out the test for bacterial endotoxin (Appendix XI E); not more than 75 EU per ml.

Other requirements Complies the general requirements for injections (Appendix I B).

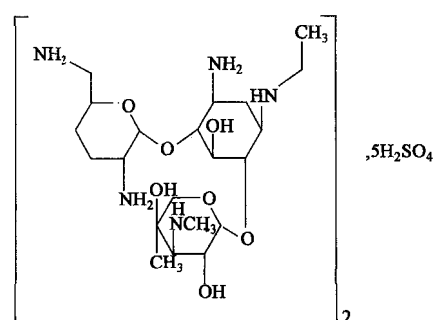
Assay Dissolve separately the contents of 3 containers in 2 ml of water, measured accurately, combine the solutions and mix well. Transfer 2 ml of the combined solution, measured accurately, to a 30 ml Kjeldahl flask, add 0.3 g of potassium sulfate and 5 drops of 30% copper sulfate solution. Add 2 ml of sulfuric acid along the wall of the flask and 6–10 drops of 30% hydrogen peroxide solution. Carry out the determination of nitrogen (Appendix VII D, method 2), and calculate the content of etifenin each container. Each mg of N is equivalent to 11.5 mg of C₁₆H₂₂N₂O₅.

Category Used for the preparation of Technetium [^{99m}Tc] Etifenin Injection.

Strength 40.0 mg of etifenin and 0.4 mg of stannous chloride (SnCl₂ · 2H₂O).

Storage Preserve in well closed containers, stored at 2–8°C in a dark place.

Etimicin Sulfate



(C₂₁H₄₃N₅O₇)₂ · 5H₂SO₄ 1445.58

Etimicin Sulfate is O-2-amino-2,3,4,6-tetradeoxy-6-amino-α-D-erythro-hexopyranosyl- (1→4)-O[3-deoxy-4C-methyl-3-(methylamino)-β-L-arabino-pyranosyl-(1→6)]-2-deoxy-N-ethyl-L-streptamine sulfate (2:5) (salt). It contains not less than 59.0 per cent of C₂₁H₄₃N₅O₇, calculated on the dried basis.

Description A white or almost white powder or friable mass; odourless; highly hygroscopic. Very soluble in water, practically insoluble in methanol, acetone, glacial acetic acid.

Specific optical rotation +100° to +115°, in a solution of 50 mg per ml in water (Appendix VI E).

Identification (1) Dissolve a quantity in water to produce a

solution containing 50 mg of the substance to be examined per ml as test solution. Dissolve a quantity of etimicin CRS in water to produce a solution of 50 mg per ml as reference solution. Dilute a quantity with test solution to produce a solution containing 2.0 mg of gentamycin C_{1a} per ml as mixture solution. Carry out the method for thin-layer chromatography described under Related substances. Apply each of above three solution. The principal spot in the chromatogram obtained with the test solution is similar in position and colour to the principal spot in the chromatogram obtained with the reference solution, and the spot of etimicin and gentamycin C_{1a} in the chromatogram obtained with the mixture solution is separated completely.

(2) The retention time of principal peak in the chromatogram obtained in the Assay with the test solution is identical with the principal peak in the chromatogram obtained with the reference solution.

(3) The aqueous solution yields the reactions characteristic of sulfates (Appendix III).

Either test (1) or (2) may be omitted.

Acidity Dissolve a quantity in water to produce a solution containing 50 mg per ml, pH 4.0-6.5 (Appendix VI H).

Clarity and colour of solution Dissolve each of 5 portions with water to produced 5 solutions containing 75 mg per ml, the solutions are clear and colourless; any opalescence produced is not more pronounced than that of reference suspension 1 (Appendix IX B); any colour produced is not more intense than that of reference solution Y_2 or YG_2 (Appendix IX A, method 1).

Sulfate Dissolve about 0.12 g, accurately weighed, in 100 ml of water, adjust pH value to 11 with concentrated ammonia solution, add accurately 10 ml of barium chloride (0.1 mol/L) VS and 5 drops of phthalein purple IS. Titrate with disodium edetate (0.05 mol/L) VS, keep pH 11 during the period of titration. When the purple colour of the solution begins to discolour slightly, add 50 ml of ethanol and continue titration until the purple colour disappears. Perform a blank determination and make any necessary correction. Each ml of barium chloride (0.1 mol/L) VS is equivalent to 9.606 mg of sulfate (SO_4). The content of sulfate is not less than 31.5% and not more than 35.0%, calculated on the anhydrous basis.

Related substances Carry out the method for thin layer chromatography (Appendix V B), using silica gel G (a mixture of silica gel G and 0.5% sodium carboxymethyl cellulose 1:3 W/V) as the coating substance and a mixture of chloroform-methanol-concentrate ammonia solution (5:3:1.5) as the mobile phase. Apply separately to the plate 2 μ l each of four solutions (1) 50 mg per ml of the substance to be examined in water, (2) 1.5 mg per ml of etimicin CRS in water, (3) 2.5 mg per ml of etimicin CRS in water, and (4) 2.0 mg per ml of gentamycin C_{1a} in solution (1). After developing and removal of the plate, allow it to dry in air, heat at 110°C for 10 minutes and expose it to iodine vapor. The spots of etimicin and gentamycin C_{1a} in the chromatogram obtained with solution (4) are separated completely, any spot in the chromatogram other than the principal spot obtained with solution (1) is not more intense than the principal spot obtained with solution (2) (3 per cent), and not more than one such spot more intense than the spot obtained with solution (3) (5 per cent).

Dichloromethane To about 0.12 g, accurately weighed, in headspace vials, add accurately 3 ml of water, dissolve and seal as test solution. Dilute a quantity with methanol to produce a solution containing 1.0 mg of dichloromethane per ml as reference stock solution, dilute a quantity of the reference stock solution, accurately measured, with water to produce a solution containing 24 μ l dichloromethane per

ml, measure accurately 3 ml of the solution into headspace vials, seal, as reference solution. Carry out the method for residual solvents (Appendix VIII P), using a capillary column packed with 5% diphenyl and 95% dimethyl silicone (or stationary phase with similar polarity). The gas chromatograph is equipped with a flame-ionization detector, the injection port temperature and the detector temperature are maintained at 120°C and 260°C, respectively. The column temperature is programmed according to the following steps. It is maintained at 50°C for 5 minutes, then increased to 200°C at a rate of 35°C per minute. Heat the sealed vial at 85°C for 30 minutes and inject 1 ml of the headspace. The resolution factor among principal peaks in the chromatogram obtained with the reference solution complies with related requirements. Inject separately each of test solution and reference solution, and record the chromatogram. Calculate the content with the peak area obtained in the chromatogram by the external standard method.

Water Not more than 10.0% (Appendix VIII M, method 1).

Residue on ignition Not more than 0.5% (Appendix VIII N), using 1.0 g.

Heavy metals Carry out the limit test for heavy metals (Appendix VIII H, method 2), using the residue obtained in the test for Residue on ignition; not more than 0.002%.

Bacterial endotoxin Carry out the test for bacterial endotoxin (Appendix XI E); not more than 0.5 EU per 1 mg Etimicin.

Assay Carry out the method for high performance liquid chromatography (Appendix V D), using a column packed with octadecylsilane bonded silica gel (pH 0.8-8.0); a mixture of 0.2 mol/L trifluoroacetate-methanol (84:16) as the mobile phase; the flow rate is 0.5 ml per minute; The temperature of the drift tube of evaporative light-scattering detector (ELSD) is at 100°C, the flow of the carrier gas at 2.6 L per minute. Dissolve a quantity of etimicin and netilmicin CRS in water to produce a solution containing 0.2 mg per ml, respectively. Inject 20 μ l into the column and record the chromatogram. The resolution factor between the peaks of etimicin and netilmicin is not less than 1.2. The relative standard deviation (RSD) for 5 replicate injections is less than 2.0%.

Procedure Inject separately 20 μ l into the column each of three solutions with the mobile phase containing (1) 1.0 mg per ml, (2) 0.5 mg per ml and (3) 0.25 mg per ml of etimicin CRS and record the chromatogram. Based on the corresponding concentrations (C) and areas (A) of etimicin of solution (1), (2), and (3), the linear regression equation of log A versus log C can be determined. The correlation coefficient (r) of the regression equation should be greater than 0.99. Dissolve a quantity of substance to be examined with the mobile phase to produce a solution of 0.5 mg per ml and inject 20 μ l of the solution into the column. Calculate the content of $C_{21}H_{43}N_5O_7$ with respect to the regression equation.

Category Antibiotic.

Storage Preserve in hermetically sealed containers, store in a dry place.

Preparation (1) Etimicin Sulfate Injection
(2) Etimicin Sulfate for Injection

Etimicin Sulfate for Injection

Etimicin Sulfate for Injection is a sterile powder of

etimicin sulfate. It contains not less than 90.0% and not more than 110.0% of the labelled amount of etimicin ($C_{21}H_{43}N_5O_7$), calculated with reference to the average weight of contents.

Description A white or almost white power or friable mass.

Identification Complies with the Identification tests described under Etimicin Sulfate.

Clarity and colour of solution To each of 5 containers add water to produce a solution of 0.25 mg per ml, the solutions are clear and colourless; any opalescence produced is not more pronounced than that of reference suspension 1 (Appendix IX B); any colour produced is not more intense than that of reference solution Y₂ or YG₂ (Appendix XI A, method 1).

Sterility Carry out the test for sterility (Appendix XI H, membrane filtration method). Dilute each vial with not less than 500 ml of 0.9% sterile Sodium Chloride Injection, the solution complies with the requirement.

pH value, Related substances, Water, Bacterial endotoxin complies with the corresponding requirements described under Etimicin Sulfate.

Other requirements Complies with the general requirements for injection (Appendix I B).

Assay Carry out the Assay described under Etimicin Sulfate, using an accurately weighed quantity of the mixed contents obtained from the test for weight variation of contents.

Category As described under Etimicin Sulfate.

Strength Calculate as $C_{21}H_{43}N_5O_7$
(1) 50 mg (2) 100 mg

Storage Preserve in well closed containers, store in a cool and dry place, protected from light.

Etimicin Sulfate Injection

Etimicin Sulfate Injection is a sterile solution of etimicin sulfate in Water for Injection. It contains not less than 90.0% and not more than 110.0% of the labelled amount of etimicin ($C_{21}H_{43}N_5O_7$).

Description A clear, colourless or almost colourless liquid.

Identification Complies with the tests for Identification described under Etimicin Sulfate.

pH value 5.0-7.0 (Appendix VI H).

Colour The solution is colourless; any colour produced is not more intense than that of reference solution Y₂ or YG₂ (Appendix XI A, method 1).

Related substances Complies with the corresponding requirements described under Etimicin Sulfate.

Sterility Carry out the test for sterility (Appendix XI H, membrane filtration method). Dilute each vial with not less than 500 ml of 0.9% sterile Sodium Chloride Injection, the solution complies with the requirement.

Bacterial endotoxin Complies with the corresponding requirements described under Etimicin Sulfate.

Other requirements Complies with the general requirements for injection (Appendix I B).

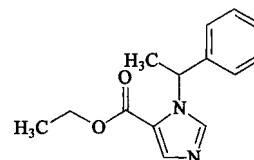
Assay Measure accurately a quantity and carry out the Assay described under Etimicin Sulfate.

Category As described under Etimicin Sulfate.

Strength Calculate as $C_{21}H_{43}N_5O_7$
(1) 1 ml : 50 mg (2) 2 ml : 100 mg

Storage Preserve in well closed containers.

Etomidate



$C_{14}H_{16}N_2O_2$ 244.29

[33125-97-2]

Etomidate is (+) -Ethyl 1- (α -methylbenzyl) imidazole-5-carboxylate. It contains not less than 98.5% of $C_{14}H_{16}N_2O_2$, calculated on the dried basis.

Description White crystals or a crystalline powder. Very soluble in ethanol or chloroform; freely soluble in dilute hydrochloric acid; insoluble in water.

Melting range 66-70°C (Appendix VI C).

Specific optical rotation +67° to +72°, in a solution of 10 mg per ml in ethanol (Appendix VI E).

Identification (1) Dissolve a quantity of etomidate in dilute hydrochloric acid. Add a few drops of potassium iodobismuthate TS; a brick-red precipitate is produced.

(2) The light absorption of the solution of 10 μ g per ml in ethanol exhibits a maximum at 241 nm.

(3) The infrared absorption spectrum (Appendix IV C) is concordant with the reference spectrum of etomidate (Appendix XVI).

Related substances Carry out the method for high performance liquid chromatography (Appendix V D), using a column packed with octadecylsilane bonded silica gel and a mixture of methanol -0.062% ammonium acetate solution (60:40) as the mobile phase. Detection wavelength is 240 nm and the number of the theoretical plates of the column is not less than 2000, calculated with reference to the peak of etomidate. The resolution factor between the peaks of etomidate and degradation products complies with the related requirements.

Procedure Dissolve a quantity of the substance being examined in mobile phase to produce a solution of 1 mg per ml, as the test solution. Dilute 1 ml of test solution, accurately measured, with the mobile phase to the volume of 100 ml volumetric flask, mix well, as prepared solution. Inject 5 μ l of prepared solution into the column, adjust the attenuation so that the height of the principal peak is about 15% of the full scale of the chart. Inject 5 μ l of test into the column, record the chromatogram. Measure the peak areas of degradation products and etomidate, the percentage of degradation products is not more than 0.5%, calculated by normalized method.

Loss on drying When dried in vacuum over phosphorous pentoxide to constant weight, loses not more than 0.5% of its weight (Appendix VIII L).

Sulfate Shake 0.5 g with 40 ml of water, add 2 ml of dilute hydrochloric acid, shake thoroughly to dissolve etomidate. Carry out the limit test for sulfate (Appendix VIII B), using the resulting solution. Any opalescence produced is not more

pronounced than that of a reference solution using 1.0 ml of potassium sulfate standard solution (0.02%).

Residue on ignition Not more than 0.1% (Appendix VIII N), using 1.0 g.

Heavy metals Carry out the limit test for heavy metals (Appendix VIII H, method 2), using the residue obtained in the test for Residue on ignition; not more than 0.002%.

Assay Dissolve about 0.2 g, accurately weighed, in 20 ml of glacial acetic acid, add two drops of naphtholbenzein IS. Titrate with perchloric acid (0.1 mol/L) VS until the solution becomes green. Perform a blank determination and make any necessary correction. Each ml of perchloric acid (0.1 mol/L) VS is equivalent to 24.43 mg of $C_{14}H_{16}N_2O_2$.

Category Anesthetic.

Storage Preserve in tight glass containers, store in cool place and protected from light.

Preparation Etomidate Injection

Etomidate Injection

Etomidate Injection is sterile solution of etomidate in Water for Injection. It contains not less than 90.0% and not more than 110.0% of the labelled amount of etomidate ($C_{14}H_{16}N_2O_2$).

Description A clear, colourless liquid.

Identification (1) To 1 ml add a few drops of potassium iodobismuthate TS; a brick-red precipitate is produced. (2) The light absorption of solution obtained in the Assay exhibits a maximum at 241 nm (Appendix IV A).

pH value 5.0-6.5 (Appendix VI H).

Related substances Dissolve a quantity of the substance being examined in mobile phase to produce a solution of 1 ml per ml. Carry out the method for related substances described under etomidate, record the chromatogram. The elution order is propylene glycol, degradation products and etomidate. Measure the peak areas of degradation products and etomidate; the percentage of degradation products is not more than 1.4%, calculated by normalization method.

Pyrogens Complies with the test for pyrogens (Appendix XI D), using 1 ml per kg of the rabbit's weight.

Other requirements Complies with the general requirements for injections (Appendix I B).

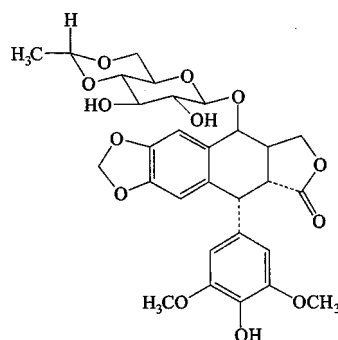
Assay Dilute 5 ml of the test solution, accurately measured, with ethanol to produce a solution of 10 µg per ml. Measure the absorbance at 241 nm (Appendix IV A). Calculate the content of $C_{14}H_{16}N_2O_2$, taking 501 as the value of A (1%, 1 cm).

Category As described under Etomidate.

Strength 10 ml:20 mg

Storage Preserve in well closed containers, stored in a cool place and protected from light.

Etoposide



$C_{29}H_{32}O_{13}$ 588.56

[33419-42-0]

Etoposide is 4'-Demethylepipodophyllotoxin 9-[4,6-O-(R)-ethylidene-β-D-glucopyranoside]. It contains not less than 95.0% and not more than 103.0% of $C_{29}H_{32}O_{13}$, calculated on the anhydrous basis.

Description A white or almost white crystalline powder; odorless; hygroscopic.

Sparingly soluble in acetone, slightly soluble in methanol or trichloromethane, very slightly soluble in ethanol, practically insoluble in water.

Specific optical rotation -110° to -118° , in a solution of 5 mg per ml in a mixture of trichloromethane-methanol (90:10) (Appendix IV E).

Identification (1) Dissolve a quantity of substance being examined in 1 ml of methanol, add a few drops of 10% α-naphthol in methanol and mix well, add cautiously 2 ml of sulfuric acid along the inner wall of the tube. A purplish-brown ring is developed at the interface of the two layers. (2) The retention time of the principal peak in the chromatogram of the test solution obtained under the Assay corresponds with that of the principal peak in the chromatogram of the reference solution. (3) The infrared absorption spectrum (Appendix IV C) is concordant with the reference spectrum of etoposide (Appendix XVI).

Related substances Dissolve a quantity of the substance being examined, accurately weighed, in a mixture of acetonitrile-acetate BS (pH 4.0) (30:70) to produce a test solution of 2 mg per ml. Measure accurately a quantity of the test solution and dilute with a mixture of acetonitrile-acetate BS (pH 4.0) (30:70) to produce a reference solution of 10 µg per ml. Carry out the method for high performance liquid chromatography (Appendix V D), using a column packed with phenylsilane bonded silica gel, a mixture of acetonitrile-acetate BS (pH 4.0) (dissolve 5.44 g of sodium acetate with 2000 ml of water, adjust to pH 4.0 with glacial acetic acid) (20:80) as mobile phase A, and the mixture of acetonitrile-acetate BS (pH 4.0) (40:60) as mobile phase B, and performing the gradient elution program as the following table. The flow rate is 1.5 ml per minute. Detection wavelength is at 254 nm. Inject 20 µl of the reference solution into the column. Adjust the attenuation so that the principal peak height in the chromatogram is 10%-15% full scale of the chart. Dissolve a quantity of propyl p-hydroxybenzoate with the mixture of acetonitrile-acetate BS (pH 4.0) (30:70) to produce a solution of 0.2 mg per ml, measure 1 ml and 1 ml of the test solution into a 200 ml volumetric flask, dilute with the mixture of acetonitrile-

acetate BS (pH 4.0) (30:70) to volume, mix well. Inject 20 μ l of the resulting solution into the column. The number of the theoretical plates of the column is not less than 3000, calculated with reference to the peak of etoposide, and the resolution factor between the peak of etoposide and propyl *p*-hydroxybenzoate is not less than 1.1. Inject separately 20 μ l each of the test solution and the reference solution into the column, record the chromatogram for 40 minutes. Disregard any peak due to the solvent and the gradient elution, the sum of the areas of all peaks other than the principal peak is not greater than 4 times of the area of principal peak in the chromatogram obtained with the reference solution.

Time (min)	Mobile Phase A	Mobile Phase B
0	100%	0%
15	100%	0%
30	40%	60%
40	40%	60%
42	0%	100%
45	0%	100%
47	100%	0%
50	100%	0%

Water Not more than 6.0% (Appendix VIII M, method 1 A).

Residue on ignition Not more than 0.1% (Appendix VIII N), using 1.0 g.

Heavy metals Carry out the limit test for heavy metals (Appendix VIII H, method 2), using the residue obtained in the test for Residue on ignition; not more than 0.002%.

Assay Carry out the method for high performance liquid chromatography (Appendix V D), using a column packed with phenylsilane bonded silica gel and a mixture of acetonitrile-acetate buffer (pH 4.0) (30:70) as the mobile phase. Detection wavelength is 254 nm, and the number of theoretical plates of the column is not less than 3000, calculated with reference to the peak of etoposide.

Procedure Dissolve a quantity of the substance being examined, accurately weighed, in the mobile phase to produce a solution of 0.2 ml per ml as test solution. Inject 20 μ l of the test solution into the column, record the peak area correspondingly obtained in the chromatogram. Repeat the operation, using the etoposide CRS instead of the substance being examined as reference solution. Calculate the content of $C_{29}H_{32}O_{13}$ with respect to the peak area obtained in the chromatogram by the external standard method.

Category Antineoplastic agent.

Storage Preserved in tightly closed containers, stored in a dry place and protected from light.

Preparation Etoposide Injection

Etoposide Injection

Etoposide Injection is a sterile solution of etoposide in a mixture of polyethylene glycol 400 and anhydrous ethanol. It contains not less than 90.0% and not more than 110.0% of the labelled amount of etoposide ($C_{29}H_{32}O_{13}$).

Description A clear, colourless to pale yellow liquid.

Identification (1) Transfer about 2 ml to a test tube, add a few drops of 10% α -naphthol in methanol, mix well, add cautiously 2 ml of sulfuric acid along the inner wall of the test tube. A purplish-brown ring is developed at the interface of two layers.

(2) The retention time of the principal peak in the chromatogram of the test preparation obtained under the Assay corresponds with that of the principal peak in the chromatogram of the reference preparation.

pH value To 5 ml, add 45 ml of water, mix well, pH 3.0-4.0 (Appendix VI H).

Colour The solution is not more intense than that of the reference solution Y_3 (Appendix IX A, method 1).

Related substances Measure accurately 1 ml into a 10 ml volumetric flask, dilute with acetonitrile-acetate BS (pH 4.0) (30:70) to volume, mix well as test solution. Carry out the method as described under Etoposide for the Related substances. Disregard any peak caused by the solvent, the gradient elution, and the ingredients such as citric acid, benzyl alcohol and benzaldehyde, the sum of areas of all peaks other than the principal peak in the chromatogram obtained with the test solution is not greater than 6 times of the area of the principal peak in the chromatogram obtained with the reference solution.

Bacterial endotoxin Carry out the test for bacterial endotoxin (Appendix XI E); less than 2 EU per mg of etoposide.

Other requirements Complies with the general requirements for injections (Appendix I B).

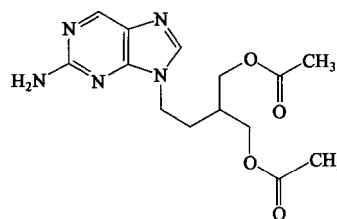
Assay Measure accurately 5 ml into a 100 ml volumetric flask, dilute with mobile phase to volume, mix well. Measure accurately 10 ml of the resulting solution into a 50 ml volumetric flask, dilute with mobile phase to volume, mix well as test solution. Carry out the method as described under Etoposide for the Assay, calculate the content of $C_{29}H_{32}O_{13}$.

Category As described under Etoposide.

Strength (1) 2 ml:40 mg (2) 5 ml:100 mg

Storage Preserved in well closed containers, protected from light.

Famciclovir



$C_{14}H_{19}N_5O_4$ 321.34

Famciclovir is 2-[2-(2-Amino-9H-purin-9-yl)ethyl]-1,3-propanediol diacetate (ester). It contains not less than 98.5% of $C_{14}H_{19}N_5O_4$, calculated on the dried basis.

Description A white or almost white crystalline powder; odorless; taste, bitter.

Freely soluble in water, methanol, ethanol or chloroform; sparingly soluble in ethyl acetate; practically insoluble in ether.

Melting point 102-104°C (Appendix VI C).

Specific absorbance Measure the absorbance of a solution of 20 µg per ml in water at 305 nm (Appendix IV A), the value of A (1%, 1 cm) is 205-220.

Identification (1) The light absorption of a solution of 10 µg per ml in water exhibits maxima at 221 nm, 243 nm and 305 nm (Appendix IV A).

(2) The retention time of principal peaks of the substance being examined in the chromatogram obtained in the Assay is identical with that of famciclovir CRS in the chromatogram of the reference solution.

(3) The infrared absorption spectrum (Appendix IV C) is concordant with the reference spectrum of famciclovir (Appendix XVI).

Acidity or alkalinity Dissolve 0.10 g in 10 ml of water, pH 6.0-7.5 (Appendix VI H).

Related substances Carry out the method as described under Assay except that detection wavelength is 221 nm. Dissolve a quantity of the substance being examined, accurately weighed, in mobile phase to produce a solution of 0.1 mg per ml as the test solution. Transfer 1 ml of test solution, accurately measured, to a 100 ml volumetric flask, dilute with mobile phase to volume to produce a reference solution. Inject 20 µl of reference solution into the column, adjust the attenuation so that the height of the principle peak in the chromatogram is 20%-25% of the full scale of the chart; inject separately 20 µl each of the test solution and the reference solution into the column, and record the chromatogram for 2.5 times of the retention time of the principal peak. Each impurity peak area in the chromatogram obtained with the test solution is not great than 1/2 of area of the principal peak in the chromatogram obtained with the reference solution, and the sum of the areas of all the peaks other than the principal peak in the chromatogram obtained with the test solution is not greater than area of the principal peak in the chromatogram obtained with the reference solution.

Residual solvents Carry out the method for determination of Residual solvents (Appendix VIII P, method 1), using a capillary column packed with 5% phenyl-methylsiloxane, maintain the column temperature at 50°C, injection port temperature at 200°C and detector temperature at 250°C, and using a flame ionization detector. To 0.25 g, accurately weighed, add accurately 5 ml of water, in a headspace sample vial. Dissolve a quantity of dichloromethane, methanol and ethyl acetate, accurately weighed, in water to produce a reference solution. Calculate the content of methanol, ethyl acetate and dichloromethane respectively with respect to the peak area obtained in the chromatogram by the external standard method.

Loss on drying When dried in vacuum to constant weight at 80°C, loses not more than 0.5% of its weight (Appendix VIII L).

Residue on ignition Not more than 0.1% (Appendix VIII N), using 1.0 g.

Heavy metals Carry out the limit test for heavy metals (Appendix VIII H, method 2), using the residue obtained in the test for Residue on ignition; not more than 0.002%.

Assay Carry out the method for high performance liquid chromatography (Appendix V D), using a column packed with octadecylsilane bonded silica gel and a mixture of acetonitrile-0.02 mol/L potassium dihydrogen phosphate solution (20:80) as the mobile phase. Detection wavelength is 305 nm and the number of the theoretical plates of the column is not less than 2500, calculated with reference to the peak of famciclovir.

Procedure Dissolve a quantity of the substance being examined, accurately weighed, in mobile phase to produce a solution of 50 µg per ml. Inject 20 µl into the column. Repeat the operation, using famciclovir CRS instead of the substance being examined. Calculate the content of $C_{14}H_{19}N_5O_4$, with respect to the peak area obtained in the chromatogram by the external standard method.

Category Antivirus.

Storage Preserve in tightly closed containers, stored in a dry place.

Preparation (1) Famciclovir Tablets
(2) Famciclovir Capsules

Famciclovir Capsules

Famciclovir Capsules contain not less than 90.0% and not more than 110.0% of labelled amount of famciclovir ($C_{14}H_{19}N_5O_4$).

Description The contents are white or almost white powder.

Identification (1) Dissolve a quantity of the contents of the capsules in water to produce a solution of 10 µg of famciclovir per ml and filter. The filtrate exhibits maxima at 221 nm, 243 nm and 305 nm (Appendix IV A).

(2) The retention time of principal peaks of the substance being examined in the chromatogram obtained in the Assay is identical with that of famciclovir CRS in the chromatogram of the reference solution.

Dissolution Carry out the dissolution test (Appendix X C, method 1), using 900 ml of water as the dissolution medium, adjust the rotational speed of the basket to 100 rpm. Withdraw 10 ml of the solution after exactly 30 minutes and filter. Dilute a quantity of successive filtrate with water to produce a solution of 25 µg per ml. Dissolve famciclovir CRS, accurately weighed, in water to produce a solution of 25 µg per ml. Measure the absorbance of the resulting solution at 305 nm respectively (Appendix IV A). Calculate the dissolution of $C_{14}H_{19}N_5O_4$ from each capsule, not less than 80% of the labelled amount is dissolved.

Other requirements Comply with the general requirements for capsules (Appendix I E).

Assay Dissolve an accurately weighed quantity of the mixed contents in the test for weight variation in mobile phase to produce a solution of 50 µg of famciclovir per ml, shake well and filter. Carry out the Assay described under Famciclovir using the successive filtrate as the test solution.

Category As described under Famciclovir.

Strength 0.125 g

Storage Preserve in tightly closed containers.

Famciclovir Tablets

Famciclovir Tablets contain not less than 90.0% and not more than 110.0% of the labelled amount of famciclovir ($C_{14}H_{19}N_5O_4$).

Description White to almost white tablets or film coated tablets with white to almost white core.

Identification (1) Dissolve a quantity of powdered tablets (with coating removed) in water to produce a solution of 10

μg of famciclovir per ml and filter. The filtrate exhibits maxima at 221 nm, 243 nm and 305 nm (Appendix IV A).
(2) The retention time of principal peaks of the substance being examined in the chromatogram obtained in the Assay is identical with that of famciclovir CRS in the chromatogram of the reference solution.

Dissolution Carry out the dissolution test (Appendix X C, method 1), using 900 ml of water as the dissolution medium, adjust the rotational speed of the basket to 100 rpm. Withdraw 10 ml of the solution after exactly 30 minutes and filter. Dilute a quantity of successive filtrate with water to produce a solution of 25 μg per ml. Dissolve famciclovir CRS, accurately weighed, in water to produce a solution of 25 μg per ml. Measure the absorbance of the resulting solution at 305 nm respectively (Appendix IV A). Calculate the dissolution of $\text{C}_{14}\text{H}_{19}\text{N}_5\text{O}_4$ from each tablet, not less than 80% of the labelled amount is dissolved.

Other requirements Comply with the general requirements for tablets (Appendix I A).

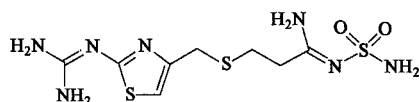
Assay Weigh accurately and powder 20 tablets. Dissolve an accurately weighed quantity of the powdered tablets in mobile phase to produce a solution of 50 μg of famciclovir per ml, mix well and filter. Carry out the Assay described under Famciclovir using the successive filtrate as the test solution.

Category As described under Famciclovir.

Strength (1) 0.125 g (2) 0.25 g

Storage Preserve in tightly closed containers.

Famotidine



$\text{C}_8\text{H}_{15}\text{N}_7\text{O}_2\text{S}_3$ 337.45

[76824-35-6]

Famotidine is [1-Amino-3-[[[2-[(diaminomethyl)amino]-4-thiazolyl]-methyl]thio]propylidene] sulfamide. It contains not less than 98.0% of $\text{C}_8\text{H}_{15}\text{N}_7\text{O}_2\text{S}_3$, calculated on the dried basis.

Description A white or almost white crystalline powder; taste, slightly bitter; gradually darkening on exposure to light.

Slightly soluble in methanol; very slightly soluble in acetone; practically insoluble in water or chloroform; freely soluble in glacial acetic acid.

Melting range 160-165°C, with decomposition (Appendix VI C).

Identification (1) The light absorption of the solution of 15 μg per ml in phosphate buffer solution (Dissolve 13.6 g of potassium dihydrogen phosphate in water to make 1000 ml and adjust the pH to 4.5 with appropriate acid or base) exhibits a maximum at 266 nm; the absorbance is 0.45-0.48 (Appendix IV A).

(2) The infrared absorption spectrum (Appendix IV C) is concordant with the reference spectrum of famotidine (Appendix XVI).

Related substances Carry out the method for thin-layer chromatography (Appendix V B), using silica GF₂₅₄ as the coating substance and a mixture of chloroform-methanol-concentrated ammonia solution (50 : 25 : 3) as the mobile phase. Apply separately to the plate 10 μl each of the

following solutions. For solution (1) dissolve 0.20 g of famotidine in 0.5 ml of dimethylformamide and dilute with methanol to 10 ml. For solution (2) measure accurately a quantity of solution (1) and dilute with methanol to produce a solution of 0.4 mg per ml. After developing and removal of the plate, dry in air and examine under ultraviolet light (254 nm). Any spot in the chromatogram other than the principal spot obtained with solution (1) is not more intense than the principal spot obtained with solution (2) (2.0%).

Methanol Carry out the method for Determination of residual solvent (Appendix VIII P, method 3). Transfer about 0.8 g of famotidine, accurately weighed, to a 10 ml volumetric flask, dilute with water to volume. Allow it to stand for 30 minutes in a water bath at about 50°C with shaking every 5 minutes, filter through a membrane with a pore size of about 0.8 μm and use the filtrate as the test solution. Dilute a quantity of methanol, accurately measured, with water to produce a solution of 10 μl (equivalent to 7.9 mg) per 100 ml as the reference solution. Using porous polymer beads of ethylvinylbenzene-divinylbenzene with a diameter of 0.18-0.25 mm as the stationary phase and maintain the column temperature at 100°C \pm 10°C.

Loss on drying When dried to constant weight at 105°C, loses not more than 0.5% of its weight (Appendix VIII L).

Residue on ignition Not more than 0.1% (Appendix VIII N), using 1.0 g.

Heavy metals Carry out the limit test for heavy metals (Appendix VIII H, method 2), using the residue obtained in the test for Residue on ignition; not more than 0.001%.

Assay Dissolve about 0.12 g, accurately weighed, in 20 ml of glacial acetic acid and 5 ml of acetic anhydride, add 1 drop of crystal violet TS, titrate with perchloric acid (0.1 mol/L) VS until the colour changes to green. Perform a blank determination and make any necessary correction. Each ml of perchloric acid (0.1 mol/L) VS is equivalent to 16.87 mg of $\text{C}_8\text{H}_{15}\text{N}_7\text{O}_2\text{S}_3$.

Category Histamine H₂ receptor antagonist.

Storage Preserve in tightly closed containers and protected from light.

Preparation (1) Famotidine Capsules
(2) Famotidine Injection
(3) Famotidine Tablets

Famotidine Capsules

Famotidine Capsules contain not less than 90.0% and not more than 110.0% of the labelled amount of famotidine ($\text{C}_8\text{H}_{15}\text{N}_7\text{O}_2\text{S}_3$).

Description Hard capsule with a white or almost white crystalline powder.

Identification (1) The light absorption of the solution obtained in Dissolution exhibits a maximum at 266 nm (Appendix IV A).

(2) The retention time of the principal peak of the substance being examined in the chromatogram obtained in the Assay is identical with that of famotidine CRS.

Dissolution Carry out the dissolution test (Appendix X C, method 1), using 900 ml of phosphate buffer solution (Dissolve 13.6 g of potassium dihydrogen phosphate in water to make 1000 ml, mix well and adjust the pH to 4.5 with appropriate acid or base) as the dissolution medium, adjust

the rotational speed of the basket to 50 rpm. Withdraw 10 ml of the solution after exactly 30 minutes and filter. Dilute an accurately measured quantity of the successive filtrate with the same dissolution medium to produce a solution of 10 µg per ml as the test solution. Dissolve an accurately weighed quantity of famotidine CRS, in phosphate buffer solution (pH4.5) to produce a solution of 10 µg per ml as the reference solution. Measure the absorbance of the resulting solutions at 266 nm (Appendix IV A). Calculate the dissolution of $C_8H_{15}N_7O_2S_3$ from each capsule. Not less than 80% of the labelled amount is dissolved.

Other requirements Comply with the general requirements for capsules (Appendix I E).

Assay Carry out the method for high performance liquid chromatography (Appendix V D), using a column packed with octadecylsilane bonded silica gel and a mixture of sodium heptanesulfonate solution (dissolve 2.0 g of sodium heptanesulfonate in 900 ml of water, adjust the pH to 3.9 with glacial acetic acid and dilute with water to 1000 ml)-acetonitrile-methanol (25 : 6 : 1) as the mobile phase. Detection wavelength is 254 nm and the number of the theoretical plates of the column is not less than 1400, calculated with reference to the peak of famotidine. Weigh accurately a quantity of the mixed contents obtained from the test for Weight variation, equivalent to about 50 mg of famotidine, into 50 ml volumetric flask, shake with a quantity of methanol to dissolve famotidine, dilute with methanol to volume, mix well and filter. Transfer 5 ml of successive filtrate, accurately measured, to a 50 ml volumetric flask, dilute with mobile phase to volume, mix well, inject accurately measured 20 µl into the column, record the chromatogram. Weigh accurately a quantity of famotidine CRS, into 50 ml volumetric flask, add a quantity of methanol to dissolve famotidine, dilute with methanol to volume, mix well and filter. Transfer 5 ml of successive filtrate, accurately measured, in 50 ml volumetric flask, dilute with mobile phase to volume, mix well. Repeat the operation, calculate the content of $C_8H_{15}N_7O_2S_3$ with respect to the peak area obtained in the chromatogram by the external standard method.

Category As described under Famotidine.

Strength 20 mg

Storage Preserve in tightly closed containers and protected from light.

Famotidine Injection

Famotidine Injection is a sterile solution of Famotidine in Water for Injection. It contains not less than 90.0% and not more than 110.0% of the labelled amount of famotidine ($C_8H_{15}N_7O_2S_3$).

Description A clear, colourless to pale yellow liquid.

Identification The retention time of the principal peak of the substance being examined in the chromatogram obtained in the Assay is identical with that of famotidine CRS.

Colour of solution Any colour produced is not more intense than that of reference solution Y₃ (Appendix IX A, method 1).

pH value 4.5-6.0 (Appendix VI H).

Other requirements Complies with the general requirements for Injections (Appendix I B).

Assay Carry out the method for high performance liquid chromatography (Appendix V D), using a column packed

with octadecylsilane bonded silica gel and a mixture of sodium heptanesulfonate solution (dissolve 2.0 g of sodium heptanesulfonate in 900 ml of water, adjust the pH to 3.9 with glacial acetic acid and dilute with water to 1000 ml) acetonitrile-methanol (25 : 6 : 1) as the mobile phase. Detection wavelength is 254 nm and the number of the theoretical plates of the column is not less than 1400, calculated with reference to the peak of famotidine. Transfer 2 ml of the injection, accurately measured, to a 50 ml volumetric flask, add 5 ml of methanol, dilute with mobile phase to volume, mix well. Measure accurately 5 ml to 20 ml volumetric flask, dilute with mobile phase to volume, mix well, inject accurately measured 20 ml into the column. Weigh accurately 50 mg of famotidine CRS in a 50 ml volumetric flask, add a quantity of methanol to dissolve famotidine and dilute to volume with methanol. Mix well, measure accurately 5 ml to a 50 ml volumetric flask, dilute to volume with mobile phase, mix well. Repeat the operation, calculate the content of $C_8H_{15}N_7O_2S_3$ with respect to the peak area obtained in the chromatogram by the external standard method.

Category As described under Famotidine.

Strength 2 ml : 20 mg.

Storage Preserve in well closed containers and protected from light.

Famotidine Tablets

Famotidine Tablets contain not less than 90.0% and not more than 110.0% of the labelled amount of famotidine ($C_8H_{15}N_7O_2S_3$).

Description White tablets, sugar coated tablets or film coated tablets with white or almost white core.

Identification (1) The light absorption of the solution obtained in Content uniformity exhibits a maximum at 266 nm (Appendix IV A).

(2) The retention time of the principal peak of the substance being examined in the chromatogram obtained in the Assay is identical with that of famotidine CRS.

Content uniformity Comply with the requirements for content uniformity (Appendix X E). To 1 tablet (for strength 10 mg) in a 100 ml volumetric flask add 40 ml of phosphate buffer solution (Dissolve 13.6 g of potassium dihydrogen phosphate in water to make 1000 ml, mix well and adjust the pH to 4.5 with appropriate acid or base) and shake to dissolve famotidine. Dilute with phosphate buffer solution (pH4.5) to volume, mix well and filter. Discard the initial filtrate. Dilute an accurately measured quantity of the successive filtrate with phosphate buffer solution (pH4.5) to produce a solution of 10 µg per ml as the test solution. Measure the absorbance of the resulting solution at 266 nm (Appendix IV A). Dissolve an accurately weighed quantity of famotidine CRS in phosphate buffer solution (pH4.5) to produce a solution of 10 µg per ml as the reference solution. Repeat the operation, Calculate the content of $C_8H_{15}N_7O_2S_3$.

Dissolution Carry out the dissolution test (Appendix X C, method 1), using 900 ml of potassium dihydrogen phosphate buffer solution (pH4.5) as the dissolution medium, adjust the rotational speed of the basket to 100 rpm. Withdraw 10 ml of the solution after exactly 30 minutes and filter. Dilute an accurately measured quantity of the successive filtrate with the same dissolution medium to produce a solution of 10 µg per ml as the test solution. Carry out the procedure

described under Content uniformity beginning at the words "Measure the absorbances of..." Calculate the dissolution of $C_{18}H_{19}Cl_2NO_4$ from each tablet. Not less than 80% of the labelled amount is dissolved.

Other requirements Comply with the general requirements for tablets (Appendix I A).

Assay Carry out the method for high performance liquid chromatography (Appendix V D), using a column packed with octadecylsilane bonded silica gel and a mixture of sodium heptanesulfonate solution (dissolve 2.0 g of sodium heptanesulfonate in 900 ml of water, adjust the pH to 3.9 with glacial acetic acid and dilute with water to 1000 ml)-acetonitrile-methanol (25 : 6 : 1) as the mobile phase. Detection wavelength is 254 nm and the number of the theoretical plates of the column is not less than 1400, calculated with reference to the peak of famotidine.

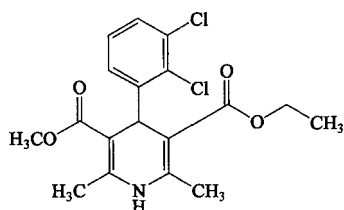
Procedure Weigh accurately and powder 20 tablets. To an accurately weighed quantity of the powdered tablets equivalent to about 50 mg of famotidine in a 50 ml volumetric flask add a quantity of methanol, shake to dissolve famotidine, dilute with methanol to volume, mix well and filter. Transfer 5 ml of successive filtrate, accurately measured, to a 50 ml volumetric flask, dilute with mobile phase to volume, mix well as the test solution. Inject accurately measured 20 μ l into the column, record the chromatogram. Weigh accurately 50 mg of famotidine CRS, in a 50 ml volumetric flask, add a quantity of methanol to dissolve famotidine and dilute to volume with methanol. Mix well, measure accurately 5 ml to a 50 ml volumetric flask, dilute to volume with mobile phase, mix well. Repeat the operation. Calculate the content of $C_{18}H_{19}Cl_2NO_4$ with respect to the peak area obtained in the chromatogram by the external standard method.

Category As described under Famotidine.

Strength (1) 10 mg (2) 20 mg

Storage Preserve in tightly closed containers and protected from light.

Felodipine



$C_{18}H_{19}Cl_2NO_4$ 384.25

Felodipine is 4-(2,3-dichlorophenyl)-1,4-dihydro-2,6-dimethyl-3,5-pyridinedicarboxylic ethyl methyl ester. It contains not less than 98.5% of $C_{18}H_{19}Cl_2NO_4$, calculated on the dried basis.

Description A white to slight yellow crystals or a crystalline powder; odourless; tasteless. Unstable on exposure to light.

Freely soluble in acetone, methanol or ethanol; practically insoluble in water.

Melting range 141-145°C (Appendix VI C).

Identification (1) Dissolve 20 mg in 1 ml of hydrochloric acid. Add 1 ml of hydroxylamine hydrochloride TS, mix well. Make the solution alkaline by adding dropwise 20%

sodium hydroxide solution. Boil for about 30 minutes on a water bath, and cool. Acidify with 1 mol/L hydrochloric acid solution. Add a few drops of ferric chloride TS, a reddish-brown colour is produced.

(2) The light absorption of a solution of 2 μ g per ml in ethanol exhibits two maxima at 238 nm and 361 nm (Appendix VI A).

(3) The infrared absorption spectrum (Appendix IV C) is concordant with the reference spectrum of felodipine (Appendix XVI).

Clarity and colour of solution Dissolve 1.0 g in 20 ml of methanol, the solution is clear and colourless; any colour produced, the absorbance of the solution at 440 nm is not more than 0.10 (Appendix IX A, method 2).

Chloride To 2.0 g add 50 ml of water, boil and cool immediately, add water to restore 50 ml. Filter, carry out the limit test for chloride (Appendix IV A) using 25 ml of the successive filtrate. Any opalescence produced is not more pronounced than that of a reference solution using 5 ml of sodium chloride standard solution (0.005%).

Related substances Dissolve a quantity of the substance being examined, accurately weighed, in the mobile phase to produce solutions of 1.0 mg per ml as test solution and 15 μ g per ml as reference solution. Carry out the method for high performance liquid chromatography (Appendix V D), using a column packed with octadecylsilane bonded silica gel and a mixture of acetonitrile-methanol-phosphate BS [mix 8.0 ml of phosphoric acid solution (6.5 \rightarrow 1000) with 50.0 ml of 15.6% sodium dihydrogen phosphate solution, dilute to 1000 ml with water] (2 : 1 : 2) as the mobile phase. Detection wavelength is 254 nm and the number of the theoretical plates of the column is not less than 1500, calculated with reference to the peak of felodipine. Inject 20 μ l of the reference solution into the column, adjust the attenuation so that the principal peak height in the chromatogram is 20% of the full scale of the chart. Inject separately 20 μ l each of the test solution and the reference solution into the column and record the chromatogram for twice the retention time of the principal peak. The sum of the areas of all peaks other than the principal peak in the chromatogram obtained with the test solution is not greater than the area of the principal peak in the chromatogram obtained with the reference solution.

Isopropyl Ether Dissolve a quantity of the substance being examined, accurately weighed, in dimethylformamide by ultrasonication to produce the test solution of 60 mg per ml. Dissolve about 0.3 g isopropyl ether, weigh accurately, in a 100 ml volumetric flask with dimethylformamide, dilute with dimethylformamide to volume and mix well. Transfer 3 ml of the solution into a 50 ml volumetric flask, accurately measured, dilute with dimethylformamide, to volume, mix well, as the reference solution. Transfer separately 15 ml each of above solutions to different headspace sample vials with a volume of 20 ml and seal. Heat the vials in water bath, maintained at 80°C for 2 hours. Withdraw separately 70 μ l each of the head space gas of the test solution and the reference solution, carry out the method for gas chromatography (Appendix V E), using a column (2 m long) packed with styrene divinylbenzene copolymer as the stationary phase, maintain the column temperature at 190°C. The peak area of isopropyl ether obtained with the test solution is not greater than that obtained with the reference solution (0.3%).

Loss on drying When dried to constant weight at 105°C, loses not more than 0.5% of its weight (Appendix VIII L).

Residue on ignition Not more than 0.1% (Appendix VIII N), using 1.0 g.

Heavy metals Carry out the limit test for heavy metals (Appendix VIII H, method 2), using the residue obtained in the test for Residue on ignition; not more than 0.001%.

Arsenic Mix 1.0 g with 1.0 g calcium hydroxide, add little water and mix. Heat gently and ignite until the incineration is complete. Dissolve the cooled residue in 8 ml of hydrochloric acid and 20 ml of water. Carry out the limit test for arsenic (Appendix VIII J, method 1); not more than 0.0002%.

Assay Dissolve about 0.3 g, accurately weighed, in 40 ml of glacial acetic acid, add 20 ml of dilute sulfuric acid TS and 2 drops of *o*-phenanthroline IS, titrate with cerium sulfate (0.1 mol/L) VS until the orange colour disappears. Perform a blank determination and make any necessary correction. Each ml of cerium sulfate (0.1 mol/L) VS is equivalent to 19.21 mg of $C_{18}H_{19}Cl_2NO_4$.

Category Calcium channel blocker.

Storage Preserve in tightly closed containers, protected from light.

Preparation Felodipine Tablets

Felodipine Tablets

Felodipine Tablets contain not less than 90% of and not more than 110.0% of the labelled amount of felodipine ($C_{18}H_{19}Cl_2NO_4$).

Description White or almost white tablets.

Identification (1) To a quantity of powdered tablets (equivalent to about 20 mg of felodipine) add 20 ml of ethanol, shake to dissolve felodipine and filter. Evaporate the filtrate to about 1 ml on a water bath, add 1 ml of hydrochloric acid, the solution complies with the test for identification (1) described under Felodipine, beginning at the words "add 1 ml of hydroxylamine hydrochloride TS...".

(2) Dilute the test solution under Related substances with the mobile phase to produce the test solution of 200 μ g per ml. Dissolve a quantity of felodipine CRS, accurately weighed, in the mobile phase to produce the reference solution of 200 μ g per ml. Carry out the method as described under Related substances. The retention time of the principal peak of the substance being examined in the chromatogram of the test solution is identical with that of felodipine CRS in the chromatogram of the reference solution.

(3) The light absorption of the solution obtained in the Assay exhibits two maxima at 238 nm and 361 nm (Appendix VI A).

Related substances Dissolve a quantity of the powdered tablets, accurately weighed, in the mobile phase to produce a solution containing felodipine of 1 mg per ml, ultrasonicate to dissolve felodipine and filter, using the successive filtrate as the test solution. Measure accurately a quantity of the test solution, dilute with the mobile phase to produce the reference solution containing felodipine of 20 μ g per ml. Carry out the method for high performance liquid chromatography (Appendix V D), using a column packed with octadecylsilane bonded silica gel and a mixture of acetonitrile-methanol-hosphate BS [mix 8.0 ml of phosphoric acid solution (6.5 → 1000) with 50.0 ml of 15.6% sodium dihydrogen phosphate solution, dilute to 1000 ml with water] (2 : 1 : 2) as the mobile phase. Detection wavelength is 254 nm and the number of the

theoretical plates of the column is not less than 1500, calculated with reference to the peak of felodipine. Inject 20 μ l of the reference solution into the column, adjust the attenuation so that the principal peak height in the chromatogram is 20% of the full scale of the chart. Inject separately 20 μ l each of the test solution and the reference solution into the column and record the chromatogram for twice the retention time of the principal peak. The sum of the areas of all peaks, other than the principal peak and the peak of auxiliary whose related retention time is about 0.3 corresponding to the principal peak, in the chromatogram obtained with the test solution is not greater than the area of the principal peak in the chromatogram obtained with the reference solution.

Content uniformity Comply with the requirements for content uniformity (Appendix X E). Triturate 1 tablet with ethanol in a mortar and transfer with ethanol in portions to a 50 ml volumetric flask, dilute with ethanol to volume, shake thoroughly and filter. Measure accurately a quantity of the successive filtrate, dilute with ethanol to produce a solution containing felodipine of 20 μ g per ml. Carry out the procedure described under Assay of Felodipine Tablets. Calculate the content of $C_{18}H_{19}Cl_2NO_4$.

Dissolution Carry out the dissolution test (Appendix X C, method 3), using 250 ml of 0.1 mol/L hydrochloric acid solution-isopropanol (3 : 2) as the dissolution medium, adjust the rotational speed of the paddle to 100 rpm. Withdraw the solution after exactly 30 minutes and filter, using the successive filtrate as the test solution. Measure the absorbance at 361 nm (Appendix IV A) in 1 cm cell (for strength 10 mg or 5 mg) or 2 cm cell (for strength 2.5 mg), calculate the dissolution of $C_{18}H_{19}Cl_2NO_4$ from each tablet, taking 182 as the value of A (1%, 1 cm). Not less than 70% of the labelled amount is dissolved.

Other requirements Comply with the general requirements for tablets (Appendix I A).

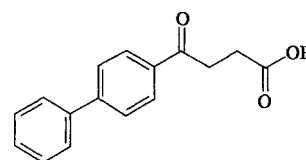
Assay Weigh accurately and powder 20 tablets. Weigh accurately a quantity of powder equivalent to about 10 mg of felodipine into a 100 ml volumetric flask, add a quantity of ethanol, shake for 15 minutes to dissolve felodipine, dilute with ethanol to volume and mix well. Filter and transfer 2 ml of the successive filtrate to a 10 ml volumetric flask, accurately measured, dilute with ethanol to volume and mix well, measure the absorbance at 361 nm (Appendix VI A), calculate the content of $C_{18}H_{19}Cl_2NO_4$, taking 182 as the value of A (1%, 1 cm).

Category As described under Felodipine.

Strength (1) 2.5 mg (2) 5 mg (3) 10 mg

Storage Preserve in tightly closed containers, protected from light.

Fenbufen



$C_{16}H_{14}O_3$ 254.28

[36330-85-5]

Fenbufen is 3-(4-diphenylcarbonyl) propionic

acid. It contains not less than 98.5% of $C_{16}H_{14}O_3$,
calcu lated on the dried basis.

Descri **ption** A white or almost white crystalline powder;
 odour less; taste, sour.
Solub le in ethanol; practically insoluble in water; freely
 solub le in hot alkaline solution.

Melti **ng point** 185-188°C (Appendix VI C).

Ident **ification** (1) To about 0.1 g add 2 ml of sulfuric acid;
 the s olution turns to orange-red colour; dilute with water,
 the c olour is disappeared and a white precipitate is produced.
 (2) To about 0.1 g add 5 ml of dehydrated ethanol, warm
 to di ssolve, cool, add dropwise of ferric trichloride TS; an
 oran; ge-yellow precipitate is produced.
 (3) The light absorption of a solution of 5 µg per ml in dehy
 drated ethanol exhibits a maximum at 281 nm; a mini
 mum at 238 nm (Appendix IV A).
 (4) The infrared absorption spectrum (Appendix IV C) is
 conc ordant with the reference spectrum of Fenbufen
 (Ap pendix XVI)

Chlo **ride** Spread 2 g of anhydrous sodium carbonate on the
 bott om and around of a crucible, place 1.0 g, upon the
 anhy drous sodium carbonate, moisten with a few quantity of
 wat er, heat to dry, then heat gently until it is thoroughly
 char red, ignite at 700-800°C until the incineration is
 com plete, allow to cool. Dissolve the residue with a
 qua ntity of water, filter, wash the crucible and the filter
 wit h water, combine the filtrate and washings to a 50 ml
 volu metric flask, dilute with water to volume, mix well,
 mea sure accurately 10 ml, dilute with water to 25 ml. Carry
 out the limit test for chlorides (Appendix VIII A). Any
 opalescence produced is not more intense than that of a
 ref erence using 6.0 ml of sodium chloride standard solution
 (0.03%).

Sul **fate** Measure accurately 10.0 ml of the remained solution
 obt ained in the test for chloride, dilute with water to 25 ml,
 car ry out the limit test for sulfates (Appendix VIII B). Any
 opa lescence produced is not more intense than that of a
 ref erence using 2.0 ml of potassium sulfate standard solution
 (0.1%).

Re **lated substances** Carry out the method for thin layer
 chr omatography (Appendix V B), using silica gel GF₂₅₄ as
 the c oating substance and a mixture of benzene-chloroform-
 glaacial acetic acid (10:10:1) as the mobile phase. Apply
 sep arately to the plate 10 µl each of two solutions of the
 su bstance being examined in dehydrate ethanol containing
 (1) 5 mg per ml, (2) 0.1 mg per ml. After developing and
 re moval of the plate, dry in air, examine under an
 ul traviolet light (254 nm). Any spot other than the
 pr incipal spot in the chromatogram, obtained with solution
 (1) is not more intense than the principal spot obtained with
 sc lution (2).

L **oss on drying** When dried to constant weight at 105°C,
 lo sses not more than 1.0% of its weight (Appendix VIII L).

R **esidue on ignition** Not more than 0.1% (Appendix VIII
 N D), use 1.0 g.

H **heavy metals** Carry out the limit test for heavy metals
 (Appendix VIII H method 2), using the residue obtained in
 the test for Residue on ignition; not more than 0.001%.

A **rsenic** Measure accurately 10.0 ml of the remained
 so lution obtained in the test for chloride, add 5 ml of
 h ydrochloric acid and 13 ml of water, carry out the limit test
 fo r arsenic (Appendix VIII J, method 1); not more
 t han 0.001%.

A **ssay** Dissolve 0.4 g, accurately weighed, in 50 ml of
 r eutral ethanol, by warming in a hot water bath, cool to

room temperature, add 2 drops of phenolphthalein IS,
 titrate with sodium hydroxide (0.1 mol/L) VS. Each ml of
 sodium hydroxide (0.1 mol/L) VS is equivalent to 25.43
 mg of $C_{16}H_{14}O_3$.

Category Analgesic, non-steroids anti-inflammatory agent.

Storage Preserve in tightly closed containers, protected
 from light.

Preparation (1) Fenbufen Capsules
 (2) Fenbufen Tablets

Fenbufen Capsules

Fenbufen Capsules contain not less than 90.0%
 and not more than 110.0% of the labelled amount
 of Fenbufen ($C_{16}H_{14}O_3$).

Identification To a quantity of the contents of capsules
 equivalent to about 0.2 g of Fenbufen add 20 ml of anhydrous
 ethanol, heat on a water bath to dissolve Fenbufen, allow to
 cool and filter. The filtrate complies with the tests (1),
 (2) and (3) for Identification described under Fenbufen
 tablets.

Dissolution Carry out the method for dissolution test
 (Appendix X C, method 1), using 900 ml of phosphate BS
 (pH 7.6) as the dissolution medium. Adjust the rotation
 speed at 100 rpm. Withdraw 10 ml of the solution after
 exactly 45 minutes, filter. Measure accurately 2 ml of the
 successive filtrate into a 50 ml volumetric flask, dilute with
 phosphate BS (pH 7.6) to volume, mix well. Measure the
 absorbance of the resulting solution at 285 nm, (Appendix
 IV A) and calculate the content of $C_{16}H_{14}O_3$, taking 868 as
 the value of A (1%, 1 cm). The dissolution for each
 capsules is not less than 70% of the labelled amount.

Other requirements Comply with the general requirements
 for capsules (Appendix I E).

Assay Dissolve a quantity, weighed accurately, of the
 mixed contents obtained in test for weight variation for
 contents equivalent to about 0.4 g of fenbufen in 50 ml of
 neutral ethanol by warming in a hot water bath. Allow to
 cool, add 2 drops of phenolphthalein IS, titrate with sodium
 hydroxide (0.1 ml/L) VS. Each ml of sodium hydroxide
 (0.1 mol/L) VS is equivalent to 25.43 mg of $C_{16}H_{14}O_3$.

Category As described under Fenbufen.

Strength 0.15 g.

Storage Preserve in tightly closed containers, protected
 from light.

Fenbufen Tablets

Fenbufen Tablets contain not less than 90.0% and
 not more than 110.0% of the labelled amount of
 Fenbufen ($C_{16}H_{14}O_3$).

Description White or almost white tablets.

Identification To a quantity of the powdered tablets
 equivalent to about 0.2 g of Fenbufen add 20 ml of anhydrous
 ethanol, heat on a water bath to dissolve Fenbufen, allow to
 cool and filter. The filtrate complies with the tests as
 follows.

(1) To 5 ml of the filtrate add 5 drops of Ferric trichloride
 TS, an orange precipitate is produced.

(2) Evaporate 10 ml of the filtrate to dryness on a water bath, add 1 ml of sulfuric acid to the residue, the solution turns gradually to orange-red colour; the colour is disappeared and a white precipitate is produced on diluting with 10 ml of water.

(3) Dilute the filtrate with anhydrous ethanol to produce a solution of 5 µg per 1 ml. The light absorption of the solution exhibits a maximum at 281 nm and a minimum at 238 nm (Appendix IV A).

Dissolution Carry out the method for dissolution test (Appendix X C, method 2) using 900 ml of phosphate BS (pH 7.6) as the dissolution medium. Adjust the rotational speed to 100 rpm. Withdraw 10 ml of solution after exactly 45 minutes and filter. Discard the initial filtrate, measure accurately 2 ml of the successive filtrate to a 50 ml (for 0.15 g strength) or 100 ml (for 0.3 g strength) volumetric flask, dilute with phosphate BS (pH 7.6) to volume and mix well. Measure the absorbance at 285 nm. (Appendix IV A) Calculate the dissolution of $C_{16}H_{14}O_3$ of each tablet, taking 868 as the value of A (1%, 1 cm). Not less than 65% of the labelled amount is dissolved.

Other requirements Comply with the general requirements for tablets. (Appendix I A).

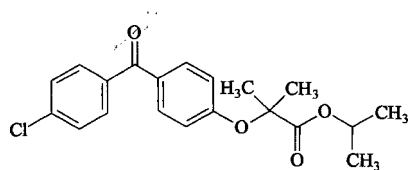
Assay Weigh accurately and powder 20 tablets. Dissolve an accurately weighed quantity of powdered tablets equivalent to about 0.4 g of Fenbufen, with 50 ml of neutral ethanol by heating on a water bath. Allow to cool, add 2 drops of phenolphthalein IS, titrate with sodium hydroxide (0.1 mol/L) VS. Each ml of sodium hydroxide (0.1 mol/L) VS is equivalent to 25.43 mg of $C_{16}H_{14}O_3$.

Category As described under Fenbufen.

Strength (1) 0.15 g (2) 0.3 g

Storage Preserve in tightly closed containers, protected from light.

Fenofibrate



$C_{20}H_{21}ClO_4$ 360.84

[49562-28-9]

Fenofibrate is Isopropyl 2- [p- (p-chlorobenzoyl) phenoxy] -2-methylpropanoate. It contains not less than 98.5% of $C_{20}H_{21}ClO_4$, calculated on the dried basis.

Description A white or almost white crystalline powder; odourless; tasteless. Very soluble in chloroform; freely soluble in acetone or ether; sparingly soluble in ethanol; practically insoluble in water.

Melting range 78-82°C (Appendix VI C).

Identification (1) The light absorption of a 10 µg per ml solution in dehydrated ethanol exhibits a maximum at 286 nm (Appendix IV A).

(2) The infrared absorption spectrum (Appendix IV C) is concordant with the reference spectrum of fenofibrate (Appendix XVI).

(3) Weigh about 20 mg, carry out the method for oxygen

flask combustion (Appendix VI C), using 10 ml of 0.4% sodium hydroxide solution as the absorbing liquid. When the process is completed, acidify the solution with dilute sulfuric acid and cool. The solution yields the reactions characteristic of chlorides (Appendix III).

Clarity and colour of ethanol solution A solution of 1.0 g in 25 ml of ethanol (heat gently if necessary) is clear and colourless; any colour produced is not more intense than that of reference solution Y_1 (Appendix IX A, method 1).

Sulfate To 1.0 g add 50 ml of water, shake and filter. Carry out the limit test for sulfate (Appendix VIII B), using 25 ml of the filtrate. Any opalescence produced is not more intense than that of a reference using 2.0 ml of potassium sulfate standard solution (0.040%).

Related substances Carry out the method for thin-layer chromatography (Appendix V B), using silica gel GF₂₅₄ as the coating substance and a mixture of benzene-ethylacetate-glacial acetic acid (90:10:1) as the mobile phase. Apply separately to the plate 10 µl each of two solutions in a mixture of chloroform-ethanol (9:1) containing (1) 50 mg per ml, (2) 0.15 mg per ml of the substance being examined. After developing and removal of the plate, dry in air and examine under ultraviolet light (254 nm). Any spot other than the principal spot obtained with solution (1) is not more intense than the principal spot obtained with solution (2).

Loss on drying When dried in vacuum to constant weight at 50°C, loses not more than 0.5% of its weight (Appendix VIII L).

Residue on ignition Not more than 0.1% (Appendix VIII N), use 1.0 g.

Heavy metals Carry out the limit test for heavy metals (Appendix VIII H, method 2), using the residue obtained in test for Residue on ignition; not more than 0.001%.

Assay To about 2 g, accurately weighed, in 10 ml of neutralized ethanol by gentle heating. Add a few drops of phenolphthalein IS and titrate with alcoholic potassium hydroxide (0.1 mol/L) VS until a pink colour is produced. Add 25 ml of alcoholic potassium hydroxide (0.5 mol/L) VS, accurately measured, heat under reflux for 30 minutes. Rinse the condenser with 10 ml of water and allow the solution to cool, add 1 ml of phenolphthalein IS, titrate with hydrochloric acid (0.5 mol/L) VS until the red colour disappears. Perform a blank determination and make any necessary correction. Each ml of alcoholic potassium hydroxide (0.5 mol/L) VS is equivalent to 180.42 mg of $C_{20}H_{21}ClO_4$.

Category Antihyperlipoproteinemic.

Storage Preserve in tightly closed containers, protected from light.

Preparation (1) Fenofibrate Capsules
(2) Fenofibrate Tablets

Fenofibrate Capsules

Fenofibrate Capsules contain not less than 90.0% and not more than 110.0% of the labelled amount of fenofibrate ($C_{20}H_{21}ClO_4$).

Identification (1) The light absorption of the solution obtained in the Assay (Appendix IV A), exhibits a maximum at 286 nm.

(2) Shake a quantity of the contents equivalent to about 0.1

g of fenofibrate with 10 ml of ether, filter, evaporate the filtrate to dryness. The residue complies with test (3) for Identification described under Fenofibrate.

Other requirements Comply with the general requirements for Ca_2^+ . Appendix I E.

Assay Mix the contents obtained in the test for Weight variation, transfer accurately a quantity equivalent to about 50 mg of fenofibrate to a 100 ml volumetric flask. Carry out the Assay described under Fenofibrate Tablets, beginning at the words "add about 75 ml of dehydrated ethanol".

Category As described under Fenofibrate.

Strength 0.1 g

Storage Preserve in tightly closed containers, protected from light.

Fenofibrate Tablets

Fenofibrate Tablets contain not less than 93.0% and not more than 107.0% of the labelled amount of fenofibrate ($\text{C}_{20}\text{H}_{21}\text{ClO}_4$).

Description White or almost white tablets.

Identification (1) The light absorption of the solution obtained in Assay exhibits a maximum at 286 nm (Appendix IV A).

(2) Shake a quantity of powdered tablets equivalent to about 0.1 g of fenofibrate with 10 ml of ether, filter, evaporate the filtrate to dryness. The residue complies with test (3) for Identification described under Fenofibrate.

Related substances Shake a quantity of powdered tablets with a mixture of chloroform-ethanol (9:1) to dissolve the fenofibrate and to produce a solution of 20 mg per ml and filter, using the filtrate as the test solution. Measure accurately a quantity of filtrate, dilute with same solvent to produce a solution of 0.2 mg per ml as a reference solution. Complies with the Related substances described under Fenofibrate, beginning at the words proceeds "carry out the method for thin-layer chromatography".

Other requirements Comply with the general requirements for tablets (Appendix I A).

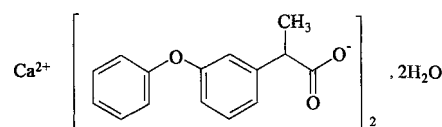
Assay Weigh accurately and powder 20 tablets. To an accurately weighed quantity of the powder equivalent to about 50 mg of fenofibrate into a 100 ml volumetric flask, add 75 ml of dehydrated ethanol, shake thoroughly, dilute with dehydrated ethanol to volume, mix well and filter. Transfer accurately 2 ml of the successive filtrate to another 100 ml volumetric flask, dilute with dehydrated ethanol to volume and mix well. Measure the absorbance of the solution at 286 nm (Appendix IV A), calculate the content of $\text{C}_{20}\text{H}_{21}\text{ClO}_4$, taking 484 as the value of A (1%, 1 cm).

Category As described under Fenofibrate.

Strength 0.1 g

Storage Preserve in tightly closed containers, protected from light.

Fenoprofen Calcium



$\text{C}_{30}\text{H}_{26}\text{CaO}_6 \cdot \text{H}_2\text{O}$ 558.64

[53746-45-5]

Fenoprofen Calcium is α -methyl-3-phenoxy-benzene-acetic acid, calcium salt (2:1) dihydrate. It contains not less than 97.5% of $\text{C}_{30}\text{H}_{26}\text{CaO}_6$, calculated on the anhydrous basis.

Description A white crystalline powder; odourless; tasteless. Soluble in ethanol; slightly soluble in methanol; very slightly soluble in water; practically insoluble in chloroform.

Identification (1) Warm to dissolve about 20 mg with 1 ml of acetic acid, add 1 drop of ammonium oxalate TS, a white precipitate is produced, which is soluble in hydrochloric acid.

(2) Dissolve about 0.1 g in 5 ml glacial acetic acid, add methanol to produce 100 ml, mix well. Dilute a quantity of the solution with methanol to produce a solution of 50 μg per ml in methanol. The light absorption of the solution exhibits maxima at 272 nm and 278 nm, a shoulder peak at 266 nm (Appendix IV A).

(3) The infra-red absorption spectrum (Appendix IV C) is concordant with the reference spectrum of fenoprofen calcium (Appendix XVI).

Related substances Carry out the method for thin layer chromatography (Appendix V B), using silica gel GF₂₅₄ as the coating substance and toluene-glacial acetic (10:1) as the mobile phase. Apply separately to the plate 20 μl each of two solutions in chloroform-methanol (1:1) containing (1) 50 mg per ml, (2) 0.25 mg per ml of the substance being examined. After developing and removal of the plate, dry in air, examine under ultraviolet light (254 nm). Any spot other than the principal spot in the chromatogram obtained with solution (1), is not more intense than the principal spot obtained with solution (2).

Water 5.0%-8.0% (Appendix VIII M, method I A).

Calcium Warm to dissolve about 0.25 g, accurately weighed, with 15 ml of ethanol and 10 ml of water, add 15 ml of sodium hydroxide TS and about 0.1 g of calcon indicator, mix well, titrate with disodium edetate (0.05 mol/L) VS until the colour turns from purplish-red to pure blue. Each ml of disodium edetate (0.05 mol/L) VS is equivalent to 2.004 mg of Ca. It contains not less than 7.3%, and not more than 8.0% of Ca, calculated on the anhydrous basis.

Assay Dissolve about 0.25 g, accurately weighed, in 20 ml of glacial acetic acid and 2 ml of acetic anhydride, add 1 drop of crystal violet IS, titrate with perchloric acid (0.1 mol/L) VS until the colour turns to bluish-green. Perform a blank determination and make any necessary correction. Each ml of perchloric acid (0.1 mol/L) VS is equivalent to 26.13 mg of $\text{C}_{30}\text{H}_{26}\text{CaO}_6$.

Category Antipyretic and analgesic, non-steroids anti-inflammatory agent.

Storage Preserve in tightly closed containers

Preparation Fenoprofen Calcium Tablets

Fenoprofen Calcium Tablets

Fenoprofen Calcium Tablets contain not less than 95.0% and not more than 105.0% of the labelled amount of Fenoprofen Calcium ($C_{15}H_{14}O_3$).

Description White tablets.

Identification (1) Dissolve a quantity of the powdered tablets equivalent to about 0.1 g of Fenoprofen Calcium in 5 ml of acetic acid, shake and filter; the filtrate complies with the Tests for identification (1) described under Fenoprofen Calcium.

(2) The light absorption of a solution obtained in the Assay exhibits maxima at 272 nm and 278 nm with a shoulder peak at 266 nm. (Appendix IV A).

Other requirements Comply with the general requirements for tablets. (Appendix I A).

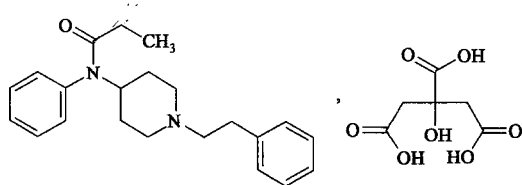
Assay Weigh and powder 20 tablets. To a quantity of the powdered tablets equivalent to about 0.2 g of Fenoprofen calcium in a 200 ml volumetric flask add 5 ml of glacial acetic acid, shake for 1 minute then add 100 ml of methanol and shake for 5 minutes, dilute with methanol to volume, mix well and filter. Measure accurately 5 ml of the successive filtrate to a 100 ml volumetric flask, dilute with methanol to volume and mix well. Measure the absorbance of the resulting solution at 272 nm (Appendix IV A), taking 80.7 as the value of A (1%, 1 cm), calculate the content of $C_{15}H_{14}O_3$.

Category As described under Fenoprofen Calcium.

Strength 0.3 g (calculated on the basis of $C_{15}H_{14}O_3$)

Storage Preserve in tightly closed containers.

Fentanyl Citrate



$C_{22}H_{28}N_2O \cdot C_6H_8O_7$ 528.60 [990-73-8]

Fentanyl Citrate is *N*-(1-phenethyl-4-piperidyl)-propionanilide citrate (1:1). It contains not less than 98.0% of $C_{22}H_{28}N_2O \cdot C_6H_8O_7$, calculated on the dried basis.

Description A white crystalline powder; taste, bitter; an aqueous solution yields acid reaction. Freely soluble in hot isopropanol; soluble in methanol; sparingly soluble in water or chloroform.

Melting point 148-151°C (Appendix VI C).

Identification (1) Dissolve about 0.1 g in 5 ml of water, add 10 ml of trinitrophenol TS with stirring, a precipitate is produced. Filter and wash the precipitate with small portions of water and dry at 105°C. The melting point of the residue is 173-176°C (Appendix VI C).

(2) The infra-red absorption spectrum (Appendix IV C) is concordant with the reference spectrum of fentanyl citrate

(Appendix XVI).

(3) The aqueous solution yields the reactions characteristic of citrates (Appendix III).

Loss on drying When dried to constant weight at 105°C, loses not more than 0.5% of its weight (Appendix VIII L).

Residue on ignition Not more than 0.2% (Appendix VIII N).

Heavy metals Mix 1.0 g with 2 ml of sodium acetate BS (pH 3.5) and add water to produce 25 ml. Carry out the limit test for heavy metals (Appendix VIII H, method 1); not more than 0.002%.

Assay Dissolve about 0.5 g, accurately weighed, in 15 ml of glacial acetic acid, add 1 drop of crystal violet IS and titrate with perchloric acid (0.1 mol/L) VS until the solution becomes green. Perform a blank determination and make any necessary correction. Each ml of perchloric acid (0.1 mol/L) VS is equivalent to 52.86 mg of $C_{22}H_{28}N_2O \cdot C_6H_8O_7$.

Category Analgesic.

Storage Preserve in tightly closed containers.

Preparation Fentanyl Citrate Injection

Fentanyl Citrate Injection

Fentanyl Citrate Injection is a sterile solution of fentanyl citrate in Water for Injection. It contains not less than 90.0% and not more than 110.0% of the labelled amount of fentanyl ($C_{22}H_{28}N_2O$).

Description A clear, colourless liquid.

Identification (1) The light absorption of the injection exhibits a maximum at 256 nm (Appendix IV A).

(2) Evaporate 20 ml of the injection to about 10 ml, it yields the reaction characteristic of citrates (Appendix III).

pH value 4.0-6.0 (Appendix VI H).

Other requirements Complies with the general requirements for injections (Appendix I B).

Assay Carry out the method for high performance liquid chromatography (Appendix V D), using a column packed with octadecylsilane bonded with silica gel and a mixture of (_____) 400 _____ r. 200 _____ glacial acetic acid 0.6 ml, mix well)-0.2% of anhydrous sodium sulfate in ammonium acetate solution (1→100) (7:3) and adjust to pH 6.5 ± 0.1 with glacial acetic acid as the mobile phase. Detection wavelength is 230 nm and the number of theoretical plates of the column is not less than 2400, calculated with reference to the peak area of fentanyl citrate.

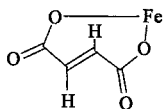
Procedure Dissolve a quantity of the substance being examined, accurately weighed, in water to produce a solution of 50 µg per ml, inject 20 µl, accurately measured, into the column and record the chromatogram. Repeat the operation, using the fentanyl citrate CRS instead of the substance being examined, calculate the content of $C_{22}H_{28}N_2O$ with respect to the peak area by the external standard method.

Category As described under Fentanyl Citrate.

Strength 2 ml : 0.1 mg

Storage Preserve in well closed containers, protected from light.

Ferrous Fumarate



$C_4H_2FeO_4$ 169.90

[141-01-5]

Ferrous Fumarate is iron (2+)(E)-2-fumarate. It contains not less than 93.0% of $C_4H_2FeO_4$, calculated on the dried basis.

Description An orange-red or reddish-brown powder; odourless.

Practically insoluble in water or ethanol.

Identification (1) To 50 mg add 100 mg of resorcinol in an evaporating dish, mix well, add 3-5 drops of sulfuric acid and heat gently. Until a deep red semi-solid mass is produced, cool, dilute with 25 ml of water and filter. To 1 ml of filtrate add 10 ml of water, and mix well. An orange-red solution with green fluorescence is produced, which turns to red with fluorescence after made alkaline with a few drops of sodium hydroxide TS.

(2) Heat about 2 g with 100 ml of hydrochloric acid solution (1→8) to dissolve, cool and filter, wash the precipitate three times with 5 ml each of hydrochloric acid solution (1→100), then wash the precipitate with water until the filtrate shows no yellow colour and dry the precipitate at 105°C. Dissolve 0.1 g of the precipitate in 2 ml of sodium carbonate TS, add a few drops of potassium permanganate TS, a dark brown colour is produced.

(3) Dissolve a quantity of the above precipitate in water to produce a solution of about 5 µg per ml. The light absorption of the solution exhibits a maximum at 206 nm (Appendix IV A).

(4) The infrared absorption spectrum (Appendix IV C) is concordant with the reference spectrum of ferrous fumarate (Appendix XVI).

(5) The filtrate obtained under test (2) yields the reactions characteristic of ferrous salt (Appendix III).

Sulfate To 0.30 g add 4 ml of dilute hydrochloric acid, heat to dissolve, add 25 ml of water immediately, heat to boil, cool, filter, divide the filtrate into two equal portions. To one portion of the filtrate add 5 ml of 25% barium chloride solution, mix, allow to stand for 10 minutes, filter repeatedly until the filtrate is clear. Transfer it to a 50 ml Nessler cylinder, dilute to 42 ml with water, add 3.0 ml of potassium sulfate standard solution and sufficient water to produce 50 ml, mix well and allow to stand for 10 minutes, use it as the reference solution. Transfer the other portion of the filtrate to a 50 ml Nessler cylinder, dilute to 42 ml with water, add 5 ml of 25% barium chloride solution and sufficient water to produce 50 ml, mix well and allow to stand for 10 minutes. Any opalescence produced is not more intense than that of the reference solution (0.2%).

Loss on drying When dried to constant weight at 120°C, loses not more than 1.5% of its weight (Appendix VIII L).

Ferric iron Dissolve 2 g, accurately weighed, in a mixture of 25 ml of water and 4 ml of hydrochloric acid in a 250 ml iodine flask with the aid of heat. Cool to room temperature rapidly, add 3 g of potassium iodide, insert the stopper, mix well and allow to stand in the dark for 5 minutes. Add 75 ml of water, titrate immediately with sodium thiosulfate (0.1 mol/L) VS, add 2 ml of starch IS towards the end of

titration, continue to titrate until the blue colour disappears. Perform a blank determination and make any necessary correction. Each ml of sodium thiosulfate (0.1 mol/L) VS is equivalent to 5.585 mg of ferric iron. It contains not more than 2% of ferric iron.

Lead Mix 0.40 g with 3 ml of nitric acid and 5 ml of perchloric acid in a 50 ml beaker. Boil gently to dryness, cool and add 15 ml of hydrochloric acid solution (1→2). Boil gently for 1 minute, cool and transfer the solution to a separator. Extract with three portions, each of 20 ml, of ether, discard the ether extracts (the solution is to be extracted further if it is still yellow in colour). Heat the acid solution on a water bath to remove the remaining ether, cool, add ammonia TS to make the solution alkaline, add 1 ml of potassium cyanide TS and sufficient water to produce 50 ml. Add 5 drops of sodium sulfide TS and mix well. Any colour produced, is not more intense than that of a reference prepared in a similar manner using 2.0 ml of standard lead solution (0.005%).

Arsenic Mix 0.50 g with 0.5 g anhydrous sodium carbonate, add 4 ml of bromine TS and mix. Evaporate to dryness on a water bath, then ignite at 500-600°C for 2 hours. Dissolve the cooled residue in 10 ml of bromine-hydrochloric acid solution (to 1 ml of potassium bromide-bromine TS add hydrochloric acid to produce 100 ml) and 15 ml of water. Transfer the solution to a distilling flask, add 1 ml of acid stannous chloride TS and distil. Collect the distillate in a receiver containing 5 ml of water. Stop distillation when about 5 ml of liquid is left in the flask. Add sufficient water to the distillate to produce 28 ml, carry out the limit test for arsenic (Appendix VIII J, method 1); not more than 0.0004%.

Assay Dissolve about 0.3 g, accurately weighed, in 15 ml of dilute sulfuric acid with the aid of heat. Cool, add 50 ml of freshly boiled and cooled water and 2 drops of o-phenanthroline IS, titrate immediately with ceric sulfate (0.1 mol/L) VS. Perform a blank determination and make any necessary correction. Each ml of ceric sulfate (0.1 mol/L) VS is equivalent to 16.99 mg of $C_4H_2FeO_4$.

Category Antianemia agent.

Storage Preserve in tightly closed containers, protected from light.

Preparation (1) Ferrous Fumarate Capsules
(2) Ferrous Fumarate Chewable Tablets
(3) Ferrous Fumarate Granules
(4) Ferrous Fumarate Tablets

Ferrous Fumarate Capsules

Ferrous Fumarate Capsules contain not less than 90.0% and not more than 105.0% of the labelled amount of ferrous fumarate ($C_4H_2FeO_4$).

Description Capsules with brown granules.

Identification Powder and dissolve a quantity of the contents in dilute hydrochloric acid, and filter. The filtrate yields the reactions characteristic of ferrous salts (Appendix III).

Ferric iron Powder the contents of 20 capsules, weigh accurately a quantity of the powder equivalent to 2 g of Ferrous Fumarate to an iodine flask, add 25 ml of water and 4 ml of hydrochloric acid to dissolve by heating, cool rapidly to room temperature, add 3 g of potassium iodide and stoppered, mix well, allow to stand in the dark for 5

minutes. Add 75 ml of water and titrate immediately with sodium thiosulfate (0.1 mol/L) VS, add 2 ml of starch IS, towards the end of titration and continue the titration until the blue colour disappears. Perform a blank determination and make any necessary correction. Not more than 14.3 ml of sodium thiosulfate (0.1 mol/L) VS is consumed.

Other requirements Comply with the general requirements for Capsules (Appendix I E).

Assay Dissolve a quantity, accurately weighed, of the powdered mixed contents obtained in test for weight variation of contents, in 15 ml of dilute sulfuric acid by gentle heating. Cool, add 50 ml of water and 2 drops of *o*-phenanthroline IS, titrate immediately with ceric sulfate (0.1 mol/L) VS. Perform a blank determination and make any necessary correction. Each ml of ceric sulfate (0.1 mol/L) VS is equivalent to 16.99 mg of $C_4H_2FeO_4$.

Category As described under Ferrous Fumarate.

Strength 0.2 g

Storage Preserve in tightly closed containers, protected from light.

Ferrous Fumarate Chewable Tablets

Ferrous Fumarate Chewable Tablets contains not less than 90.0% and not more than 105.0% of the labelled amount of ferrous fumarate ($C_4H_2FeO_4$).

Description Grey brown to dark brown tablets; taste, sweet.

Identification Dissolve a quantity of powdered tablets equivalent to about 50 mg of ferrous fumarate with diluted hydrochloric acid. The filtrate yields the reactions characteristic of ferrous salts (Appendix III).

Ferric iron Weigh a quantity of powdered tablets equivalent to about 1 g of ferrous fumarate into an iodine flask, add 25 ml of water and 4 ml of hydrochloric acid, heat to dissolve ferrous fumarate, quickly cool to room temperature. Add 3 g of potassium iodide, insert the stopper tightly, mix well and allow to stand in dark place for 5 minutes. Add 75 ml of water, immediately titrate with sodium thiosulfate (0.1 mol/L) VS. Add 2 ml starch IS towards the end of titration. Continue to titrate until the blue colour disappears. Perform a blank determination and make any necessary correction. Not more than 7.2 ml of sodium thiosulfate (0.1 mol/L) VS is consumed.

Other requirements Comply with the general requirements for tablets (Appendix I A).

Assay Weigh accurately 20 tablets and powder. Weigh accurately a quantity equivalent to about 0.3 g of ferrous fumarate, add 15 ml of diluted sulfuric acid, heat to dissolve ferrous fumarate, cool, add 50 ml of freshly boiled and cooled water and 2 drops of orthophenanthroline IS, immediately titrate with ceric sulfate (0.1 mol/L) VS. Perform a blank determination and make any necessary correction. Each ml of ceric sulfate (0.1 mol/L) VS is equivalent to 16.99 mg $C_4H_2FeO_4$.

Category As described under ferrous fumarate.

Strength (1) 0.1 g (2) 0.2 g

Storage Preserve in tightly closed containers and protected from light.

Ferrous Fumarate Granules

Ferrous Fumarate Granules contains not less than 90.0% and not more than 105.0% of the labelled amount of ferrous fumarate ($C_4H_2FeO_4$).

Description Grey brown to dark brown granules; odour, fragrant; taste, sweet.

Identification (1) Weigh a quantity of powdered granules equivalent to about 2 g of ferrous fumarate, add 100 ml of hydrochloric acid solution (1→8), heat to boil. Cool, filter and keep the filtrate. Wash the residue with several portions of hydrochloric acid solution (1→100), each of 5 ml. Continue to wash with water until the filtrate clear. Dissolve 0.1 g with 2 ml of sodium carbonate solution after dried at 105°C, add several drops of potassium permanganate TS, a brown colour is produced immediately.

(2) The filtrate obtained in identification (1) yields the reactions characteristic of ferrous salts (Appendix III).

Ferric iron Weigh a quantity of powdered granules equivalent to about 2 g of ferrous fumarate into an iodine flask, add 25 ml of water and 4 ml of hydrochloric acid, heat to dissolve ferrous fumarate, quickly cool to room temperature. Add 3 g of potassium iodide, insert the stopper tightly, mix well and allow to stand in dark place for 5 minutes. Add 75 ml of water, immediately titrate with sodium thiosulfate (0.1 mol/L) VS. Add 2 ml starch IS towards the end of titration. Continue to titrate until the blue colour disappears. Perform a blank determination and make any necessary correction. Not more than 14.3 ml of sodium thiosulfate (0.1 mol/L) VS is consumed.

Other requirements Except Solubility Test, comply with the general requirements for Granules (Appendix I N).

Assay Weigh accurately a quantity of the mixed powdered contents obtained in the Test for Weight Variation of Contents, equivalent to about 0.3 g of ferrous fumarate, add 15 ml of diluted sulfuric acid, heat to dissolve ferrous fumarate, cool, add 50 ml of freshly boiled and cooled water and 2 drops of orthophenanthroline IS, immediately titrate with ceric sulfate (0.1 mol/L) VS. Perform a blank determination and make any necessary correction. Each ml of ceric sulfate (0.1 mol/L) VS is equivalent to 16.99 mg $C_4H_2FeO_4$.

Category As described under ferrous fumarate.

Strength (1) 1 g±0.1 g (2) 2 g±0.2 g

Storage Preserve in tightly closed containers and protected from light.

Ferrous Fumarate Tablets

Ferrous Fumarate Tablets contain not less than 90.0% and not more than 105.0% of the labelled amount of ferrous fumarate ($C_4H_2FeO_4$).

Description Sugar-coated tablets with reddish-brown core.

Identification Powder the tablets with sugar coating removed. Dissolve the powdered tablets in dilute hydrochloric acid and filter; the filtrate yields the reactions characteristic of ferrous salts (Appendix III).

Ferric iron Powder 10 tablets with sugar coating removed. Dissolve the powdered tablets in 25 ml of water and 4 ml of

hydrochloric acid in an iodine flask with the aid of heat. Cool immediately to room temperature, add 3 g of potassium iodide, insert the stopper, mix and allow to stand in dark for 5 minutes. Add 75 ml of water and titrate immediately with sodium thiosulfate (0.1 mol/L) VS, add 2 ml of starch IS towards the end of titration, then continue to titrate until the blue colour disappears. Perform a blank determination and make any necessary correction. Not more than 14.3 ml (strength 0.2 g), 7.2 ml (strength 0.1 g) or 3.6 ml (strength 0.05 g) of sodium thiosulfate (0.1 mol/L) VS is consumed.

Other requirements Comply with the general requirements for tablets (Appendix I A).

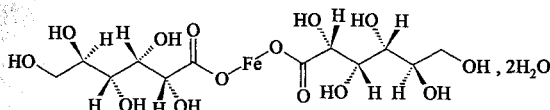
Assay Weigh accurately and powder 10 tablets with sugar coating removed. Dissolve a quantity of the powdered tablets equivalent to about 0.3 g of ferrous fumarate, accurately weighed, in 15 ml of dilute sulfuric acid by heating. Cool, add 50 ml of freshly boiled and cooled water and 2 drops of o-phenanthroline IS, titrate immediately with ceric sulfate (0.1 mol/L) VS. Perform a blank determination and make any necessary correction. Each ml of ceric sulfate (0.1 mol/L) VS is equivalent to 16.99 mg of $C_6H_8FeO_4$.

Category As described under Ferrous Fumarate.

Strength (1) 0.05 g (2) 0.1 g (3) 0.2 g

Storage Preserve in tightly closed containers, protected from light.

Ferrous Gluconate



$C_{12}H_{22}FeO_{14} \cdot 2H_2O$ 482.17

[299-29-6]

Ferrous Gluconate is the ferrous salts of D-gluconic acid, dihydrate. It contains not less than 97.0% and not more than 102.0% of $C_{12}H_{22}FeO_{14}$, calculated on the dried basis.

Description A greenish grey or pale yellow powder or granules; odour of caramel; taste, astringent. Freely soluble in hot water; soluble in water; practically insoluble in ethanol.

Identification (1) Dissolve about 0.5 g in 5 ml of water by warming, add 0.7 ml of glacial acetic acid and 1 ml of freshly distilled phenylhydrazine, heat on a water bath for 20 minutes and cool. Scratch the inner surface of the test tube with a glass rod; yellow crystals are produced gradually. (2) Dissolve 0.1 g in 20 ml of water, add potassium ferricyanide TS; a dark blue precipitate is produced.

Acidity Dissolve 1.0 g in 20 ml of water, pH 3.7-6.0 (Appendix VI H).

Clarity and Colour of solution A solution of 0.50 g in 10 ml of cold water freshly boiled is clear, with slightly greenish brown colour.

Chloride Carry out the limit test for chlorides (Appendix III A), using 50 mg. Any opalescence produced is not more intense than that of a reference solution using 3.0 ml of sodium chloride standard solution (0.06%).

Sulfate To 1 ml of 5% ferrous gluconate solution add 3 ml of 3 mol/L acetic acid solution and dilute with water to 15

ml. Carry out the limit test for sulfate (Appendix VIII B), any opalescence produced is not more intense than that of a reference solution, using 1.0 ml of potassium sulfate standard solution (0.2%).

Barium Dissolve 1.0 g in 100 ml of water, filter. Divide the filtrate into two equal portions. To one portion add 5 ml of dilute sulfuric acid; to the other portion add 5 ml of water, allow to stand for 5 minutes. The solutions are equal in clarity.

Calcium Dissolve 2.0 g in 100 ml of water, divide the solution into two equal portions. To one portion add 5 ml of ammonium oxalate TS; to the other portion add 5 ml of water, allow to stand for 5 minutes. The solutions are equal in clarity.

Oxalates Dissolve 5.0 g in the mixture of 10 ml of (6 mol/L) sulfuric acid solution and 40 ml of water, add 50 ml of ether, shake for 5 minutes, separate the water layer, add 20 ml of ether again, shake for 20 minutes. Combine the ether extracts, evaporate to dryness, dissolve the residue with 15 ml of water and filter. Concentrate the filtrate to 5 ml, add 1 ml of acetic acid solution (1 mol/L) and 1 ml of 10% calcium chloride solution; no turbidity is produced within 30 minutes.

Ferric Iron Dissolve 5.0 g, accurately weighed, in a 250 ml of iodine flask with 100 ml of water and 10 ml of hydrochloric acid, add 3 g of potassium iodide, insert the stopper, mix well, allow to stand in the dark for 5 minutes and titrate with sodium thiosulfate (0.1 mol/L) VS, adding 0.5 ml of starch IS towards the end of titration. Continue to titrate until the blue colour disappears. Perform a blank determine and make any necessary correction. Each ml of sodium thiosulfate (0.1 mol/L) VS is equivalent to 5.585 mg of Fe. It contains not more than 1.0% of ferric iron.

Loss on drying When dried to constant weight at 100-105°C for 5 hours, loses not less than 7.0% and not more than 10.5% of its weight (Appendix VIII L).

Heavy metals To a 50 ml Nessler cylinder A. Add sufficient water, 2 ml of dilute acetic acid, 1 g of ascorbic acid, and a few drops of dilute caramel solution to adjust the colour matched with the test preparation, then add 1.25 ml of standard lead solution, dilute with water to 25 ml as the reference solution. To another Nessler cylinder B add 5 ml of a solution of 0.5 g in 20 ml of water, then add 2 ml of dilute acetic acid, 1 g of ascorbic acid and 1 ml of standard lead solution and sufficient water to 25 ml as the test solution. To each cylinder add 10 ml of hydrogen sulfide TS and mix well, allow to stand in the dark for 10 minutes. Compare the colour produced by viewing down the vertical axis of the cylinder against a white background. The colour produced in cylinder B is not more intense than that produced in cylinder A. It contains not more than 0.002% of heavy metals.

Arsenic Dissolve 0.5 g in 23 ml of water, add 5 ml of hydrochloric acid, carry out the limit test for Arsenic (Appendix VIII J, method 1); not more than 0.0004%.

Assay Dissolve about 1.5 g, accurately weighed, in a conical flask with stopper, with 75 ml of water and 15 ml of 1 mol/L sulfuric acid solution. Add 0.75 g of zinc powder, insert the stopper, allow to stand for about 20 minutes until the colour of solution disappears, filter the solution through NO. 4 sintered glass filter spread with zinc powder. Remove the precipitate, wash the filter with 20 ml of freshly boiled and cooled water. Combine the filtrate and washings, add 0.2 ml of o-phenanthroline IS, titrate with ceric sulfate (0.1 mol/L) VS until the colour of solution turns from

orange yellow to green. Perform a blank determine and make any necessary correction. Each ml of ceric sulfate (0.1 mol/L) VS is equivalent to 44.61 mg of $C_{12}H_{22}FeO_{14}$.

Category Antianemia.

Storage Preserve in tightly closed container.

Preparation (1) Ferrous Gluconate capsules
(2) Ferrous Gluconate syrup
(3) Ferrous Gluconate tablets

Ferrous Gluconate Capsules

Ferrous Gluconate Capsules contain not less than 93.0% and not more than 107.0% of the labelled amount of Ferrous Gluconate ($C_{12}H_{22}FeO_{14} \cdot 2H_2O$).

Identification The contents of capsules comply with the tests for Identification (1) (2) described under Ferrous Gluconate.

Loss on drying When dried about 1 g of the contents of capsules at 105°C for 5 hours, loses not more than 11.0% of its weight. (Appendix VIII L).

Other requirements Comply with the general requirements for capsules (Appendix I E).

Assay Weigh accurately a quantity of the mixed contents obtained in the test of weight variation, equivalent to about 1.5 g of ferrous gluconate, carry out the Assay described under Ferrous Gluconate. Each ml of ceric sulfate (0.1 mol/L) VS is equivalent to 48.22 mg of $C_{12}H_{22}FeO_{14} \cdot 2H_2O$.

Category As described under Ferrous Gluconate.

Strength (1) 0.25 g (2) 0.3 g (3) 0.4 g

Storage Preserve in tightly closed containers.

Ferrous Gluconate Syrup

Ferrous Gluconate Syrup contains not less than 92.0% and not more than 110.0% of the labelled amount of ferrous gluconate ($C_{12}H_{22}FeO_{14} \cdot 2H_2O$).

Description A clear, pale yellowish-brown dense liquid; odour, fragrant of flavours; taste, sour and sweet.

Identification To 0.5 ml add 5 ml of water, the solution yields the reactions characteristic of Ferrous salts (Appendix III).

pH value 3.5-4.5 (Appendix IV H).

Clarity of solution To 10 ml add 50 ml of water, mix well, the solution is clear.

Relative density Not less than 1.25 (Appendix IV A).

Other requirements Complies with the general requirements for syrups (Appendix I K).

Assay Transfer 25 ml, accurately measured, into a conical flask with stopper, add 75 ml of water and 15 ml of dilute sulfuric acid; mix well. Add 0.38 g of zinc powder, allow to stand for 20 minutes, filter with No. 4 sintered glass filter spread with zinc powder, wash the filter with 20 ml of water. Combine the filtrate and washings, add 4 drops of α -phenanthroline IS. Titrate with ceric sulfate (0.1 mol/L) VS until the colour turns from orange-yellow to green.

Perform a blank determination and make any necessary correction. Each ml of ceric sulfate (0.1 mol/L) VS is equivalent to 48.22 mg of $C_{12}H_{22}FeO_{14} \cdot 2H_2O$.

Category As described under Ferrous Gluconate.

Strength (1) 10 ml: 0.25 g (2) 10 ml: 0.30 g

Storage Preserve in tightly closed containers, protected from light.

Ferrous Gluconate Tablets

Ferrous Gluconate Tablets contain not less than 93.0% and not more than 107.0% of the labelled amount of ferrous gluconate ($C_{12}H_{22}FeO_{14} \cdot 2H_2O$).

Description Sugar coated tablets, with a greyish-green or pale yellow core.

Identification The powdered tablets comply with tests for Identification (1) (2) described under Ferrous Gluconate.

Other requirements Comply with the general requirements for tablets (Appendix I A).

Assay Weigh and powder 40 tablets (for 0.1 g strength) and 20 tablets (for 0.3 g strength) with sugar coating removed. Dissolve a quantity of the powder equivalent to about 1.5 g of ferrous gluconate, accurately weighed, in a conical flask with a stopper in a mixture of 75 ml of water and 15 ml of 1 mol/L sulfuric acid solution. Add 0.75 g of zinc powder, insert the stopper, allow to stand for 20 minutes until the colour of solution disappears. Filter with No. 4 sintered glass filter spread with zinc powder. Remove the precipitate and wash the filter with 20 ml of freshly boiled and cooled water. Combine the filtrate and washings, add 0.2 ml of α -phenanthroline IS, titrate with ceric sulfate (0.1 mol/L) VS until the colour turns from orange-yellow to green. Perform a blank determination and make any necessary correction. Each ml of ceric sulfate (0.1 mol/L) VS is equivalent to 48.22 mg of $C_{12}H_{22}FeO_{14} \cdot 2H_2O$.

Category As described under Ferrous Gluconate.

Strength (1) 0.1 g (2) 0.3 g

Storage Preserve in tightly closed containers, protected from light, stored in dry place.

Ferrous Sulfate

$FeSO_4 \cdot 7H_2O$ 278.01 [7782-63-0]

Ferrous Sulfate contains not less than 98.5% and not more than 104.0% of $FeSO_4 \cdot 7H_2O$.

Description Pale bluish-green prismatic crystals or granules; odourless; taste, salty and astringent; effloresce in dry air and rapidly oxidized in damp air forming yellowish-brown basic ferric sulfate on the surface. Soluble in water; insoluble in ethanol.

Identification The aqueous solution yields the reactions characteristic of ferrous salts and sulfates (Appendix III).

Acidity Dissolve 0.50 g in 10 ml of water, pH 3.0-4.0 (Appendix VI H).

Basic sulfate Dissolve 1.0 g in 2 ml of freshly boiled and cooled water, the solution is clear.

Heavy metals Dissolve 1.0 g in 10 ml of 7 mol/L

hydrochloric acid solution, add 2 ml of 30% hydrogen peroxide, evaporate to about 5 ml on a water bath, cool and transfer to a separator, wash the vessel with 10 ml of 7 mol/L hydrochloric acid in portions, and combine the washings to the same separator. Extract with three portions, each of 20 ml, of methyl isobutyl ketone (add 1 ml of 7 mol/L hydrochloric acid to 100 ml of methyl isobutyl ketone distilled freshly). Heat the water layer on a water bath for 20 minutes, cool, add 1 drop of phenolphthalein IS. Add dropwise concentrate ammonia solution until the solution turns to pale red, then add 2 ml of acetate BS (pH 3.5) and a quantity of water to produce 25 ml. Carry out the limit test for heavy metals (Appendix VIII H, method 1); not more than 0.002%.

Arsenic Dissolve 1.0 g in 23 ml of water, add 5 ml of hydrochloric acid. Carry out the limit test for arsenic (Appendix VIII J, method 1); not more than 0.0002%.

Assay Dissolve about 0.5 g, accurately weighed, in 15 ml of dilute sulfuric acid and 15 ml of freshly boiled and cooled water, titrate immediately with potassium permanganate (0.02 mol/L) VS until the solution is persistently pink. Each ml of potassium permanganate (0.02 mol/L) VS is equivalent to 27.80 mg of $\text{FeSO}_4 \cdot 7\text{H}_2\text{O}$.

Category Anti-anemia agent.

Storage Preserve in tightly closed containers.

Preparation (1) Ferrous Sulfate Sustained-release Tablets
(2) Ferrous Sulfate Tablets

Ferrous Sulfate Sustained-release Tablets

Ferrous Sulfate Sustained Release Tablets contain not less than 95.0% and not more than 105.0% of the labelled amount of ferrous sulfate ($\text{FeSO}_4 \cdot 7\text{H}_2\text{O}$).

Description Film coated Tablets with pale bluish green core.

Identification Powder the tablets after removing the film coating. Shake a quantity of the powdered tablets equivalent to 0.2 g of ferrous sulfate with a drop of dilute hydrochloric acid and 20 ml of water, filter. The filtrate yields the reactions characteristic of ferrous salts and sulfates (Appendix III).

Drug release Carry out drug release test (Appendix X D, method 1), using the apparatus described under Dissolution test (Appendix X C, method 1) and 900 ml of 0.1 mol/L hydrochloric acid solution as the release medium, adjust the rotational speed of the basket to 100 rpm. Withdraw 10 ml of the solution after exactly 2 and 6 hours respectively and filter (Add 10 ml of the release medium to vessel to compensate the volume immediately). Measure accurately 5 ml of the successive filtrate into a 50 ml volumetric flask, dilute with water to volume. Carry out the method for atomic absorption spectrophotometry (Appendix IV D, method 1), measure directly the content of ferrous in the solution, calculate the drug release of ferrous sulfate from each tablet at 2 and 6 hours, respectively. The drug release of ferrous sulfate complies with the requirement: the quantity released from each tablet is 20%-40% and 50%-75% of the labelled amount at 2 and 6 hours respectively.

Other requirements Comply with the general requirements for tablets (Appendix I A).

Assay To 3 tablets with film coating removed add 30 ml of dilute sulfuric acid and a quantity of freshly boiled and cooled water in a 200 ml of volumetric flask, shake to dissolve ferrous sulfate. Add freshly boiled and cooled water to volume, mix well. Filter quickly through a piece of dry filter paper. Measure accurately 50 ml of the successive filtrate, add a few drops of *o*-phenanthroline IS, titrate with ceric sulfate (0.1 mol/L) VS immediately. Each ml of ceric sulfate (0.1 mol/L) VS is equivalent to 27.80 mg of $\text{FeSO}_4 \cdot 7\text{H}_2\text{O}$.

Category As described under Ferrous Sulfate.

Strength 0.45 g

Storage Preserve in tightly closed containers, stored in a dry place.

Ferrous Sulfate Tablets

Ferrous Sulfate Tablets contain not less than 95.0% and not more than 110.0% of the labelled amount of ferrous sulfate ($\text{FeSO}_4 \cdot 7\text{H}_2\text{O}$).

Description Sugar-coated tablets with pale bluish-green core.

Identification Powder the tablets with sugar coating removed. Weigh accurately a quantity equivalent to about 0.2 g of ferrous sulfate, shake with 1 drop of dilute hydrochloric acid and 20 ml of water to dissolve ferrous sulfate, filter. The filtrate yields the reactions characteristic of ferrous salts and sulfates (Appendix III).

Other requirements Comply with the general requirements for tablets (Appendix I A).

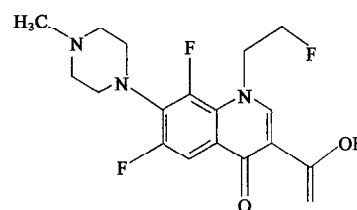
Assay To 10 tablets in a 200 ml volumetric flask add 60 ml of dilute sulfuric acid and a quantity of freshly boiled and cooled water, shake to dissolve ferrous sulfate. Add freshly boiled and cooled water to volume, shake well, filter quickly with dry filter paper. Measure accurately 30 ml of the successive filtrate, add a few drops of *o*-phenanthroline IS, titrate immediately with ceric sulfate (0.1 mol/L) VS. Each ml of ceric sulfate (0.1 mol/L) VS is equivalent to 27.80 mg of $\text{FeSO}_4 \cdot 7\text{H}_2\text{O}$.

Category As described under Ferrous Sulfate.

Strength 0.3 g

Storage Preserve in tightly closed containers, stored in a dry place.

Fleroxacin



$\text{C}_{17}\text{H}_{18}\text{F}_3\text{N}_3\text{O}_3$ 369.34

Fleroxacin is 6,8-Difluoro-1-(2-fluoroethyl)-1,4-dihydro-7-(4-methyl-1-piperazinyl)-4-oxo-3-quinoline carboxylic acid. It contains not less than

98.5% and not more than 102.0% of $C_{17}H_{18}F_3N_3O_3$, calculated on the dried basis.

Description A white or slight yellow crystalline powder; odourless; taste, bitter.

Slightly soluble in chloroform; very slightly soluble in water or methanol; practically insoluble in acetic ether; freely soluble in glacial acetic acid; sparingly soluble in sodium hydroxide TS.

Identification (1) Carry out the method for thin-layer chromatography (Appendix V B), using silica gel G as the coating substance and a mixture of chloroform-methanol-ammonia solution (15 : 10 : 2) as mobile phase. Apply separately to the plate 10 μ l each of two solutions in a mixture of chloroform-methanol (4 : 1) containing (1) 1 mg per ml of the substance being examined and (2) 1 mg per ml of fleroxacin CRS. After developing and removal of the plate, dry in air, examine under UV (254 nm). The fluorescence and position of the four principal spots in the chromatogram obtained with solution (1) correspond to that of the principal spots obtained with solution (2).

(2) The retention time of the principal peak of the substance being examined in the chromatogram obtained in the Assay is identical with the principal peak in the chromatogram of fleroxacin CRS.

(3) The infrared absorption spectrum (Appendix IV C) is concordant with the reference spectrum of fleroxacin (Appendix X VI).

Test (1) or (2) may be used alternatively.

Clarity and colour of solution Dissolve 5 portions each of 0.5 g with 10 ml of sodium dioxide TS, the solutions are clear. Any opalescence produced is not more pronounced than that of reference suspension II (Appendix IX B). Any colour produced (for injection) is not more intense than that of reference solution Y₅ or YG₅ (Appendix IX A, method 1).

Related substances Carry out the method described under Assay. Dissolve a quantity of the substance being examined, in the mobile phase to produce solutions of 2.0 mg per ml (solution 1) and 20 μ g per ml (solution 2). Inject 20 μ l of the solution (2) into the column, adjust the attenuation so that the principal peak height in the chromatogram is 20% to 25% of the full scale of the chart. Inject 20 μ l of the above two solutions into the column and record the chromatogram for two times the retention time of the principal peak. The sum of all secondary peak areas in the chromatogram obtained with solution (1) is not greater than the area of the principal peak in the chromatogram obtained with solution (2).

Loss on drying When dried to constant weight at 105°C, loses not more than 0.5% of its weight (Appendix VIII L).

Residue on ignition Not more than 0.2% (Appendix VIII N), using 1.0 g in a platinum crucible.

Heavy metals Carry out the limit test for heavy metals (Appendix VIII H, method 2), using the residue obtained in the test for Residue on ignition: not more than 0.002%.

Assay Carry out the method for high performance liquid chromatography (Appendix V D), using a column packed with octadecylsilane bonded silica gel and a mixture of triethylamine phosphate solution (add 5 ml of triethylamine and 7 ml of phosphoric acid to water, and dilute to a volume of 1000 ml)-acetonitrile (82 : 18) as the mobile phase. Detection wavelength is 286 nm and the number of theoretical plates of the column is not less than 2000, calculated with reference to the peak of fleroxacin. The resolution factor between the peak of fleroxacin and adjacent peaks is not less than 1.5.

Procedure Dissolve about 100 mg, accurately weighed, in

the mobile phase and dilute to 100 ml, mix well. Measure accurately 5 ml of the above solution to a 100 ml volumetric flask, dilute with the mobile phase and mix well. Inject 10 μ l of the solution into the column. Repeat the operation, using fleroxacin CRS instead of the substance being examined, calculate the content of $C_{17}H_{18}F_3N_3O_3$.

Category Quinolone antibiotic.

Storage Preserve in tightly closed containers, protected from light, stored in a dry place.

Preparation (1) Fleroxacin Tablets
(2) Fleroxacin Capsules

Fleroxacin Capsules

Fleroxacin capsules contain not less than 90.0% and not more than 110.0% of the labeled amount of fleroxacin ($C_{17}H_{18}F_3N_3O_3$).

Description Capsules containing white or slight yellow granule or powder.

Identification (1) The retention time of the principal peak of the substance being examined in the chromatogram obtained in the Assay is identical with the principal peak in the chromatogram of fleroxacin CRS.

(2) Dissolve a quantity of the content of the capsules in 0.1 mol/L hydrochloric acid to produce a solution of 6 μ g of fleroxacin per ml, filter. The light absorption of the filtrate exhibits maxima at 286 nm and 320 nm (Appendix IV A).

Dissolution Carry out the dissolution test (Appendix X C, method 1), using 900 ml of hydrochloride acid solution (9→1000) as the dissolution medium, adjust the rotational speed of the paddle to 75 r/min. Withdraw 10 ml of the solution after exactly 30 minutes and filter. Dilute an accurately measured quantity of the successive filtrate with hydrochloride acid solution (9→1000) to produce a solution of 4 μ g of fleroxacin per ml. Dissolve a quantity of fleroxacin CRS in hydrochloride acid solution (9→1000) to produce a solution of 4 μ g per ml. Measure the absorbance of the resulting solutions at 286 nm (Appendix IV A). Calculate the dissolution of $C_{17}H_{18}F_3N_3O_3$ from each capsule. Not less than 80% of the labelled amount is dissolved.

Other requirements Comply with the general requirements for capsules (Appendix I E).

Assay Transfer an accurately weighed quantity of the mixed contents of capsules obtained in the test for Weight variation of contents, equivalent to about 100 mg of fleroxacin to a 100 ml volumetric flask, add a quantity of mobile phase to dissolve, and dilute to volume, mix well and filter. Measure accurately 5 ml of the successive filtrate to a 100 ml volumetric flask, dilute with the mobile phase to volume and mix thoroughly. Inject 10 μ l to the column and proceed as described under Fleroxacin.

Category As described under Fleroxacin.

Strength 0.1 g

Storage Preserve in tightly closed containers, protected from light, stored in a dry place.

Fleroxacin Tablets

Fleroxacin Tablets contain not less than 90.0%

and not more than 110.0% of the labeled amount of fleroxacin ($C_{17}H_{18}F_3N_3O_3$).

Description White or slight yellow tablets or film coated tablets with white or slight yellow core.

Identification (1) The retention time of the principal peak of the substance being examined in the chromatogram obtained in the Assay is identical with the principal peak in the chromatogram of fleroxacin CRS.

(2) Dissolve a quantity of the powdered tablets in 0.1 mol/L hydrochloric acid to produce a solution of 6 μ g of fleroxacin per ml, filter. The light absorption of the filtrate exhibits maxima at 286 nm and 320 nm (Appendix IV A).

Dissolution Carry out the dissolution test (Appendix X C, method 1), using 900 ml of hydrochloride acid solution (9 \rightarrow 1000) as the dissolution medium, adjust the rotational speed of the paddle to 75 rpm. Withdraw 10 ml of the solution after exactly 30 minutes and filter. Dilute an accurately measured quantity of the successive filtrate with hydrochloride acid solution (9 \rightarrow 1000) to produce a solution of 4 μ g of fleroxacin per ml. Dissolve a quantity of fleroxacin CRS in hydrochloride acid solution (9 \rightarrow 1000) to produce a solution of 4 μ g per ml. Measure the absorbance of the resulting solutions at 286 nm (Appendix IV A). Calculate the dissolution of $C_{17}H_{18}F_3N_3O_3$ from each tablet. Not less than 80% of the labelled amount is dissolved.

Other requirements Comply with the general requirements for tablets (Appendix I A).

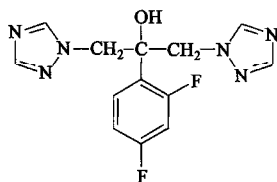
Assay Weigh accurately and powder 10 tablets. Dissolve an accurately weighed quantity of powder equivalent to about 100 mg of fleroxacin with mobile phase and dilute to 100 ml, mix well and filter. Measure accurately 5 ml of the successive filtrate to a 100 ml volumetric flask, dilute with the mobile phase to volume and mix thoroughly. Inject 10 μ l to the column and proceed as described under Fleroxacin.

Category As described under Fleroxacin.

Strength 0.1 g

Storage Preserve in tightly closed containers, protected from light, stored in a dry place.

Fluconazole



$C_{13}H_{12}F_2N_6O$ 306.28

[86386-73-4]

Fluconazole is 2-(2,4-difluorophenyl)-1,3-bis (1H-1,2,4-triazol-1-yl) propan-2-ol. It contains not less than 98.5% of $C_{13}H_{12}F_2N_6O$, calculated on the dried basis.

Description White or almost white crystals or a crystalline powder; odourless or slightly characteristic odour; taste, bitter.

Freely soluble in methanol; soluble in ethanol; slightly soluble in dichloromethane, water or acetic acid; insoluble in ether.

Melting range 137-141°C (Appendix VI C).

Identification (1) The light absorption of the solution of 200 μ g per ml in ethanol exhibits maxima at 261 nm and 267 nm, and a minimum at 264 nm (Appendix IV A).

(2) The infrared absorption spectrum (Appendix IV C) is concordant with the spectrum of fluconazole (Appendix XVI).

(3) Yields the reaction characteristic of organic fluorinated compounds (Appendix III).

Clarity of solution Dissolve 20 mg in 10 ml of water, the solution is clear; any opalescence produced is not more pronounced than that of reference suspension I (Appendix IX B) (for injection).

Fluorine Weigh accurately about 15 mg and carry out the method for determination of fluorine (Appendix VIII E). It contains not less than 11.1% and not more than 12.4% of fluorine.

Related substances Carry out the method for high performance liquid chromatography (Appendix V D), using a column packed with octadecylsilane bonded silica gel and a mixture of phosphate BS (pH 7.0)-methanol (55:45) as the mobile phase. Detection Wavelength is 260 nm and the number of the theoretical plates of the column is not less than 2000, calculated with reference to the peak of fluconazole. Dissolve a quantity of the substance being examined with the mobile phase to produce a solution of about 1 mg per ml as the test solution (1). Measure accurately 1 ml of solution (1) into a 100 ml volumetric flask, dilute by mobile phase to the volume, mix well as the reference solution (2). Inject 10 μ l of solution (2) into the column, adjust the attenuation so that the principal peak height in the chromatogram is about 20% of full scale of the chart. Inject separately accurately 20 μ l each of the solution (1) and (2) into the column and record the chromatogram for twice the retention time of the principal peak. The sum of the areas of all peaks other than the principal peak in the chromatogram of solution (1) is not greater than the area of the principal peak of solution (2).

Chloride Weigh accurately about 20 mg, carry out the method for oxygen flask combustion, using 20 ml of 0.4% sodium hydroxide solution as the absorbing liquid. When the combustion is complete, shake vigorously for 5 minutes, add 10 ml of dilute nitric acid, transfer the solution to a 50 ml Nessler cylinder. Carry out the limit test for chlorides (Appendix VIII A). Any opalescence produced is not more pronounced than that of a reference solution prepared in the same manner, using 6.0 ml of sodium chloride standard solution instead of the substance being examined (0.3%).

Loss on drying When dried to constant weight at 105°C, % loss is not more than 0.5% (Appendix VIII D).

Residue on ignition Not more than 0.1% (Appendix VIII N), using 1.0 g.

Heavy metals Carry out the limit test for heavy metals (Appendix VIII H, method 1), using the residue obtained in the test for Residue on ignition; not more than 0.002%.

Assay Dissolve about 0.1 g, accurately weighed, in 50 ml of glacial acetic acid, carry out the method for potentiometric titration (Appendix VII A), titrate with perchloric acid (0.1 mol/L) VS. Perform a blank determination and make any necessary correction. Each ml of perchloric acid (0.1 mol/L) VS is equivalent to 15.31 mg of $C_{13}H_{12}F_2N_6O$.

Category Antifungal.

Storage Preserve in tightly closed containers, stored in a dry place.

Preparation (1) Fluconazole Capsules
(2) Fluconazole and sodium chloride Injection
(3) Fluconazole Tablets

Fluconazole and Sodium Chloride Injection

Fluconazole and sodium chloride Injection is a sterile isotonic solution of fluconazole in Water for Injection containing sodium chloride. It contains not less than 95.0% and not more than 105.0% of the labelled amount of fluconazole ($C_{13}H_{12}F_2N_6O$) and sodium chloride (NaCl).

Description A clear, colourless solution.

Identification (1) Carry out the method for thin-layer chromatography (Appendix V B), using silica gel GF₂₅₄ as the coating substance and a mixture of acetone-dichloromethane (70:30) as the mobile phase. Apply separately to the plate 20 μ l each of the injection and a reference solution containing 2 mg of fluconazole CRS per ml in 0.9% sodium chloride solution. After developing and removal of the plate, dry in air and examine under ultraviolet light (254 nm). The colour and position of the principal spot in the chromatogram obtained with the test solution correspond to the principal spot obtained with the reference solution.

(2) The light absorption of the solution obtained in the Assay exhibits two maxima at 261 nm and 267 nm, and a minimum at 264 nm (Appendix IV A).

(3) Yields the reactions characteristic of sodium salts and chlorides (Appendix III).

Acidity 4.0-6.0 (Appendix VI H).

Heavy metals Evaporate 50 ml of injection to 20 ml and cool, add 2 ml of acetate BS (pH 3.5) and a quantity of water to 25 ml. Carry out the limit test for heavy metals (Appendix VIII H, method 1); not more than 0.00003%.

Pyrogens Complies with the test for pyrogens (Appendix XI D), using 10 ml per kg of the rabbit's weight.

Sterility Complies with the test for sterility (Appendix XI H), using the injection treated by membrane filtration method.

Other requirements Complies with the general requirements for injection (Appendix I B).

Fluconazole Carry out the method for high performance liquid chromatography (Appendix V D), using a column packed with octadecylsilane bonded silica gel and a mixture of phosphate BS (pH 7.0)-methanol (55:45) as the mobile phase. Detectable Wavelength is 260 nm. The number of theoretical plates of the column, calculated with respect to the peak of fluconazole, is not less than 2000.

Procedure Measure accurately a quantity of the substance being examined and dilute with mobile phase to produce a solution of about 0.5 mg of fluconazole per ml as the test solution. Inject 20 μ l into the column and record the chromatogram. Dissolve a quantity of fluconazole CRS, accurately weighed, and dilute with mobile phase to produce a solution of about 0.5 mg per ml, repeat the operations, calculate the content of $C_{13}H_{12}F_2N_6O$ with respect to the peak area obtained in the chromatogram by the external standard method.

Sodium Chloride Measure accurately 10 ml of the substance being examined, add 40 ml of water, 5 ml of 2% dextrin solution and 5-8 drops of fluorescein IS and titrate with silver nitrate (0.1 mol/L) VS. Each ml of silver nitrate (0.1 mol/L) VS is equivalent to 5.844 mg of NaCl.

Category As described under Fluconazole.

Strength (1) 50 ml : fluconazole 0.1 g and sodium chloride

0.45 g

(2) 100 ml : fluconazole 0.1 g and sodium chloride 0.9 g

(3) 100 ml : fluconazole 0.2 g and sodium chloride 0.9 g

Storage Preserve in well closed containers, protected from light.

Fluconazole Capsules

Fluconazole Capsules contain not less than 90.0% and not more than 110.0% of the labelled amount of fluconazole ($C_{13}H_{12}F_2N_6O$).

Description Capsules containing white or almost white powder.

Identification (1) To a quantity equivalent to about 0.1 g of fluconazole, add 10 ml of methanol, shake thoroughly to dissolve fluconazole and filter, using the filtrate as solution (1). Dissolve 0.1 g of fluconazole CRS in 10 ml of methanol as solution (2). Carry out the method for thin-layer chromatography (Appendix V B), using silica gel GF₂₅₄ as the coating substance and a mixture of dichloromethane-methanol-concentrated ammonia solution (80:20:1) as the mobile phase. Apply separately to the plate 10 μ l of each of the solutions. After developing and removal of the plate, dry in air and examine under ultra-violet light (254 nm). The colour and position of the principal spot in the chromatogram obtained with solution (1) correspond to the principal spot obtained with solution (2).

(2) The light absorption of the solution obtained in the Assay exhibits two maxima at 261 nm and 267 nm, and a minimum at 264 nm.

Dissolution Carry out the dissolution test (Appendix X C, method 1), using 500 ml (for strength 50 mg) or 1000 ml (for strength 0.1 g, 0.15 g) of hydrochloric acid solution (9→1000) as the dissolution medium, adjust the rotational speed of the paddle to 100 rpm. Withdraw the solution after exactly 45 minutes, filter and discard the initial filtrate, using the successive filtrate as the test solution. Dissolve an accurately weighed quantity of fluconazole CRS in the dissolution medium to produce a solution of about 0.1 mg per ml. Measure the absorbance of the resulting solutions at 261 nm (Appendix IV A). Calculate the dissolution of $C_{13}H_{12}F_2N_6O$ from each capsule. Not less than 80% of the labelled amount is dissolved.

Other requirements Comply with the general requirements for capsules (Appendix I D).

Assay Triturate and weigh accurately a quantity of the mixed contents obtained in the test for weight variation of contents, equivalent to about 50 mg of fluconazole, to a 100 ml volumetric flask, add a quantity of hydrochloric acid solution (9 → 1000), shake thoroughly to dissolve fluconazole, dilute to volume, mix well and filter. Measure accurately 10 ml of the successive filtrate to a 25 ml volumetric flask, dilute with the above solvent to volume, mix well. Dissolve an accurately weighed quantity of fluconazole CRS, in hydrochloric acid solution (1→1000) to produce a solution of about 0.2 mg per ml, mix well. Measure the absorbance of the resulting solutions at 261 nm (Appendix IV A) and calculate the content of $C_{13}H_{12}F_2N_6O$.

Category As described under Fluconazole.

Strength (1) 50 mg (2) 0.1 g (3) 0.15 g

Storage Preserve in tightly closed containers, stored in a

dry place.

Fluconazole Tablets

Fluconazole Tablets contain not less than 90.0% and not more than 110.0% of the labelled amount of fluconazole ($C_{13}H_{12}F_2N_6O$).

Description White or almost white tablets or film coated tablets with white or almost white core.

Identification (1) The retention time of principal peak in the substance being examined in the chromatogram obtained in the Assay is identical with that the principal peak of fluconazole CRS.

(2) Dissolve a quantity of the powdered tablets in ethanol to produce a solution of 0.2 mg of fluconazole per ml and filter. The light absorption of the filtrate exhibits two maxima at 261 nm and 267 nm, and a minimum at 264 nm (Appendix IV A).

Dissolution Carry out the dissolution test (Appendix X C, method 1), using 500 ml (for strength 50 mg) or 1000 ml (for strength 0.1 g, 0.15 g) of hydrochloric acid solution (9→1000) as the dissolution medium, adjust the rotational speed of the paddle to 100 rpm. Withdraw the solution after exactly 45 minutes, filter and discard the initial filtrate, using the successive filtrate as the test solution. Dissolve an accurately weighed quantity of fluconazole CRS in the above solvent to produce a solution of about 0.1 mg per ml. Measure the absorbance of the resulting solutions at 261 nm (Appendix IV A). Calculate the dissolution of $C_{13}H_{12}F_2N_6O$ from each tablet. Not less than 80% of the labelled amount is dissolved.

Other requirements Comply with the general requirements for tablets (Appendix I A).

Assay Carry out the method for high performance liquid chromatography (Appendix V D), using a column packed with octadecylsilane bonded silica gel and a mixture of phosphate BS (pH 7.0)-methanol (55 : 45) as the mobile phase. Detection wavelength is 261 nm and the number of the theoretical plates of the column is not less than 1500, calculated with reference to the peak of fluconazole.

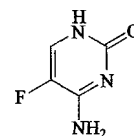
Procedure Weighed accurately and powder 10 tablets. Dissolve an accurately weighed quantity (equivalent to about 50 mg of fluconazole) with the mobile phase in a 100 ml volumetric flask and dilute to volume, mix well, filter. Inject 20 μ l of the successive filtrate into the column and record the chromatogram. Dissolve an accurately weighed quantity of fluconazole CRS in the mobile phase to produce a reference solution of 0.5 mg of fluconazole CRS per ml. Repeat the operation and calculate the content of fluconazole with respect to the peak area obtained in the chromatogram by the external standard method.

Category as described under Fluconazole.

Strength (1) 50 mg (2) 0.1 g (3) 0.15 g

Storage Preserve in tightly closed containers, protected from light.

Flucytosine



$C_4H_4FN_3O$ 129.09

[2022-85-7]

Flucytosine is 5-fluoropyrimidin-4-amino-2(1H)-one. It contains not less than 98.5% of $C_4H_4FN_3O$, calculated on the dried basis.

Description A white or almost white crystalline powder; odourless or odour slightly.

Sparingly soluble in water; slightly soluble in absolute ethanol; practically insoluble in chloroform or ether; freely soluble in dilute hydrochloric acid TS or dilute sodium hydroxide TS.

Identification (1) To 5 ml of aqueous solution (1→100) add 0.15 of bromine TS and shake, the colour is discharged. (2) The light absorption of a solution of about 10 μ g per ml in hydrochloric acid (9→100) exhibits a maximum at 286 nm; the absorbance is about 0.71 (Appendix IV A). (3) The infrared absorption spectrum (Appendix IV C) is concordant with the reference spectrum of flucytosine (Appendix XVI).

Fluorouracil Carry out the method for thin-layer chromatography (Appendix V B), using silica gel GF₂₅₄ as the coating substance and chloroform-glacial acetic acid (13 : 7) as the mobile phase. Apply separately to the plate 20 μ l each of two solutions in a mixture of glacial acetic acid-water (8 : 2) containing (1) 50 μ g per ml of fluorouracil CRS, (2) 25 mg per ml of the substance being examined. After developing and removal of the plate, dry in air, and examine under ultraviolet light (254 nm). The fluorescence of the secondary spot in the chromatography obtained with solution (2) is not more intense than that of the principal spot obtained with solution (1).

Loss on drying When dried to constant weight at 105°C, loses not more than 0.5% of its weight (Appendix VIII L).

Residue on ignition Not more than 0.2% (Appendix VIII N), using 1.0 g.

Heavy metals Carry out the limit test for heavy metals (Appendix VIII H, method 2), using the residue obtained in the test for residue on ignition; not more than 0.002%.

Assay Dissolve about 0.1 g, accurately weighed, in 20 ml of glacial acetic acid, add 10 ml of acetic anhydride, heat slightly, cool. Carry out the method for potentiometric titration (Appendix VII A), titrate with perchloric acid (0.1 mol/L) VS. Perform a blank determination and make any necessary correction. Each ml of perchloric acid (0.1 mol/L) VS is equivalent to 12.91 mg of $C_4H_4FN_3O$.

Category Antifungal.

Storage Preserve in tightly closed containers, protected from light.

Preparation Flucytosine Injection

Flucytosine Injection

Flucytosine Injection is a sterile and isotonic solution of flucytosine in Water for Injection containing a quantity of sodium chloride. It contains not less than 93.0% and not more than 107.0% of the labelled amount of flucytosine ($C_4H_4FN_3O$).

Description A clear, colourless or almost colourless liquid.

Identification (1) Rotate the test tube containing about 1-2 ml of saturated solution of potassium dichromate in sulfuric acid, the solution is spread evenly on the wall; add 1 drop of the substance being examined and heat gently, the solution can no longer be spread evenly on the wall, but attached to it with greasy substance.

(2) To 5 ml add a few drops of bromine TS, perform a blank test at the same time, the colour of bromine in the test solution is discharged or obviously faint than that in the blank.

(3) The light absorption of the solution obtained in the Assay exhibits a maximum at 286 nm and a minimum at 245 nm (Appendix IV A).

pH value 6.0-8.0 (Appendix VI H).

Related substances Carry out the method for thin layer chromatography (Appendix V B), using silica gel GF₂₅₄ as the coating substance and a mixture of chloroform-glacial acetic acid (13:7) as the mobile phase. Apply separately to the plate 20 μ l each of the substance being examined and a reference solution of 0.1 mg per ml of flucytosine CRS in a mixture of methanol-water (2:1). After developing and removal of the plate, dry in air, examine under ultra-violet light (254 nm). The fluorescence of any secondary spot in the chromatography obtained with the substance being examined is not more intense than that of the principal spot obtained with the reference solution (1.0%).

Pyrogens Complies with the test for pyrogens (Appendix XI D), using 10 ml per kg of rabbit's weight.

Other requirements Complies with the general requirements for injection (Appendix I B).

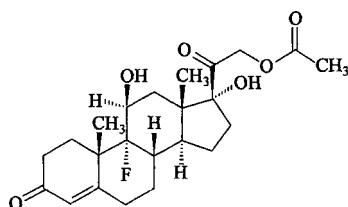
Assay Dilute an accurately measured quantity with 0.1 mol/L hydrochloric acid solution to produce a solution of 5 μ g per ml and measure the absorbance at 286 nm (Appendix IV A). Calculate the content of $C_4H_4FN_3O$, taking 709 as the value of A (1%, 1 cm).

Category As described under Flucytosine.

Strength 250 ml:2.5 g

Storage Preserve in well closed containers, stored in a cool place and protected from light.

Fludrocortisone Acetate



$C_{23}H_{31}FO_6$ 422.49

[514-36-3]

Fludrocortisone Acetate is 11 β , 17 α , 21-trihydroxy-9 α -fluoro-pregna-4-ene-3,20-dione-21-acetate. It contains not less than 97.0% and not more than 102.0% of $C_{23}H_{31}FO_6$, calculated on the dried basis.

Description A white to slightly yellow crystalline powder; odourless; tasteless; hygroscopic.

Sparingly soluble in ethanol or chloroform; slightly soluble in ether; insoluble in water.

Melting range 223-232°C, with decomposition (Appendix VI C).

Specific optical rotation +148° to +156°, in a solution of about 10 mg per ml in dioxane (Appendix VI E).

Identification (1) Dissolve about 10 mg in 1 ml of methanol by warming, add 1 ml of hot alkaline cupric tartrate TS; a red precipitate is produced.

(2) The retention time of principal peak of the substance being examined is identical with that of principal peak of the reference solution in the chromatogram obtained in Assay.

(3) The infra-red absorption spectrum (Appendix IV C) is concordant with the reference spectrum of fludrocortisone acetate (Appendix XVI).

(4) Yields the reaction characteristic of organic fluorine compounds (Appendix III).

Related substances Carry out the method for thin-layer chromatography (Appendix V B), using silica gel G as the coating substance and a mixture of dichloromethane-ether-methanol-water (385:75:40:6) as the mobile phase. Apply separately to the plate 5 μ l each of two solutions in chloroform-methanol (9:1) containing (1) 3 mg per ml, (2) 60 μ g per ml of the substance being examined. After developing and removal of the plate, dry in air and then at 105°C for 10 minutes, cool and spray with alkaline tetrazolium blue TS. Not more than 2 secondary spots are obtained in the chromatogram of solution (1); and no secondary spot is more intense than the principal spot in the chromatogram obtained with solution (2).

Loss on drying When dried to constant weight at 105°C, loses not more than 1.0% of its weight (Appendix VIII L).

Residue on ignition Not more than 0.1% (Appendix VIII N).

Assay Carry out the method for high performance liquid chromatography (Appendix V D), using a column packed with octadecylsilane bonded silica gel and a mixture of methanol-water (58:42) as the mobile phase. Detection wavelength is 240 nm, and the number of theoretical plates of the column is not less than 4500, calculated with reference to the peak of fludrocortisone acetate. The resolution factor between the peaks of fludrocortisone acetate and internal standard complies with the related requirements.

Internal standard solution Dissolve hydrocortisone in mobile phase to produce a solution of 0.16 mg per ml.

Procedure Dissolve about 18 mg of fludrocortisone acetate CRS, accurately weighed, in 58 ml of methanol in a 100 ml volumetric flask, and dilute with water to volume, mix well, as the reference solution. Transfer 5 ml each of the reference solution and internal standard solution, both accurately measured, in a 50 ml volumetric flask, and dilute with mobile phase to volume, mix well, inject 20 μ l of the resulting solution into the column, record the chromatogram. Repeat the operations using about 18 mg of the substance being examined instead of fludrocortisone acetate CRS. Calculate the content of $C_{23}H_{31}FO_6$ with respect to the peak area in the chromatogram by internal standard method.

Category Corticosteroid.

Storage Preserve in tightly closed containers.

Preparation Fludrocortisone Acetate Cream

Fludrocortisone Acetate Cream

Fludrocortisone Acetate Cream contains not less than 85.0% and not more than 115.0% of the labelled amount of fludrocortisone acetate ($C_{23}H_{31}FO_6$).

Description Creamy white cream.

Identification The retention time of principal peak of the substance being examined is identical with that of principal peak of the reference solution in the chromatogram obtained in Assay.

Other requirements Complies with the general requirements for cream (Appendix I F).

Assay Carry out the method for high performance liquid chromatography (Appendix V D), using a column packed with octadecylsilane bonded silica gel and a mixture of methanol-water (60 : 40) as the mobile phase. Detection wavelength is 240 nm and the number of theoretical plates of the column is not less than 1000, calculated with reference to the peak of fludrocortisone acetate. The resolution factor between the peaks of fludrocortisone acetate and internal standard complies with the related requirements.

Internal standard solution Dissolve dexamethasone acetate in methanol to produce a solution of about 0.30 mg per ml.

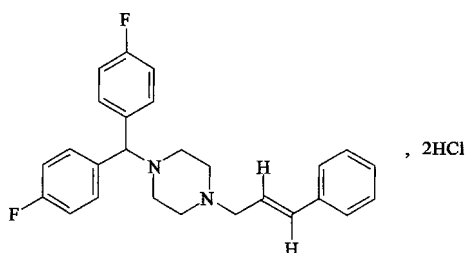
Procedure Dissolve a quantity of fludrocortisone acetate CRS, accurately weighed, in methanol to produce a solution of about 0.125 mg per ml as the reference solution. Transfer 10 ml of the reference solution and 5 ml of internal standard solution, both accurately measured, in a 50 ml volumetric flask, dilute with methanol to volume, mix well, inject 20 μ l of the resulting solution into the column and record the chromatogram. To a quantity of the substance being examined, accurately weighed, equivalent to about 1.25 mg of fludrocortisone acetate add 30 ml of methanol, heat and stir in a water bath at 80°C for 2 minutes. Cool to room temperature, add 5 ml of internal standard solution, accurately measured, dilute with methanol to 50 ml, mix well. Cool the resulting solution in an ice bath for at least 2 hours, filter quickly, discard the initial filtrate, inject 20 μ l of the successive filtrate into the column. Calculate the content of $C_{23}H_{31}FO_6$ with respect to the peak area in the chromatogram by internal standard method.

Category Corticosteroid.

Strength 10 g : 2.5 mg

Storage Preserve in tightly closed containers, stored in a cool place.

Flunarizine Hydrochloride



$C_{26}H_{26}F_2N_2 \cdot 2HCl$ 477.42

[30484-77-6]

Flunarizine Hydrochloride is (*E*)-1-[bis (4-fluorophenyl) methyl]-4-(2-propenyl-3-phenyl) piperazine dihydrochloride. It contains not less than 99.0% of $C_{26}H_{26}F_2N_2 \cdot 2HCl$, calculated on the dried basis.

Description White or almost white crystals or a crystalline powder; odourless; tasteless. Sparingly soluble in methanol or ethanol; slightly soluble in chloroform; very slightly soluble in water; practically insoluble in benzene.

Melting range 204-210°C, with decomposition (Appendix VI C).

Identification (1) Shake 10 mg with 3 ml of ethanol, add 2 drops of potassium hydroxide TS and mix well, add 1 drop of potassium permanganate TS, the violet colour disappears immediately.

(2) Dissolve 6 mg in 5 ml of ethanol and 5 ml of dilute hydrochloric acid solution (24 → 1000) and mix well. Measure a quantity of the solution and dilute with the same dilute hydrochloric acid solution to produce a solution of 12 μ g per ml. The light absorption of the solution exhibits two maxima at 226 nm and 253 nm and two minima at 221 nm and 234 nm (Appendix IV A).

(3) The infrared absorption spectrum (Appendix IV C) is concordant with the reference spectrum of flunarizine hydrochloride (Appendix XVI).

(4) Dissolve 5 mg of flunarizine hydrochloride in 1 ml of ethanol, the solution yields the reactions characteristic of chlorides (Appendix III).

(5) Yields the reactions characteristic of organic fluorine compounds (Appendix III).

Acidity Stir 0.25 g with 20 ml of water for 5 minutes and filter, pH is 1.5-3.0 using the filtrate. (Appendix VI H).

Clarity and colour of solution Dissolve 2.5 g in a quantity of a mixture of polyethylene glycol 400-water-ethanol (5:2:3) in a 25 ml volumetric flask by ultrasonic treatment, dilute to volume and mix well. The solution is clear and colourless; any opalescence produced is not more pronounced than that of reference suspension I (Appendix IX B); the absorbance of the solution at 400 nm (Appendix IV A) is not more than 0.07 if any colour is produced.

Related substances Carry out the method for high performance liquid chromatography (Appendix V D), using a column packed with octadecylsilane bonded silica gel and a mixture of methanol-phosphate buffer solution (dissolve 1.36 g potassium dihydrogen phosphate in 1000 ml of water, add 4 ml of triethylamine, adjust the pH value with phosphoric acid to 3.5) (75:25) as the mobile phase. Detection wavelength is 253 nm and the number of theoretical plates of the column is not less than 3000, calculated with reference to the peak of flunarizine hydrochloride. The resolution factor between the peaks of flunarizine hydrochloride and adjacent peak complies with the related requirements. Dissolve the substance being examined in the mobile phase to produce a solution of 0.1 mg per ml as the test solution. Measure accurately a quantity of the test solution, and dilute with the mobile phase to produce a solution of 1 μ g per ml as the reference solution. Inject 20 μ l of the reference solution into the column, adjust the attenuation so that the height of the principal peak is not more than 20% and not less than 10% on the full scale of the chart. Inject separately 20 μ l each of the test solution and the reference solution, both accurately measured, into the column, record the chromatogram for twice the retention time of the principal peak. The sum of peak areas due to the impurities is not greater than the principal peak area in the chromatogram obtained with the reference solution.

Flucytosine Injection

Flucytosine Injection is a sterile solution of sodium salt of flucytosine in water and not more than 0.5% of sodium chloride.

Description—It is a white, crystalline powder.

It is (E)-1-[2-(2-propenyl-3-phenyl)-5-oxo-1,2,4-triazin-4-yl]-1H-imidazole-4-carboxamide hydrochloride.

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dihydrogen phosphate in 1000 ml of water, add 4 ml of triethylamine, adjust the pH value with phosphoric acid to 3.5) (75:25) as the mobile phase. Detection wavelength is 253 nm and the number of theoretical plates of the column is not less than 3000, calculated with reference to the peak of flunarizine hydrochloride. The resolution factor between the peaks of flunarizine hydrochloride and adjacent peak complies with the related requirements.

Procedure Dissolve an accurately weighed quantity of the mixed contents obtained in weight variation equivalent to 10 mg of flunarizine in 100 ml volumetric flask with 10 ml of ethanol, shake well. Dilute with hydrochloric acid solution (dilute 24 ml of dilute hydrochloric acid with water to 1000 ml) to volume, mix well and filter. Measured accurately 5 ml of the successive filtrate to a 50 ml volumetric flask, dilute with the same hydrochloric acid solution to volume and mix well. Inject accurately measured 20 µl of the resulting solution into the column. Dissolve an accurately weighed quantity of flunarizine hydrochloride CRS in 100 ml volumetric flask with 10 ml of ethanol, shake well, dilute with the same hydrochloric acid solution to produce a solution of 12 µg per ml. Repeat the operation, calculate the content of $C_{26}H_{26}F_2N_2$ with respect to the peak area obtained in the chromatogram by the external standard method, multiply the result by 0.8473.

Category As described under Flunarizine Hydrochloride.

Strength 5 mg (calculated as $C_{26}H_{26}F_2N_2$)

Storage Preserve in tightly closed containers, protected from light.

Preserve in tightly closed containers, protected from light.

Preparation Flunarizine Hydrochloride Capsules

Flunarizine Hydrochloride Capsules

Flunarizine Hydrochloride Capsules contain not less than 90.0% and not more than 110.0% of the labelled amount of flunarizine hydrochloride, calculated on the basis of flunarizine ($C_{26}H_{26}F_2N_2$).

Identification (1) Dissolve a quantity of the contents equivalent to about 50 mg of flunarizine hydrochloride in 10 ml of ethanol with shaking. Filter, to 2 ml of the successive filtrate add 2 drops of potassium hydroxide TS and mix well, add 1-2 drops of potassium permanganate TS, the violet colour disappears immediately.

(2) The retention time of principal peaks of the substance being examined in the chromatogram obtained in the Assay is identical with that of flunarizine hydrochloride CRS.

(3) Measure 1 ml of the filtrate obtained in test (1) for Identification, it yields the reactions characteristic of chlorides (Appendix III).

Content uniformity Comply with the requirements for content uniformity (Appendix X E).

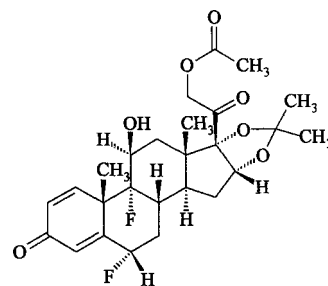
Transfer the content of 1 capsule to a 100 ml volumetric flask, add 5 ml of ethanol, shake well, and dilute with hydrochloric acid solution (dilute 24 ml of dilute hydrochloric acid with water to 1000 ml) to volume, mix well and filter. Measure accurately 10 ml of the successive filtrate to a 50 ml volumetric flask, dilute with the same hydrochloric acid solution to volume and mix well. Proceed as described under Assay.

Dissolution Carry out the dissolution test (Appendix X C, method 1), using 600 ml of hydrochloric acid solution (dilute 24 ml of dilute hydrochloric acid with water to 1000 ml) as the dissolution medium, adjust the rotational speed of the basket to 100 rpm. Withdraw 10 ml of the solution after exactly 30 minutes and filter, use the successive filtrate as the test solution. Proceed as described under Assay. Calculate the dissolution of $C_{26}H_{26}F_2N_2$ from each capsule. Not less than 80% of the labelled amount is dissolved.

Other requirements Comply with the general requirements for capsules (Appendix I E).

Assay Carry out the method for high performance liquid chromatography (Appendix V D), using a column packed with octadecylsilane bonded silica gel and a mixture of methanol-phosphate buffer solution (dissolve 1.36 g potassium

Fluocinonide



$C_{26}H_{32}F_2O_7$ 494.53

[356-12-7]

Fluocinonide is 21-(acetyloxy) 6α, 9-difluoro-11β-hydroxy-16α, 17-[(1-methyl-ethylidene) bis (oxy)]-pregna-1,4-diene-3,20-dione. It contains not less than 97.0% and not more than 103.0% of $C_{26}H_{32}F_2O_7$, calculated on the dried basis.

Description A white or almost white crystalline powder; odourless; tasteless. Sparingly soluble in acetone or dioxane; slightly soluble in ethanol; insoluble in water or petroleum ether.

Specific optical rotation +80° to +88°, in a solution of about 10 mg per ml in dioxane (Appendix VI E).

Identification (1) Dissolve about 10 mg in 1 ml of methanol by warming, add 1 ml of hot alkaline cupric tartrate TS; a red precipitate is produced.

(2) The retention time of principal peak of the substance being examined is identical with that of principal peak of the reference solution in the chromatogram obtained in Assay.

(3) The infrared absorption spectrum (Appendix IV C) is

concordant with the reference spectrum of fluocinonide acetate (Appendix XVI).

(4) It yields the reaction characteristic of organic fluorine compounds (Appendix III).

Fluorine Carry out the test for fluorine (Appendix VIII E): not less than 7.0%.

Related substances Carry out the method for thin-layer chromatography (Appendix V B), using silica gel G as the coating substance and a mixture of chloroform-methanol (97:3) as the mobile phase. Apply separately to the plate 5 μ l each of two solutions in chloroform-methanol (9:1) containing (1) 3 mg per ml, (2) 60 μ g per ml of the substance being examined. After developing and removal of the plate, dry in air and then at 105°C for 10 minutes, cool and spray with alkaline tetrazolium blue TS. Examine immediately, not more than 2 secondary spots are obtained in the chromatogram of solution (1); and no secondary spot is more intense than the principal spot in the chromatogram obtained with solution (2).

Loss on drying When dried to constant weight at 105°C, loses not more than 0.5% of its weight (Appendix VIII L).

Residue on ignition Not more than 0.1% (Appendix VIII N).

Selenium Carry out the limit test for selenium (Appendix VIII D), using 50 mg of the substance being examined. Complies with the requirement (0.010%).

Assay Carry out the method for high performance liquid chromatography (Appendix V D), using a column packed with octadecylsilane bonded silica gel and a mixture of methanol-acetonitrile-water (60:10:30) as the mobile phase. Detection wavelength is 240 nm and the number of theoretical plates of the column is not less than 2000, calculated with reference to the peak of fluocinonide. The resolution factor between the peaks of fluocinonide and internal standard is not less than 4.0.

Internal Standard Solution Dissolve hydrocortisone in mobile phase to produce a solution of 0.12 mg per ml.

Procedure Dissolve about 14 mg of fluocinonide CRS, accurately weighed, in a 100 ml volumetric flask, with 60 ml of methanol and 10 ml of acetonitrile, dilute with water to volume, mix well, use as the reference solution. Measure accurately 5 ml each of the reference solution and the internal standard solution into a 50 ml volumetric flask, dilute with mobile phase to volume, mix well, inject 20 μ l of the resulting solution into the column, record the chromatogram. Repeat the operations using a quantity of the substance being examined instead of fluocinonide CRS. Calculate the content of $C_{26}H_{32}F_2O_7$ with respect to the peak area in the chromatogram by internal standard method.

Category Corticosteroid.

Storage Preserve in tightly closed containers.

Preparation Fluocinonide Cream

Fluocinonide Cream

Fluocinonide Cream contains not less than 85.0% and not more than 115.0% of the labelled amount of fluocinonide ($C_{26}H_{32}F_2O_7$).

Description White cream.

Identification The retention time of principal peak of the substance being examined is identical with that of principal

peak of the reference solution in the chromatogram obtained in Assay.

Other requirements Complies with the general requirements for cream (Appendix I F).

Assay Carry out the method for high performance liquid chromatography (Appendix V D), using a column packed with octadecylsilane bonded silica gel and a mixture of methanol-water-ether (62:38:2) as the mobile phase. Detection wavelength is 240 nm, and the number of the theoretical plates of the column is not less than 2500, calculated with reference to the peak of fluocinonide. The resolution factor between the peaks of fluocinonide and internal standard complies with related requirements.

Internal Standard Solution Dissolve an accurately weighed quantity of norethisterone CRS in methanol to produce a solution of about 0.15 mg per ml.

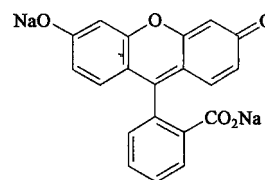
Procedure Dissolve an accurately weighed quantity of fluocinonide CRS in methanol to produce a solution of about 0.125 mg per ml as the reference solution. Transfer 10 ml of the reference solution and 5 ml of the internal standard solution, accurately measured, to a 50 ml volumetric flask, dilute with methanol to volume, mix well, inject 20 μ l into the column, record the chromatogram. Weigh accurately a quantity of the substance being examined equivalent to about 1.25 mg of fluocinonide, add 30 ml of methanol, heat in a water bath at 80°C for 2 minutes, shake to dissolve fluocinonide. Cool to room temperature, add 5 ml of internal standard solution, accurately measured, dilute with methanol to volume and mix well. Allow the mixture to cool in an ice bath for at least 2 hours, filter quickly, inject 20 μ l of the successive filtrate into the column. Calculate the content of $C_{26}H_{32}F_2O_7$ with respect to the peak area in the chromatogram by internal standard method.

Category As described under Fluocinonide.

Strength (1) 10 g: 2.5 mg (2) 20 g: 5 mg

Storage Preserve in tightly closed containers, stored in a cool place.

Fluorescein Sodium



$C_{20}H_{10}Na_2O_5$ 376.28

[518-47-8]

Fluorescein Sodium is 3', 6''-dihydroxy-spiro [isobenzofuran-1 (3H), 9'-[9H] xanthene]-3-one disodium salt. It contains not less than 98.5% of $C_{20}H_{10}Na_2O_5$, calculated on the dried basis.

Description An orange-red powder; odourless; almost tasteless; Hygroscopic.

Freely soluble in water; sparingly soluble in ethanol.

Identification (1) Place 1 drop of a solution (1→2000) on a piece of filter paper, a yellow spot is produced, when exposed while moist to bromine vapour for 1 minute and then to ammonia vapour, the spot becomes deep pink.

(2) An aqueous solution is strongly fluorescent, even in extreme dilution; the fluorescence disappears when the

solution is acidified and reappears when it is made alkaline.

(3) The infrared absorption spectrum (Appendix IV A) is concordant with the reference spectrum of fluorescein sodium (Appendix XVI).

(4) The incinerated residue yields the reactions characteristic of sodium salts (Appendix III).

Chloride Dissolve 0.10 g in 50 ml of water, carry out the limit test for chlorides (Appendix VIII A), using 10 ml of the resulting solution. Any opalescence produced is not more pronounced than that of a reference using 7.0 ml of sodium chloride standard solution (0.35%).

Sulfate Carry out the limit test for sulfates (Appendix VIII B), using 25 ml of the solution described under test for Chloride. Any opalescence produced is not more pronounced than that of a reference using 2.5 ml of potassium sulfate standard solution (0.50%).

Loss on drying When dried to constant weight at 105°C, loses not more than 7.0% of its weight (Appendix VIII L).

Zinc Dissolve 0.10 g in 10 ml of a saturated solution of sodium chloride, add 2 ml of dilute hydrochloric acid, mix well and filter. Add 1 ml of potassium ferrocyanide TS to the filtrate, no turbidity is produced.

Assay Dissolve about 0.5 g, accurately weighed, in 20 ml of water, add 5 ml of dilute hydrochloric acid and extract with four portions, each of 20 ml, of a mixture of *n*-butanol-chloroform (1:1). Wash the combined extracts with 10 ml of water, extract the washings with 5 ml of a mixture of *n*-butanol-chloroform (1:1), and transfer the combined extracts to a container, previously dried to constant weight at 105°C. Evaporate the extracts to dryness on a water bath in current air. Dissolve the residue in 10 ml of ethanol, evaporate to dryness on a water bath, and dry to constant weight at 105°C, weigh accurately. Each g of residue is equivalent to 1.132 g of $C_{20}H_{10}Na_2O_5$.

Category Diagnostic agent.

Storage Preserve in tightly closed containers.

Preparation Fluorescein Sodium Injection

Fluorescein Sodium Injection

Fluorescein sodium Injection is a sterile solution of fluorescein sodium in Water for Injection. It contains not less than 90.0% and not more than 110.0% of the labelled amount of fluorescein sodium ($C_{20}H_{10}Na_2O_5$).

Description A brown clear liquid.

Identification Complies with tests (1) and (2) for Identification described under Fluorescein Sodium.

pH value 8.0-9.8 (Appendix VI H).

Pyrogens Complies with the test for pyrogens (Appendix XI D), using 2.5 ml (for strength 0.3 g) or 2.5 ml of a dilute solution (for strength 0.6 g) (diluted with equal volume of Water for Injection) per kg of rabbit's weight.

Other requirements Complies with the general requirements for injections (Appendix I B).

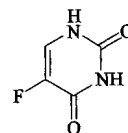
Assay Dilute a quantity equivalent to about 0.5 g of fluorescein sodium with water to 20 ml, shake well. Carry out the Assay described under Fluorescein Sodium, beginning at the words "add 5 ml of dilute hydrochloric acid until fluorescein is precipitated...".

Category As described under Fluorescein Sodium.

Strength (1) 3 ml:0.3 g (2) 3 ml:0.6 g

Storage Preserve in well closed containers.

Fluorouracil



$C_4H_3FN_2O_2$ 130.08

[51-21-8]

Fluorouracil is 5-fluoro-2,4 (1*H*, 3*H*)-pyrimidinedione. It contains not less than 97.0% and not more than 103.0% of $C_4H_3FN_2O_2$, calculated on the dried basis.

Description White or almost white crystals or a crystalline powder.

Sparingly soluble in water; slightly soluble in ethanol; practically insoluble in chloroform; soluble in dilute hydrochloric acid or sodium hydroxide solution.

Identification (1) Shake 5 ml of the water solution (1→100) with 1 ml of bromine TS, the colour of bromine is disappeared; add 2 ml of barium hydroxide TS, a violet precipitate is produced.

(2) Rotate the test tube containing about 1 ml of saturated solution of chromium trioxide in sulfuric acid, the solution is spread evenly on the wall; add about 2 mg of the finely powdered substance being examined, heat gently and rotate the test tube, the solution can no longer be spread evenly on the wall, but attached to it with greasy substance.

(3) The light absorption of the solution obtained in the Assay exhibits a maximum at 265 nm and a minimum at 232 nm (Appendix IV A).

(4) The infrared absorption spectrum (Appendix XVI A) is concordant with the reference spectrum of fluorouracil (Appendix XVI).

Chloride Dissolve 2.0 g, with heating, in 100 ml of water, cool and filter. Carry out the limit test for chlorides (Appendix VIII A), using 25 ml of the filtrate. Any opalescence produced is not more pronounced than that of a reference using 7.0 ml of sodium chloride standard solution (0.014%).

Sulfate Carry out the limit test for sulfates (Appendix VIII B), using 50 ml of the filtrate obtained in the test for chlorides. Any opalescence produced is not more pronounced than that of a reference using 2.0 ml of potassium sulfate standard solution (0.02%).

Fluorine Weigh accurately about 15 mg, Carry out the method for determination of fluorine (Appendix VIII E). It contains not less than 13.1% and not more than 14.6% of fluorine.

Loss on drying When dried to constant weight at 105°C, loses not more than 0.5% of its weight (Appendix VIII L).

Heavy metals Carry out the limit test for heavy metals (Appendix VIII H, method 3), using 0.50 g; not more than 0.002%.

Assay To a quantity, accurately weighed, add 0.1 mol/L hydrochloric acid solution to produce a solution of 10 µg per ml and measure the absorbance at 265 nm (Appendix IV A).

Calculate the content of $C_4H_3FN_2O_2$, taking 552 as the value of A (1%, 1 cm).

Category Antineoplastic.

Storage Preserve in tightly closed containers, protected from light.

Preparation (1) Fluorouracil Cream
(2) Fluorouracil Injection

Fluorouracil Cream

Fluorouracil Cream contains not less than 90.0% and not more than 110.0% of the labelled amount of fluorouracil ($C_4H_3FN_2O_2$).

Description A white cream.

Identification Place 1 g of the cream in a beaker, add 35 ml of water and melt by heating on a water bath, cool in an ice bath, filter and evaporate the filtrate to dryness. The residue complies with tests (1) and (2) for Identification described under Fluorouracil.

Other requirements Complies with the general requirements for cream (Appendix I F).

Assay Place a quantity of the cream, accurately weighed, equivalent to about 0.1 g of fluorouracil in a beaker, add 1 g of sodium chloride and melt by heating on a water bath, add 50 ml of water, boil and allow to cool. Filter and transfer the filtrate to a 200 ml volumetric flask, repeat the extraction three times, wash the filter, transfer the washings into the flask and dilute with water to volume. Carry out the method for determination of nitrogen (Appendix VII D, method 1), using 100 ml of the resulting solution, accurately measured. Each ml of sulfuric acid (0.05 mol/L) VS is equivalent to 6.504 mg of $C_4H_3FN_2O_2$.

Category As described under Fluorouracil.

Strength (1) 4 g:20 mg (2) 4 g:100 mg

Storage Preserve in tightly closed containers, stored in a cool place.

Fluorouracil Injection

Fluorouracil Injection is a sterile solution of fluorouracil in Water for Injection. It contains not less than 93.0% and not more than 107.0% of the labelled amount of fluorouracil ($C_4H_3FN_2O_2$).

Description A clear, colourless or almost colourless liquid.

Identification (1) To 2 ml add 1 ml of bromine TS, shake, the colour of bromine is discharged, then add 2 ml of barium hydroxide TS, a violet precipitate is produced.

(2) Rotate the test tube containing about 1 ml of saturated solution of chromium in trioxide-sulfuric acid, the solution is spread evenly on the wall; Add 2 drops of the injection and heat gently, the solution can no longer be spread evenly on the wall, but attached to it with greasy substance.

(3) The light absorption of the solution obtained in the Assay exhibits a maximum at 265 nm and a minimum at 232 nm (Appendix IV A).

pH value 8.4-9.2 (Appendix VI H).

Other requirements Complies with the general requirements for Injections (Appendix I B).

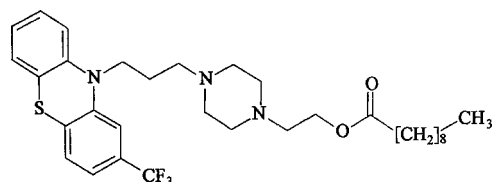
Assay Dilute an accurately measured quantity with hydrochloric acid solution (9→1000) to produce a solution of 10 µg per ml and measure the absorbance at 265 nm (Appendix IV A). Calculate the content of $C_4H_3FN_2O_2$, taking 552 as the value of A (1%, 1 cm).

Category As described under Fluorouracil.

Strength (1) 5 ml:0.125 g (2) 10 ml:0.25 g

Storage Preserve in tightly closed containers, protected from light.

Fluphenazine Decanoate



$C_{32}H_{44}F_3N_3O_2S$ 591.78

[69-23-8]

Fluphenazine Decanoate is 4-[3-[2-(trifluoromethyl)-10-*H*-phenothiazin-10-yl]propyl]-1-piperazine ethanol decanoate. It contains not less than 98.0% and not more than 102.0% of $C_{32}H_{44}F_3N_3O_2S$, calculated on the dried basis.

Description A pale yellow to yellowish-brown viscous liquid; the colour is intensified gradually on exposure to light.

Very soluble in methanol, ethanol, chloroform, anhydrous ether or vegetable oil; insoluble in water.

Identification (1) Mix well about 15-20 mg with 0.1 g of sodium carbonate and 0.1 g of potassium carbonate in a crucible. Ignite at 600°C for 15-20 minutes, cool. Add 2 ml of water to dissolve the residue, acidify with hydrochloric acid solution (1→2). Filter, add 0.5 ml of zirconyl alizarin TS to the filtrate, a yellow colour is produced.

(2) Dissolve about 50 mg in 2 ml of methanol, add 3 ml of 0.1% palladium chloride solution, a red precipitate is produced and the colour is intensified on adding excess palladium chloride solution.

(3) The light absorption of a 10 µg per ml solution in ethanol exhibits a maximum at 260 nm (Appendix IV A).

(4) The infrared absorption spectrum (Appendix IV C) is concordant with the reference spectrum of fluphenazine decanoate (Appendix XVI).

Colour of acetone solution The colour of a 5% solution in acetone is not more intense than that of reference solution Y_4 (Appendix IX A, method 1).

Related substances Carry out the method for thin-layer chromatography (Appendix V B), using silica gel GF₂₅₄ as the coating substance and a mixture of acetone-cyclohexane-concentrated ammonia solution (80:30:5) as the mobile phase. Apply separately to the plate 20 µl each of two solutions in methanol containing (1) 25 mg per ml of the substance being examined, (2) 0.50 mg per ml of fluphenazine hydrochloride CRS. After developing and removal of the plate, allow it to dry in air and examine under ultraviolet light (254 nm). Then spray the plate with sulfuric acid solution (1→2) and examine in day light. By both methods of visualisation, any spot other than the principal spot in the chromatogram obtained with solution (1) is not more intense than the principal spot obtained with

solution (2).

Loss on drying When dried in vacuum at 60°C for 3 hours, loses not more than 1.0% of its weight. (Appendix VIII L).

Residue on ignition Not more than 0.2% (Appendix VIII N), using 1.0 g.

Heavy metals Carry out the limit test for heavy metals (Appendix VIII H, method 2), using the residue obtained in the test for Residue on ignition; not more than 0.002%.

Assay Dissolve about 0.25 g, accurately weighed, in 20 ml of glacial acetic acid, add 1 drop of crystal violet IS. Titrate with perchloric acid (0.1 mol/L) VS until the solution becomes bluish-green. Perform a blank determination and make any necessary correction. Each ml of perchloric acid (0.1 mol/L) VS is equivalent to 29.59 mg of $C_{32}H_{44}F_3N_3O_2S$.

Category Antipsychotic.

Storage Preserve in tightly closed containers, protected from light.

Preparation Fluphenazine Decanoate Injection

Fluphenazine Decanoate Injection

Fluphenazine Decanoate Injection is a sterile solution of fluphenazine decanoate in oil for injection. It contains not less than 90.0% and not more than 110.0% of the labelled amount of fluphenazine decanoate ($C_{32}H_{44}F_3N_3O_2S$).

Description A clear yellow or orange-yellow oily liquid.

Identification Complies with tests (1), (2) and (3) for Identification described under Fluphenazine Decanoate.

Colour The colour is not more intense than that of the reference solution of Y_{10} (Appendix IX A, method 1).

Related substances Carry out the method for thin-layer chromatography (Appendix V B), using silica gel GF₂₅₄ as the coating substance and a plate of 20 cm × 20 cm in size. For the first development use chloroform as the mobile phase. Apply 1 µl of the injection to an appropriate position on right corner at the bottom of the plate and develop until the solvent reaches at a distance of 12 cm from the upper edge of the plate. After removal of the plate, allow it to dry in air. Turn the plate clockwise through an angle of 90°. Apply 10 µl of a 0.02% solution of fluphenazine hydrochloride CRS in methanol to an appropriate position on right corner at the bottom of the plate. For the second development use a mixture of acetone-cyclohexane-concentrated ammonia solution (80 : 30 : 5) as the mobile phase. After developing and removal of the plate, dry in air and examine under ultraviolet light (254 nm). Spray the plate with sulfuric acid solution (1 → 2) and examine in day light. By both methods of visualization, any spot other than the principal spot in the chromatogram obtained with the injection is not more intense than the principal spot obtained with the reference solution.

Other requirements Complies with the general requirements for injections (Appendix I B).

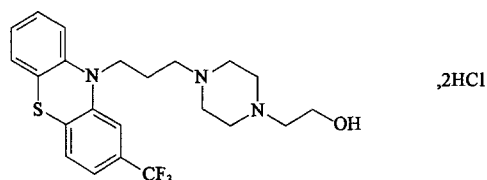
Assay Dissolve about 5 ml with a "to contain" pipet, accurately measured, in 20 ml of glacial acetic acid, and add 1 drop of crystal violet IS. Titrate with perchloric acid (0.1 mol/L) VS until the colour changes to bluish-green. Perform a blank determination and make any necessary correction. Each ml of perchloric acid (0.1 mol/L) VS is equivalent to 29.59 mg of $C_{32}H_{44}F_3N_3O_2S$.

Category As described under Fluphenazine Decanoate.

Strength 1 ml : 25 mg

Storage Preserve in well closed containers, protected from light, stored in a cool place.

Fluphenazine Hydrochloride



$C_{22}H_{26}F_3N_3OS \cdot 2HCl$ 510.44

[69-23-8]

Fluphenazine Hydrochloride is 4-[3-[2-(trifluoromethyl)-10H-phenothiazin-10-yl]propyl]-1-piperazineethanol dihydrochloride. It contains not less than 98.0% and not more than 102.0% of $C_{22}H_{26}F_3N_3OS \cdot 2HCl$, calculated on the dried basis.

Description A white or almost white crystalline powder; odourless; taste, slightly bitter; colour changed easily on exposure to light.

Freely soluble in water; sparingly soluble in ethanol; slightly soluble in acetone; insoluble in benzene and ether.

Melting range 226-233°C, with decomposition (Appendix VI C).

Specific absorbance Measure the light absorbance at 255 nm (Appendix IV A) of a solution of 10 µg per ml in hydrochloric acid solution (9 → 1000), the value of A (1%, 1 cm) is 553-593.

Identification (1) Rotate the test tube containing about 1 ml of saturated solution of chromium trioxide in sulfuric acid, the solution is spread evenly on the wall; add about 2 mg of the substance being examined, heat gently and rotate the test tube, the solution can no longer be spread evenly on the wall, but attached to it with greasy substance.

(2) Dissolve 5 mg in 5 ml of sulfuric acid, a pale red colour is produced, which changes to reddish-brown on warming.

(3) The infrared absorption spectrum (Appendix IV C) is concordant with the reference spectrum of fluphenazine hydrochloride (Appendix XVI).

(4) The aqueous solution yields the reactions characteristic of chlorides (Appendix III).

Acidity Dissolve 1.0 g in 20 ml of water, pH 1.9-2.3 (Appendix VI H).

Loss on drying When dried to constant weight at 80°C, loses not more than 1.0% of its weight (Appendix VIII L).

Residue on ignition Ignite 1.0 g, not more than 0.2% (Appendix VIII N).

Heavy metals Carry out the limit test for heavy metals (Appendix VIII H, method 2), using the residue obtained in the test for Residue on ignition; not more than 0.002%.

Assay Dissolve about 0.3 g, accurately weighed, in 20 ml of glacial acetic acid and 5 ml of mercuric acetate TS, add 1 drop of crystal violet IS. Titrate with perchloric acid (0.1 mol/L) VS until the colour changes to bluish-green. Perform a blank determination and make any necessary correction. Each ml of perchloric acid (0.1 mol/L) VS is

equivalent to 25.52 mg of $C_{22}H_{26}F_3N_3OS \cdot 2HCl$.

Category Antipsychotic agent.

Storage Preserve in tightly closed containers, protected from light.

Preparation (1) Fluphenazine Hydrochloride Tablets
(2) Fluphenazine Hydrochloride Injection

Fluphenazine Hydrochloride Injection

Fluphenazine Hydrochloride Injection is a sterile solution of Fluphenazine Hydrochloride in Water for Injection. It contains not less than 95.0% and not more than 110.0% of the labelled amount of fluphenazine hydrochloride ($C_{22}H_{26}F_3N_3OS \cdot 2HCl$).

Description A clear, colourless liquid.

Identification (1) Mix a quantity equivalent to about 20 mg of fluphenazine hydrochloride with 100 mg of sodium carbonate and 100 mg of potassium carbonate. Gently, with caution, heat the mixture, then evaporate to dryness, then ignite at 600°C until the incineration complete. Dissolve the residue in 2 ml of water, acidify with hydrochloric acid solution (1:2) and filter. Add 0.5 ml of zirconium alizarin TS to the filtrate; the colour of the solution changes from red to yellow.

(2) To a quantity equivalent to about 3 mg of fluphenazine hydrochloride add a few drops of sulfuric acid; a reddish yellow colour appears which changes to green on warming.

(3) Yields the reactions characteristic of chloride (Appendix III).

pH value 4.5-5.5 (Appendix VI H).

Other requirements Complies with the general requirements for injection (Appendix I B).

Assay Transfer an accurately measured quantity equivalent to about 50 mg of fluphenazine hydrochloride to a 50 ml beaker. Add 2 ml of 6 mol/L hydrochloric acid solution and mix well. Heat to 70-80°C on a water bath, add dropwise 8 ml of silicotungstic acid TS, allow to stand for 2 minutes. Filter through a tared sintered glass crucible, wash the precipitate with 20 ml of hydrochloric acid solution (1→20) in portions, then with three 5 ml portions of water. Dry to constant weight at 105°C and weigh accurately. Each g of precipitate is equivalent to 0.2721 g of $C_{22}H_{26}F_3N_3OS \cdot 2HCl$.

Category As described under Fluphenazine Hydrochloride.

Strength 2 ml:10 mg

Storage Protected from light.

Fluphenazine Hydrochloride Tablets

Fluphenazine Hydrochloride Tablets contain not less than 90.0% and not more than 110.0% of the labelled amount of fluphenazine hydrochloride ($C_{22}H_{26}F_3N_3OS \cdot 2HCl$).

Description Sugar-coated tablets with white core.

Identification To a quantity of powdered tablets with coating removed equivalent to about 30 mg of fluphenazine hydrochloride add 15 ml of ethanol, shake to dissolve fluphenazine hydrochloride and filter. Evaporate the filtrate to dryness. The residue complies with the tests (1), (2),

(4) for Identification described under Fluphenazine Hydrochloride.

Content uniformity Comply with the requirements (Appendix X E).

Triturate 1 tablet (with coating removed) with 70 ml of hydrochloric acid solution (9→1000), transfer to a 100 ml volumetric flask, shake thoroughly to dissolve fluphenazine hydrochloride, dilute with the same solvent to volume and filter. Measure accurately 10 ml of the successive filtrate to a 25 ml volumetric flask, dilute with the same solvent to volume and mix well. Determine the content of fluphenazine hydrochloride as described under the Assay.

Other requirements Comply with the general requirements for tablets (Appendix I A).

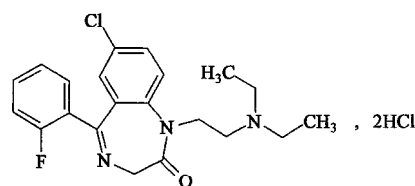
Assay Weigh accurately and powder 20 tablets with coating removed. Weigh accurately a quantity of the powder equivalent to about 10 mg of fluphenazine hydrochloride into a 100 ml volumetric flask, add about 70 ml of hydrochloric acid solution (9→1000), shake 30 minutes to dissolve fluphenazine hydrochloride, dilute with the same solvent to volume. Mix well and filter. Measure accurately 5 ml of the successive filtrate to a 50 ml volumetric flask, dilute with the same solvent to volume and mix well. Measure the light absorbance of the resulting solution at 255 nm (Appendix IV A). Calculate the content of $C_{22}H_{26}F_3N_3OS \cdot 2HCl$, taking 573 as the value of A (1%, 1 cm).

Category As described under Fluphenazine Hydrochloride.

Strength 2 mg

Storage Preserve in tightly closed containers, protected from light.

Flurazepam Hydrochloride



$C_{21}H_{23}ClFN_3O \cdot 2HCl$ 460.81 [1172-18-5]

Flurazepam Hydrochloride is 7-chloro-1-[2-(diethylamino)ethyl]-5-(*o*-fluorophenyl)-1,3-dihydro-2*H*-1,4-benzodiazepin-2-one dihydrochloride. It contains not less than 98.5% of $C_{21}H_{23}ClFN_3O \cdot 2HCl$, calculated on the dried basis.

Description An almost white to pale yellow crystalline powder; almost odourless; taste, bitter; hygroscopic; deteriorated on exposure to light. Very soluble in water; freely soluble in methanol; soluble in ethanol or chloroform.

Identification (1) Dissolve about 10 mg in 1 ml of water, add potassium iodobismuthate TS, an orange red precipitate is produced.

(2) The light absorption of a solution of 10 µg per ml in methanolic sulfuric acid solution (1→36) exhibits three maxima at 239 nm, 284 nm and 363 nm, the ratio of the absorbance at 239 nm to that at 284 nm is 1.95-2.50.

(3) The infrared absorption spectrum (Appendix IV C) is concordant with the reference spectrum of flurazepam hydrochloride (Appendix XVI).

(4) The aqueous solution yields the reactions characteristic

of chlorides (Appendix III).

Fluorides *Reference solution* Dissolve 221 mg of sodium fluoride, accurately weighed, in 20 ml of water in a 100 ml volumetric flask, add 1 ml of sodium hydroxide solution (1→2500), dilute with water to volume and mix well. Store in a well closed plastic container. (each ml is equivalent to 1 mg of F).

Test solution Dissolve about 1 g, accurately weighed, in sodium citrate BS (pH 5.25) in a 100 ml volumetric flask and dilute to volume, mix well.

Procedure Dilute a quantity of the reference solution with sodium citrate BS (pH 5.25) to produce solutions of 1, 3, 5 and 10 µg per ml as standard solutions. Place a quantity each of the standard solutions and the test solution in separate 150 ml plastic beakers containing stirring rod coated with polytetrafluoro-ethylene. Measure the electric potentials of the solutions with a potentiometer equipped with fluoride selective electrode and calomel electrode (use a saturated solution of potassium chloride in 30% isopropanol as the salt bridge). A calibration curve produced by plotting the concentrations of fluoride (µg/ml) against the corresponding electric potentials (mV) with semilogarithmic paper. Measure the potential of the test solution, the content of fluoride is not more than 0.05%.

Related substances Protected from light throughout the procedure. Carry out the method for thin-layer chromatography (Appendix V B), using silica GF₂₅₄ as the coating substance and a mixture of ether-diethylamine (150:4) as the mobile phase. Apply separately to the plate 10 µl each of three solutions in methanol containing (1) 0.10 g of the substance being examined per ml, (2) 0.1 mg of 7-chloro-5-(2-fluorophenyl)-1,3-dihydro-2H-1,4-benzodiazepin-2-one CRS per ml, (3) 0.1 mg of 5-hydro-2-(2-diethylaminoethyl (amino)-2'-fluorobenzophenone hydrochloride CRS per ml. Equilibrate by lining the inner wall of the chromatographic chamber with filter paper, previously soaked by the mobile phase. Place the freshly prepared mobile phase in the chamber, develop immediately. After developing and removal of the plate, allow to stand in air for 5 minutes. Repeat developing with new freshly prepared mobile phase, after removal of the plate, dry in air and examine under ultraviolet light (254 nm). The colour of any secondary spot, corresponding to the spots obtained with reference solution (2) or (3), in the chromatogram obtained with solution (1) is not more intense than that of the principal spot obtained with solution (2) or (3) (0.1%).

Loss on drying When dried at 105°C for 4 hours, loses not more than 1.5% of its weight (Appendix VIII L).

Residue on ignition Not more than 0.1% (Appendix VIII N); using 1.0 g.

Heavy metals Carry out the limit test for heavy metals (Appendix VIII, method 2), using the residue obtained in the test for Residue on ignition; not more than 0.002%.

Assay Dissolve about 0.2 g, accurately weighed, in 20 ml of acetic anhydride in a 100 ml beaker on warming, add 5 ml of mercuric acetate TS. Carry out the method for potentiometric titration with glass-calomel electrode system, titrate with perchloric acid (0.1 mol/L) VS. Perform a blank determination and make any necessary correction. Each ml of perchloric acid (0.1 mol/L) VS is equivalent to 23.04 mg of C₂₁H₂₃ClFN₃O • 2HCl.

Category Antianxiety agent.

Storage Preserve in tightly closed containers, stored in a cool place and protected from light.

Preparation Flurazepam Hydrochloride Capsules

Flurazepam hydrochloride Capsules

Flurazepam hydrochloride Capsules contain not less than 90.0% and not more than 110.0% of the labelled amount of flurazepam hydrochloride (C₂₁H₂₃ClFN₃O • 2HCl).

Identification (1) Shake a quantity of the contents equivalent to about 10 mg of flurazepam hydrochloride with 2 ml of water and filter. The filtrate complies with test (1) and (4) for Identification described under Flurazepam Hydrochloride.

(2) Measure the light absorption of the solution obtained in Assay, the ratio of the absorbance at 239 nm to that at 284 nm is 1.95-2.50.

Content uniformity Protect from light throughout the procedure. Comply with the requirements for content uniformity (Appendix X E). Transfer the content of 1 capsule to a 100 ml volumetric flask, wash the shell with methanolic sulfuric acid solution (1→36), transfer the washings to the same volumetric flask. Shake with about 70 ml of methanolic sulfuric acid solution (1→36) to dissolve flurazepam hydrochloride, dilute to volume with the same solvent, mix well and filter. Transfer 2 ml of the successive filtrate, accurately measured, to a 25 ml volumetric flask, dilute to volume with methanolic sulfuric acid solution (1→36) and mix well. Carry out the procedure described under Assay, beginning at the words "Measure the absorbance of the resulting solution..." (Appendix IV A).

Related substances Protect from light throughout the procedure. Carry out the method for thin-layer chromatography (Appendix V B), using silica GF₂₅₄ as the coating substance and a mixture of ether-diethylamine (150:4) as the mobile phase. Apply separately to the plate 20 µl each of the following solutions. For solution (1) shake a quantity of the contents equivalent to about 10 mg of flurazepam hydrochloride with 2 ml of methanol, centrifuge and use the supernatant solution. Solution (2) contains 0.05 mg of 7-chloro-5-(2-fluorophenyl)-1,3-dihydro-2H-1,4-benzodiazepin-2-one CRS per ml in methanol. Solution (3) contains 0.05 mg of 5-hydro-2-(2-diethylaminoethyl (amino)-2'-fluorobenzophenone hydrochloride CRS per ml in methanol. Add the mobile phase to the chromatographic chamber, equilibrate by lining the inner wall of the chamber with filter paper, previously soaked by the mobile phase. Place the freshly prepared mobile phase in the chamber and develop immediately. After developing and removal the plate, allow to stand in air for 5 minutes. Repeat developing with another freshly prepared mobile phase. After removal of the plate, dry in air and examine under ultraviolet light (254 nm). The colour of any secondary spot, corresponding to the spots obtained with reference solution (2) or (3), in the chromatogram obtained with solution (1) is not more intense than that of the principal spot obtained with solution (2) or (3).

Other requirements Comply with the general requirements for capsules (Appendix I E).

Assay Protect from light throughout the procedure. Weigh accurately 20 capsules, remove the contents, weigh accurately the shell of each capsule and calculate the average content of the capsules. Weigh accurately a quantity of the mixed contents equivalent to about 10 mg of flurazepam hydrochloride in 100 ml volumetric flask, shake with about 80 ml of methanolic sulfuric acid solution (1→36) to dissolve flurazepam hydrochloride, dilute with methanolic

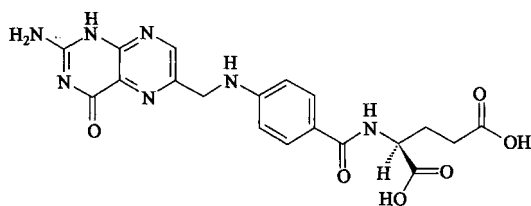
sulfuric acid solution (1 → 36) to volume, mix well and filter. Dilute a quantity of successive filtrate, accurately measured, with methanolic sulfuric acid solution (1 → 36) to produce a solution of 10 µg per ml. Measure the absorbance of the resulting solution at 239 nm (Appendix IV A). Repeat the operation, using a solution containing 10 µg of flurazepam hydrochloride CRS per ml, in methanolic sulfuric acid solution (1 → 36). Calculate the content of $C_{21}H_{23}ClFN_3O \cdot 2HCl$.

Category As described under Flurazepam Hydrochloride.

Strength 15 mg

Storage Preserve in tightly closed containers, stored in a dry place and protected from light.

Folic Acid



$C_{19}H_{19}N_7O_6$ 441.40

[59-30-3]

Folic Acid is N-[4-[(2-amino-1,4-dihydro-4-oxo-6-pteridiny] methyl amino] benzoyl]-L-glutamic acid. It contains not less than 95.0% and not more than 102.0% of $C_{19}H_{19}N_7O_6$, calculated on the anhydrous basis.

Description A yellow or orange-yellow crystalline powder; odourless; tasteless.

Insoluble in water, ethanol, acetone, chloroform or ether; freely soluble in dilute solution of sodium hydroxide or sodium carbonate.

Identification (1) Dissolve about 0.2 mg in 10 ml of 0.4% sodium hydroxide solution with shaking, add 1 drop of potassium permanganate TS and mix well; the solution becomes bluish-green and shows a bluish-green fluorescence under ultraviolet light.

(2) The light absorption of a solution containing 10 µg per ml in 0.4% sodium hydroxide solution exhibits maxima at 256 nm, 283 nm and 365 nm \pm 4 nm, the ratio of the absorbance at 256 nm to that at 365 nm is 2.8-3.0 (Appendix IV A).

(3) The infrared absorption spectrum (Appendix IV C) is concordant with the reference spectrum of folic acid (Appendix XVI).

Water To about 0.1 g, accurately weighed, add 5 ml of a mixture of chloroform-dehydrated methanol (4:1); carry out the determination of water (Appendix VIII M, method 1 A); not more than 8.5%.

Residue on ignition Not more than 0.1% (Appendix VIII N).

Assay Carry out the method for high performance liquid chromatography (Appendix V D), using a column packed with octadecylsilane bonded silica gel. Dissolve 6.8 g of potassium dihydrogen phosphate in 70 ml of 0.1 mol/L potassium hydroxide solution, dilute with water to 850 ml and adjust to pH 6.3 \pm 0.1, then add 80 ml of methanol and dilute with water to 1000 ml as the mobile phase. Detection wavelength is 254 nm.

Procedure Dissolve about 5 mg, accurately weighed, in 15 ml of 0.5% ammonia solution in a 25 ml volumetric flask, dilute with water to volume and mix well. Inject 10 µl into the column and record the chromatogram. Repeat the operation, using folic acid CRS instead of the substance being examined. Calculate the content of $C_{19}H_{19}N_7O_6$ with respect to the peak area obtained in the chromatogram by the external standard method.

Category Vitamin.

Storage Preserve in tightly closed containers, protected from light.

Preparation Folic Acid Tablets

Folic Acid Tablets

Folic Acid Tablets contain not less than 90.0% and not more than 110.0% of the labelled amount of folic acid ($C_{19}H_{19}N_7O_6$).

Description Yellow or orange-yellow tablets.

Identification (1) To a quantity of the powdered tablets equivalent to about 0.4 mg of folic acid add 20 ml of 0.4% sodium hydroxide solution, shake to dissolve folic acid and filter. The filtrate complies with test (1) for Identification described under Folic Acid, using 10 ml.

(2) Comply with test (2) for Identification described under Folic Acid, using the remaining filtrate obtained in Identification test (1) diluted with an equal volume of 0.4% sodium hydroxide solution.

Content uniformity Comply with the requirements for content uniformity (Appendix X E).

(1) Place 1 tablet in a 25 ml volumetric flask, proceed as described under Assay, beginning at the words "transfer to a 25 ml volumetric flask...". (strength 5 mg).

(2) Place 1 tablet in a 10 ml volumetric flask, add 5 ml of 0.5% ammonia solution and heat on a water bath for 20 minutes to dissolve folic acid with shaking. Allow to cool, dilute with water to volume, mix well and filter, take the successive filtrate as the test solution. Dissolve about 10 mg of folic acid CRS, accurately weighed, in 50 ml of 0.5% ammonia solution and mix well. Transfer 2 ml to a 10 ml volumetric flask, dilute with water to volume, mix well, take the solution as the reference solution. Carry out the method described under Assay, inject 10 µl of the resulting solutions separately into the column, calculate the content of $C_{19}H_{19}N_7O_6$ (strength 0.4 mg).

Dissolution (1) Carry out the dissolution test (Appendix X C, method 1), using 900 ml of phosphate BS (pH 6.8) as the dissolution medium, adjust the rotational speed of the basket to 100 rpm. Withdraw a quantity of the solution after exactly 45 minutes and filter, take the successive filtrate as the test solution. Dissolve a quantity of folic acid CRS in phosphate BS (pH 6.8) to produce a solution of 6 µg per ml. Measure the absorbance of the resulting solutions at 281 nm (Appendix IV A). Calculate the dissolution of $C_{19}H_{19}N_7O_6$ from each tablet. Not less than 70% of the labelled amount is dissolved (strength 5 mg).

(2) Carry out the dissolution test (Appendix X C, method 3), using 100 ml of phosphate BS (pH 6.8) as the dissolution medium, adjust the rotational speed of the paddle to 70 rpm. Withdraw 10 ml of the solution after exactly 30 minutes and filter, take the successive filtrate as the test solution. Dissolve a quantity of folic acid CRS in phosphate BS (pH 6.8) to produce a solution of 4 µg per ml. Measure the absorbance of the resulting solutions at 281

nm (Appendix IV A). Calculate the dissolution of $C_{19}H_{19}N_7O_6$ from each tablet. Not less than 75% of the labelled amount is dissolved (strength 0.4 mg).

Other requirements Comply with the general requirements for tablets (Appendix I A).

Assay Weigh accurately and powder 50 tablets (0.4 mg) or 20 tablets (5 mg). Transfer a quantity, accurately weighed, equivalent to about 5 mg of folic acid to a 25 ml volumetric flask, add 15 ml of 0.5% ammonia solution and heat in a water bath for 20 minutes with shaking to dissolve folic acid. Allow to cool, dilute with water, mix well and filter. Carry out the Assay as described under Folic acid, using the successive filtrate as the test solution. Calculate the content of $C_{19}H_{19}N_7O_6$.

Category As described under Folic Acid.

Strength (1) 0.4 mg (2) 5 mg

Storage Preserve in tightly closed containers, protected from light.

Formaldehyde Solution

Formaldehyde Solution contains not less than 36.0% (g/g) of formaldehyde CH_2O . It contains 10%-12% of methanol to prevent polymerization.

Description A colourless or almost colourless clear liquid; odour, characteristic, pungent and irritating to the mucous membrane of the throat and nose. It easily becomes turbid when kept at a cold place for a long time. Miscible with water or ethanol.

Identification (1) dilute 5 drops with 1 ml of water in a test tube, add 3 drops of ammoniated silver nitrate TS; a grey precipitate, or a silver mirror is formed.

(2) Add a few drops of fuchsin-sulfurous acid TS and dilute hydrochloric acid to a small volume of the solution being examined, a red colour is produced.

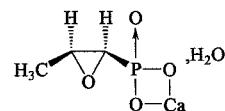
Acidity Dilute 5.0 ml with 5 ml of water, add 2 drops of phenolphthalein IS and titrate with sodium hydroxide (0.1 mol/L) VS to pink colour; not more than 1.0 ml of sodium hydroxide (0.1 mol/L) VS is consumed.

Assay To about 1.5 ml, accurately weighed, add a mixture of 10 ml of water, 25 ml of hydrogen peroxide TS and 2 drops of bromothymol blue IS, add sodium hydroxide (1 mol/L) VS dropwise until a blue colour is obtained; then add accurately 25 ml of sodium hydroxide (1 mol/L) VS, put a small glass funnel on the mouth of the conical flask, heat the mixture on a water bath for 15 minutes, shake occasionally, allow it to cool, wash the funnel with water, add 2 drops of bromothymol blue IS and titrate with hydrochloric acid (1 mol/L) VS until a yellow colour is obtained. Perform a blank determination and make any necessary correction. Each ml of sodium hydroxide (1 mol/L) VS is equivalent to 30.03 mg of CH_2O .

Category Antiseptic and Disinfectant.

Storage Preserve in tightly closed containers, protect from freezing.

Fosfomycin Calcium



$C_3H_5CaO_4P \cdot H_2O$ 194.14

Fosfomycin calcium is calcium (-)-(1R, 2S)-1,2-epoxypropyl phosphonic acid monohydrate. It has a potency of not less than 720 Fosfomycin Units per mg, calculated on the anhydrous basis.

Description A white crystalline powder; odorless. Slightly soluble in water; practically insoluble in acetone, chloroform, methanol, ether and benzene.

Specific optical rotation -3.5° to -5.0° , in a solution of 50 mg per ml in 0.2 mol/L disodium edetate solution (sonicate for 30 minutes) (Appendix VI E).

Identification (1) Carry out the method for thin-layer chromatography (Appendix V B), using silica gel G as the coating substance and a mixture of isopropanol-ethyl acetate-water-glacial acetic acid (4:2:3:1) as the mobile phase. Apply separately to the plate 2 μ l each of solution (1) containing 20 mg per ml of the substance being examined in 0.2 mol/L disodium edetate solution (sonicate for 30 minutes) and solution (2) containing 20 mg per ml of fosfomycin RS in 0.2 mol/L disodium edetate solution (sonicate for 30 minutes), after developing and removal of the plate, dry in air and spray with a solution (containing 5 g of phosphomolybdic acid in 100 ml of acetic acid and 5 ml of sulfuric acid), heat at 105°C for 20 minutes. the colour and position of the principal spot in the chromatogram obtained with solution (1) corresponds to that of the principal spot obtained with solution (2).

(2) The infrared absorption spectrum (Appendix VI E) is concordant with the reference spectrum of Calcium fosfomycin.

(3) Yields the flame reaction of calcium salts (Appendix III).

Crystallinity Complies with the test for crystallinity (Appendix IX D).

Alkalinity Dissolve 0.1 g in 25 ml of water, pH 8.5-12.0 (Appendix VI H).

Fosfomycin calcium diol substances Dissolve about 0.1 g, accurately weighed, in 100 ml of water and 50 ml of potassium biphthalate BS (pH 6.4) (Dissolve 100 g of potassium biphthalate with 600 ml of water by warming in a 1000 ml volumetric flask, adjust pH to 6.4 ± 0.1 by adding about 40 ml of sodium hydroxide (4 \rightarrow 10), dilute to volume with water). in a 250 ml iodine flask. Add accurately 10 ml of 0.005 mol/L of sodium periodate solution, mix well. Stopper the flask and allow to stand in the dark place for 90 minutes at 25°C . Add 10 ml of 10% potassium iodide solution, stopper the flask and allow to stand in the dark place for 2 minutes. Titrate with sodium thiosulfate (0.01 mol/L) VS, add 1 ml of starch IS towards the end of the titration and continue titrating until the blue colour just disappears. Perform a blank determination and make any necessary correction. Each ml of sodium thiosulfate (0.01 mol/L) VS is equivalent to 0.5304 mg of $C_3H_7CaO_5P \cdot H_2O$. Not more than 2.0%.

Water 8.5%-12.0% (Appendix VIII M, method 1 A),

dissolve the substance being examined with a mixture of formamide-methanol (1:1).

Heavy metals Dissolve 1.0 g in 2 ml of dilute hydrochloric acid, add 2 ml of dilute acetic acid and sufficient water to produce 25 ml. Carry out the limit test for heavy metals (Appendix VIII H, method 1); not more than 0.002%.

Assay Carry out the Microbiological Assay of Antibiotics (Appendix XI A), using a solution of about 500 Units per ml in sterile water. 1000 fosfomycin units is equivalent to 1 mg of $C_3H_7O_4P$.

Category Antibiotic.

storage Preserve in tightly closed containers, stored in a cool, dark and dry place.

preparation (1) Fosfomycin Calcium Tablets
(2) Fosfomycin Calcium Capsules
(3) Fosfomycin Calcium Granules

Fosfomycin Calcium Capsules

Fosfomycin Calcium Capsules contain not less than 90.0% and not more than 110.0% of the labelled amount of fosfomycin ($C_3H_7O_4P$).

Description Capsules containing white or almost white granules or powder.

Identification Dissolve a quantity of the contents of capsules in 0.2 mol/L disodium edetate solution (sonicate for 30 minutes) to produce a solution of 20 mg per ml of fosfomycin. Filter, the successive filtrate complies with test (1) for Identification described under Fosfomycin Calcium.

Dissolution Carry out the dissolution test (Appendix X C, method 2), using 1000 ml of 0.1 mol/L hydrochloric acid solution as the dissolution medium, adjust the rotational speed of the paddle to 75 rpm. Withdraw the solution after exact 30 minutes and filter. Dilute a quantity of the successive filtrate with 0.1 mol/L hydrochloric acid solution to produce a solution of 0.1 mg per ml of fosfomycin. Filter, measure accurately 5 ml of the successive filtrate in a 25 ml volumetric flask. Weigh accurately a quantity of the mixed contents obtained from the test for weight variation of contents equivalent to about the weight of contents of one capsule, add 0.1 mol/L hydrochloric acid solution, shake, dilute to produce a solution of 0.1 mg per ml of fosfomycin. Filter, measure accurately 5 ml of the successive filtrate in another 25 ml volumetric flask. Add 1 ml of a freshly prepared solution of ammonium persulfate (Dissolve 1 g of ammonium persulfate in 15 ml of water) respectively. Using a little water washing the wall of flask, boiling in water bath for 10 minutes. Add 2 ml of 1% urea solution, boiling in water bath for 10 minutes again, cool to room temperature, add 1.5 ml of 5% ammonium molybdate solution (Dissolve 10 g of ammonium molybdate with 100 ml of 5 mol/L sulfuric acid solution, add water to 200 ml) and 1 ml of 0.5% of sodium sulfite (Dissolve 0.5 g of sodium sulfite with 80 ml of water, add 0.2 g of *p*-methylaminophenol sulfate and 30 g of sodium metabisulfite, add 100 ml of water and mix well), dilute to volume with water, allow to stand for 20 minutes. Measure the absorbance of the resulting solutions at 650 nm using water as blank solution (Appendix IV A). Calculate the dissolution of $C_3H_7O_4P$ from each capsule. Not less than 75% of the labelled amount is dissolved.

Other requirements Comply with the general requirements for capsules (Appendix I E).

Assay To the mixed contents obtained from the test for

weight variation of contents, weigh accurately, add sterile water to produce a solution of about 500 Units per ml and mix well. Measure accurately a quantity of the supernatant liquid and carry out the Assay described under fosfomycin calcium. 1000 fosfomycin units is equivalent to 1 mg of $C_3H_7O_4P$.

Category As described under Fosfomycin Calcium.

Strength Calculated as $C_3H_7O_4P$
(1) 0.1 g (100000 units)
(2) 0.125 g (125000 units)
(3) 0.2 g (200000 units)

storage Preserve in tightly closed containers, stored in a dry place.

Fosfomycin Calcium Granules

Fosfomycin Calcium Granules contain not less than 90.0% and not more than 110.0% of the labelled amount of fosfomycin ($C_3H_7O_4P$).

Description Suspension granules, taste, sweet, fragrant.

Identification (1) Weigh a quantity equivalent to about 0.1 g of fosfomycin to a tube with stopper, add 10 ml of 0.1 mol/L sodium periodate solution and 10 ml of 0.1 mol/L hydrochloric acid solution, warm in a water bath for 20 minutes, cool and filter. Add 1% sodium sulfite dropwise to 4 ml of the successive filtrate until the yellow colour disappears. Add fuchsin sulfurous acid solution, a purple-red colour appears after about 10 minutes.

(2) To produce a solution containing 20 mg per ml of the substance being examined in 0.2 mol/L disodium edetate solution (sonicate for 30 minutes) as the test solution and a solution containing 20 mg of per ml of fosfomycin RS in 0.2 mol/L disodium edetate solution (sonicate for 30 minutes) as the reference solution, mix equal volumes of the test solution and the reference solution as the mixing solution, filter. Carry out the test (1) for Identification described under Fosfomycin Calcium with the filtrate. The colour and position of the principal spot in the chromatogram obtained with the test solution correspond to that of the principal spot obtained with the reference solution, only one spot in the chromatogram is obtained with the mixing solution.

Acidity or alkalinity A suspension of 40 mg per ml in water, pH 6.5-7.5 (Appendix VI H).

Size of granules Carry out the method of granules size test (Appendix IX E). The total weight of granules, which can not pass through No. 5 sieve but can pass through No. 9 sieve should not be more than 10.0 per cent.

Other requirements Comply with the general requirements for granules (Appendix I N).

Assay Triturate the mixed contents obtained from the test for weight variation of contents, weigh accurately a quantity of the powder equivalent to about 50 mg of fosfomycin, add sterile water, shake thoroughly to produce a solution of about 500 Units per ml and mix well. Allow it to stand, measure accurately a quantity of the supernatant liquid and carry out the Assay described under Fosfomycin Calcium. 1000 fosfomycin units is equivalent to 1 mg of $C_3H_7O_4P$.

Category As described under Fosfomycin Calcium.

Strength Calculated as $C_3H_7O_4P$
(1) 0.1 g (100000 units)
(2) 0.5 g (500000 units)

storage Preserve in tightly closed containers, stored in a

dry place.

Fosfomycin Calcium Tablets

Fosfomycin Calcium Tablets contain not less than 90.0% and not more than 110.0% of the labelled amount of fosfomycin ($C_3H_7O_4P$).

Description White or almost white tablets.

Identification Dissolve a quantity of powdered tablets in 0.2 mol/L disodium edetate solution (sonicate for 30 minutes) to produce a solution of 20 mg per ml of fosfomycin. Filter, the successive filtrate complies with test (1) for Identification described under Fosfomycin Calcium.

Dissolution Carry out the dissolution test (Appendix X C, method 2), using 1000 ml of 0.1 mol/L of hydrochloric acid solution as the dissolution medium, adjust the rotational speed of the paddle to 75 rpm. Withdraw the solution after exact 30 minutes and filter. Dilute a quantity of the successive filtrate with 0.1 mol/L hydrochloric acid solution to produce a solution of 0.1 mg per ml of fosfomycin. Filter, measure accurately 5 ml of the successive filtrate to a 25 ml volumetric flask. Weigh accurately and powder 10 tablets. Weigh accurately a quantity of powder equivalent to about the average weight of one tablet, add 0.1 mol/L hydrochloric acid solution, shake, dilute to produce a solution of 0.1 mg per ml of fosfomycin. Filter, measure accurately 5 ml of the successive filtrate to a 25 ml volumetric flask. Add 1 ml of a freshly prepared solution of ammonium persulfate (Dissolve 1 g of ammonium persulfate in 15 ml of water) respectively. Using a little water to wash the wall of flask, boiling in water bath for 10 minutes. Add 2 ml of 1% urea solution, boiling in water bath for 10 minutes again, cool to room temperature, add 1.5 ml of 5% ammonium molybdate solution (Dissolve 10 g of ammonium molybdate with 100 ml of 5 mol/L sulfuric acid solution, add water to 200 ml) and 1 ml of 0.5% sodium sulfite (Dissolve 0.5 g of sodium sulfite with 80 ml of water, add 0.2 g of *p*-methylaminophenol sulfate and 30 g of sodium metabisulfite, add 100 ml of water and mix well), dilute to volume with water, allow to stand for 20 minutes. Measure the absorbance of the resulting solutions at 650 nm using water as blank solution (Appendix IV A). Calculate the dissolution of $C_3H_7O_4P$ from each tablet. Not less than 75% of the labelled amount is dissolved.

Other requirements Comply with the general requirements for tablets (Appendix I A).

Assay Weigh accurately and powder 10 tablets. To an accurately weighed quantity, add sterile water to produce a solution of about 500 Units per ml and mix well. measure accurately a quantity of the supernatant liquid and carry out the Assay described under Fosfomycin Calcium. 1000 fosfomycin Units is equivalent to 1 mg of $C_3H_7O_4P$.

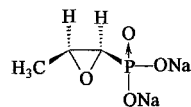
Category As described under Fosfomycin Calcium.

Strength Calculated as $C_3H_7O_4P$

- (1) 0.1 g (100000 Units)
- (2) 0.2 g (200000 Units)
- (3) 0.5 g (500000 Units)

storage Preserve in tightly closed containers, stored in a dry place.

Fosfomycin Sodium



$C_3H_5Na_2O_4P$ 182.02

Fosfomycin Sodium is disodium (-)-(1R, 2S) - 1,2-epoxypropyl phosphonic acid. It has a potency of not less than 700 Fosfomycin Units per mg, calculated on the anhydrous basis.

Description A white crystalline powder; odourless; taste, salty; readily deliquescent in air. Freely soluble in water; slightly soluble in methanol; practically insoluble in ethanol or ether.

Specific optical rotation -4.2° to -5.5° , in a solution of 50 mg per ml in water (Appendix VI E).

Identification (1) Carry out the method for thin-layer chromatography (Appendix V B), using silica gel G as the coating substance and a mixture of isopropanol-ethyl acetate-water-acetic acid glacial (4:2:4:1) as the mobile phase. Apply separately to the plate 2 μ l each of solution (1) containing 20 mg per ml of the substance being examined and solution (2) containing 20 mg per ml of fosfomycin RS in 0.2 mol/L disodium edetate solution. After developing and removal of the plate, dry in air and spray with a solution (containing 5 g of phosphomolybdic acid in 100 ml of acetic acid and 5 ml of sulfuric acid), heat at 105°C for 20 minutes and examine. The colour and position of the principal spot in the chromatogram obtained with solution (1) correspond to that of the principal spot obtained with solution (2). (2) The infrared absorption spectrum (Appendix IV C) is concordant with the spectrum of fosfomycin CRS. (3) Yields the flame reaction of sodium salts (Appendix III).

Alkalinity Dissolve a quantity in water to produce a solution of 50 mg per ml, pH 9.0-10.5 (Appendix VI H).

Clarity and colour of solution To 5 portions each of 1.1 g add 5 ml of water respectively, the solutions are clear and colourless; any opalescence produced is not more pronounced than that of reference suspension I (Appendix IX B); any colour produced is not more intense than that of reference solution Y₁ (Appendix IX A, method 1).

Fosfomycin sodium diol substances Dissolve about 0.2 g, accurately weighed, in 100 ml of water and 50 ml of potassium biphthalate BS (pH 6.4) in a 250 ml iodine flask. Add accurately 10 ml of 0.005 mol/L sodium periodate solution, mix well. Stopper the flask and allow to stand in the dark place at 25°C for 90 minutes. Add 10 ml of 10% potassium iodide solution, stopper the flask and allow to stand in the dark place for 2 minutes. Titrate with sodium thiosulfate (0.01 mol/L) VS, add 1 ml of starch IS towards the end of the titration and continue titrating until the blue colour just disappears. Perform a blank determination and make any necessary correction. Each ml of sodium thiosulfate (0.01 mol/L) VS is equivalent to 0.5001 mg of $C_3H_7Na_2O_5P$. Not more than 0.5%.

Water Not more than 1.5% (Appendix VIII M, method 1 A).

Heavy metals Carry out the limit test for heavy metals (Appendix VIII H, method 3), using 1.0 g; not more than

0.001%.

Bacterial endotoxin Carry out the test for bacterial endotoxin (Appendix XI E): not more than 0.033 EU per 1000 Fosfomycin Units.

Sterility Dissolve a quantity in a suitable solvent, transfer to not less than 500 ml of 0.9% sterile sodium chloride solution, the solution complies with the test for sterility (Appendix XI H, membrane filtration method).

Assay Carry out the Microbiological Assay of Antibiotics (Appendix XI A), using a solution of about 500 Units per ml in sterile water. 1000 Fosfomycin Units are equivalent to 1 mg of $C_3H_7O_4P$.

Category Antibiotic.

Storage Preserve in hermetically sealed containers, stored in a cool, dark and dry place.

Preparation Fosfomycin Sodium for Injection

Fosfomycin Sodium for Injection

Fosfomycin Sodium for Injection is a sterile mixture of fosfomycin sodium and suitable amount of citric acid. It contains not less than 90.0% and not more than 110.0% of the labelled amount of fosfomycin ($C_3H_7O_4P$).

Description A white crystalline powder.

Identification Complies with the tests (1), (3) for Identification described under Fosfomycin Sodium.

Acidity or alkalinity Dissolve a quantity in water to produce a solution containing 50 mg per ml, pH 6.5-8.5 (Appendix VI H).

Clarity and colour of solution To each of 5 containers add water to produce solutions of 0.15 g of fosfomycin per ml, the solutions are clear and colourless; any opalescence produced is not more pronounced than that of reference suspension I (Appendix IX B); any colour produced is not more intense than that of reference solution Y_1 (Appendix IX A, method 1).

Fosfomycin sodium diol substances Carry out the test for Fosfomycin sodium diol substance described under Fosfomycin Sodium, not more than 1.0%.

Water Not more than 2.0% (Appendix VIII M, method 1 A).

Bacterial endotoxin and Sterility Complies with the corresponding requirements described under Fosfomycin Sodium.

Other requirements Complies with the general requirements for injections (Appendix I B).

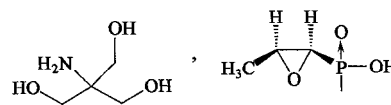
Assay Carry out the Assay described under Fosfomycin Sodium, using an accurately weighed quantity of the mixed contents obtained in the test for weight variation of contents.

Category As described under Fosfomycin Sodium.

Strength Calculated as $C_3H_7O_4P$
 (1) 1 g (1000000 Units)
 (2) 2 g (2000000 Units)
 (3) 4 g (4000000 Units)

Storage Preserve in well closed containers, stored in a cool and dry place.

Fosfomycin Trometamol



$C_7H_{18}NO_7P$ 259.20

Fosfomycin Trometamol is disodium of fosfomycin and trometamol. It contains $C_7H_{18}NO_7P$ not less than 490 Fosfomycin Units per mg, calculated with reference to the anhydrous substance.

Description A white or almost white powder, odourless, taste, salty, hygroscopic.

Very soluble in water, soluble in methanol and slightly soluble in alcohol, practically insoluble in chloroform.

Specific optical rotation -2.0° to -4.0° , in a solution of 50 mg per ml in water (Appendix IV E).

Identification (1) To about 50 mg, add 2 ml of sodium periodate TS, add several drops of ammonium molybdate TS and nitric acid respectively, heat, a yellow precipitate is produced, which is soluble in ammonia TS after isolation.

(2) Carry out the method for thin-layer chromatography (Appendix V B), using silica gel G as the coating substance and a mixture of isopropanol-ethyl acetate-water-glacial acetic acid (4:2:3:1) as the mobile phase. Apply separately to the plate 2 μ l each of solution (1) containing 20 mg per ml of the substance being examined and solution (2) containing 20 mg per ml of fosfomycin RS in 0.2 mol/L disodium edetate solution. After developing and removal of the plate, dry in air and spray with a solution (containing 5 g of phosphomolybdic acid in 100 ml of acetic acid and 5 ml of sulfuric acid), heat at 100°C for 20 minutes and examine. The colour and position of the principal spot in the chromatogram obtained with solution (1) correspond to that of the principal spot obtained with solution (2).

(3) The infrared absorption spectrum is concordant with the reference spectrum of Fosfomycin Trometamol.

Test (1) and (2) may be omitted if test (3) is carried out.

Crystallinity Comply with the requirements for crystallinity test (Appendix IX D).

Acidity Dissolve 1 g in 20 ml of water, pH 3.5-5.5 (Appendix VI H).

Water Not more than 1.0% (Appendix VIII M, method 1).

Fosfomycin Ditrometamol Dissolve 0.25 g in water, accurately weighed, in 25 ml volumetric flask, add 0.1 ml of methyl red-bromocresol green (freshly prepared, used in a week), dilute with water to volume, mix well. Measure the light absorption at 527 nm and 615 nm separately (Appendix IV A). The ratio of the absorbance at 527 nm to that at 615 nm is not less than 1.76 (1 per cent, calculated as Fosfomycin ditrometamol).

Heavy metals Carry out the limit test for heavy metals (Appendix VIII H, method 3), using 1.0 g. Not more than 0.001%.

Assay Carry out the Microbiological Assay of Antibiotics (Appendix XI A), using a solution of about 500 Units per ml in sterile water. 1000 Fosfomycin Units are equivalent to 1 mg of $C_3H_7O_4P$.

Category Antibiotic.

Storage Preserve in tightly closed containers, stored in a dry place.

Preparation Fosfomycin Trometamol Powder

Fosfomycin Trometamol Powder

Fosfomycin Trometamol Powder contains not less than 90.0 per cent and not more than 110.0 per cent of Fosfomycin Trometamol, calculated with reference to Fosfomycin ($C_3H_7O_4P$).

Discription A power, taste sweet.

Identification (1) To a quantity equivalent to about 50 mg of fosfomycin trometamol, add 2 ml of sodium periodate TS, add several drops of ammonium molybdate TS and nitric acid respectively, a yellow precipitate is produced, which is soluble in ammonia TS after isolation.

(2) Carry out the method for thin-layer chromatography (Appendix V B), using silica gel G as the coating substance and a mixture of isopropanol-ethyl acetate-water-glacial acetic acid (4:2:3:1) as the mobile phase. Apply separately to the plate 2 μ l each of solution (1) containing 20 mg per ml of the substance being examined and solution (2) containing 20 mg per ml of fosfomycin RS in 0.2 mol/L disodium edetate solution. After developing and removal of the plate, dry in air and spray with a solution (containing 5 g of phosphomolybdic acid in 100 ml of acetic acid and 5 ml of sulfuric acid), heat at 100°C for 20 minutes and examine. The colour and position of the principal spot in the chromatogram obtained with solution (1) correspond to that of the principal spot obtained with solution (2).

Water Not more than 1.0% (Appendix VIII M, method 1).

Acidity Dissolve a quantity of the powder equivalent to about 1 g of fosfomycin in 20 ml of water, pH 3.5-5.0 (Appendix VI H).

Other requirements Complies with the general requirements for power.

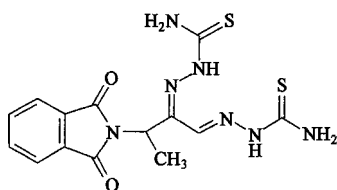
Assay Weigh accurately a quantity of the mixed contents obtained in the test for weight variation of contents, produce a solution of about 500 Units per ml in sterile water. Carry out the Assay described under Fosfomycin Trometamol.

Category As described under Fosfomycin Trometamol.

Strength 3 g (3000000 Units) calculated as $C_3H_7O_4$.

Storage Preserve in tightly closed containers, stored in a dry place.

Ftibamzone



$C_{14}H_{15}N_7O_2S_2$ 377.45

Ftibamzone is an inclusion compound of 3-

phthalamoyl-2-oxobutylal-1,2-bis-(thiosemicarbazone) and dioxane. It contains not less than 97.0% and not more than 103.0% of $C_{14}H_{15}N_7O_2S_2$, calculated on the dried dioxane-free basis.

Description A yellow, crystalline powder; odourless; taste, slightly bitter; colour intensified gradually on exposure to light.

Freely soluble in dimethylformamide; slightly soluble in dioxane; practically insoluble in ethanol, ether or water; freely soluble in sodium hydroxide solution.

Identification (1) Dissolve about 10 mg in 2 ml of 0.4% sodium hydroxide solution. Acidify slightly with dilute hydrochloric acid and add copper sulfate TS, a brown precipitate is produced.

(2) The infrared absorption spectrum (Appendix IV A) is concordant with the reference spectrum of ftibamzone (Appendix XVI).

Clarity of alkaline solution Dissolve 0.10 g in 5 ml of sodium hydroxide TS, add 15 ml of water, the solution is clear.

Dioxane Carry out the method for gas chromatography (Appendix V E), using a column packed with GDX-102 polymer porous beads; maintain the column temperature at 115°C, the number of theoretical plates of the column is not less than 300, calculated with reference to the peak of dioxane, the resolution factor between the peaks of dioxane and isobutanol (internal standard) is not less than 1.5. Weigh accurately about 50 mg of dioxane in a 25 ml volumetric flask, add accurately 2 ml of 1.5% (ml/ml) isobutanol solution, dilute with water to volume and mix well (solution A). Weigh accurately 0.25 g of the substance being examined in another 25 ml volumetric flask, dissolve in a quantity of 1% sodium hydroxide solution, neutralize with hydrochloric acid solution (9 \rightarrow 100) dropwise. Add accurately 2 ml of 1.5% (ml/ml) isobutanol solution, dilute with water to volume and mix well (solution B). The content of dioxane is not less than 14.0% and not more than 20.0%.

Loss on drying When dried to constant weight at 105°C, loses not more than 1.0% of its weight (Appendix VIII L).

Residue on ignition Not more than 0.1% (Appendix VIII N), using 1.0 g.

Heavy metals Carry out the limit test for heavy metals (Appendix VIII H, method 2), using the residue obtained in Residue on ignition; not more than 0.002%.

Assay Dissolve about 25 mg, accurately weighed, in 5 ml of dimethylformamide in a 50 ml amber volumetric flask and add dilute ethanol to volume. Dilute an accurately measured quantity with dilute ethanol to produce a solution of about 10 μ g per ml and measure the absorbance at 347 nm (Appendix IV A). Repeat the operation using ftibamzone CRS (calculated on the dried, dioxane-free basis) instead of the substance being examined, and calculate the content of $C_{14}H_{15}N_7O_2S_2$.

Category Antivirotic agent.

Storage Preserve in tightly closed containers, protect from light.

Preparation (1) Ftibamzone Cream
(2) Ftibamzone Eye Drops
(3) Ftibamzone Liniment

Ftibamzone Cream

Ftibamzone Cream contains not less than 90.0% and not more than 110.0% of labelled amount of Ftibamzone ($C_{14}H_{15}N_7O_2S_2$).

Description A yellow cream.

Identification (1) To 0.3 g add 5 ml of 0.4% sodium hydroxide, mix well and shake with 10 ml of chloroform in a separator, allow to stand, acidify the aqueous layer with dilute hydrochloric acid to weak acidity, add copper sulfate TS, a brown precipitate is produced.

(2) The light absorption of the solution obtained in Assay exhibits a maximum at 347 nm (Appendix IV A).

Other requirement Complies with general requirements for creams (Appendix I F).

Assay Protect from light. Dissolve a quantity equivalent to 25 mg of ftibamzone, accurately weighed, in a 50 ml volumetric flask in about 30 ml of *N*, *N*-dimethylformamide by warming for 5 minutes, allow to stand and dilute to 50 ml with *N*, *N*-dimethylformamide and cool in ice bath for 15 minutes, filter, cool the filtrate to room temperature. Dilute 5 ml of successive filtrate, accurately measured, in a 50 ml volumetric flask, to volume with ethanol and shake well. Dilute 5 ml, accurately measured, of the solution to 25 ml with dilute ethanol. Measure the absorbance of the resulting solution at 347 nm (Appendix IV A). Repeat the operation using ftibamzone CRS (Calculated on dried dioxane-free basis) instead of the substance being examined, calculate the content of $C_{14}H_{15}N_7O_2S_2$.

Category As described under Ftibamzone.

Strength (1) 10 g:0.1 g (2) 10 g:0.3 g

Storage Preserve in well closed containers.

Ftibamzone Eye Drops

Ftibamzone Eye Drops contain not less than 80.0% and not more than 120.0% of the labelled amount of ftibamzone ($C_{14}H_{15}N_7O_2S_2$).

Description Pale yellow suspensions.

Identification (1) Centrifuge the content of 1 vial, discard most of the supernatant liquid. The residue complies, with the test (1) for Identification described under ftibamzone.

(2) The light absorption of the solution obtained in the Assay exhibits a maximum at 347 nm (Appendix IV A).

pH value 4.0-7.0 (Appendix VI H).

Other requirements Comply with the general requirements for Eye preparations (Appendix I G).

Assay Measure accurately a quantity of mixed eye drops equivalent to about 5 mg of ftibamzone in a 50 ml amber volumetric flask. Add 1 ml of dimethylformamide, shake thoroughly, add dilute ethanol to volume and mix well. Transfer 5 ml, accurately measured, to another 50 ml amber volumetric flask, add dilute ethanol to volume and mix well, measure the absorbance of the resulting solution and that of a solution of 10 µg per ml Ftibamzone CRS in dilute ethanol (calculated on the dried, dioxane-free basis) at 347 nm (Appendix IV A). Calculate the content of $C_{14}H_{15}N_7O_2S_2$.

Category As described under Ftibamzone.

Strength 8 ml : 8 mg

Storage Preserve in well closed containers, protected from light.

Ftibamzone Liniment

Ftibamzone Liniment contains not less than 90.0% and not more than 110.0% of the labelled amount of Ftibamzone ($C_{14}H_{15}N_7O_2S_2$).

Description A clear, pale yellow liquid.

Identification (1) To about 2 ml add 2 ml of water, add dilute hydrochloric acid with stirring to acidify the solution weakly, then add cupric sulfate TS, mix well; a reddish-brown colour is produced in the lower layer.

(2) The light absorption of the solution obtained in the Assay exhibits a maximum at 345 nm (Appendix IV A).

Other requirements Complies with the general requirements for liniments (Appendix I T).

Assay *Reference solution* To an accurately weighed quantity of Ftibamzone CRS, equivalent to 25 mg of Ftibamzone calculated on dioxane free basis, in a 250 ml amber volumetric flask, add 125 ml of glacial acetic acid to dissolve, dilute with water to volume, and mix well. Dilute 5 ml of the solution, accurately measured, in a 50 ml amber volumetric flask, with glacial acetic acid solution (1→2) to volume and mix well.

Test solution Dilute an accurately measured quantity, equivalent to about 5 mg of Ftibamzone, in a 50 ml amber volumetric flask, with glacial acetic acid solution (1→2) to volume and mix well. Transfer 5.0 ml of the solution, accurately measured, to a 50 ml amber volumetric flask, dilute with glacial acetic acid solution (1→2) to volume and mix well.

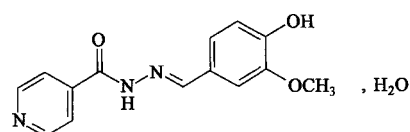
Procedure Measure the absorbance of the above two solutions at 345 nm (Appendix IV A), and calculate the content of Ftibamzone.

Category As described under Ftibamzone.

Strength (1) 5 ml:25 mg (2) 10 ml:50 mg

Storage Preserve in well closed containers, stored in a cool place and protected from light.

Ftivazide



$C_{14}H_{13}N_3O_3 \cdot H_2O$ 289.29

Ftivazide is *N*-(3-methoxy-4-hydroxybenzylidene)-*N'* isoniazide monohydrate. It contains not less than 98.0% of $C_{14}H_{13}N_3O_3 \cdot H_2O$.

Description A slightly yellow crystalline powder. Slightly soluble in ethanol; insoluble in water.

Melting range 227-231°C (Appendix VI C).

Identification To 50 mg add 50 mg of 2,4-dinitrochlorobenzene and 3 ml of ethanol, boil in a water bath for 2-3 minutes, cool, then add two drops of 10% sodium hydroxide solution, a red colour is produced.

Acidity Dissolve 0.25 g in 25 ml of water, shake for two minutes and filter. To the filtrate add two drops of sodium hydroxide (0.2 mol/L) VS and two drops of cresol red IS, a pink colour is produced.

Chlorides Dissolve 0.50 g in 25 ml of water, shake for two minutes and filter. To the filtrate add two drops of dilute nitric acid (Appendix VIII A), using 10 ml of filtrate. Any opalescence produced is not more pronounced than that of a reference solution using 7.0 ml of sodium chloride standard solution (0.035%).

Sulfates Carry out the limit test for sulfate (Appendix VIII B), using 10 ml of the filtrate obtained in the test for Chlorides. Any opalescence produced is not more pronounced than that of a reference solution using 1.0 ml of potassium sulfate standard solution (0.05%).

Free isoniazide Dissolve 50 mg in 30 ml of cool water (0°C), shake and filter. To the filtrate add dilute hydrochloric acid TS until the colour of congo red IS changes, then add 0.1 ml of 0.1 mol/L sodium nitrite and mix. 1 drop of the resulting solution produces a blue spot on potassium iodidestarch TP and does not discharge within 5 minutes.

Loss on drying When dried to constant weight at 120°C, loses not more than 7.0% of its weight (Appendix VIII L).

Residue on ignition Not more than 0.1% (Appendix VIII N), using 1.0 g.

Heavy metals Carry out the limit test for heavy metals (Appendix VIII H, method 2), using the residue obtained in the test for residue on ignition; not more than 0.001%.

Assay Dissolve about 0.15 g, accurately weighed, in 10 ml of glacial acetic acid, add 10 ml of acetic anhydride, heat gently, cool. Titrate with perchloric acid (0.1 mol/L) VS, using calomel-glass electrode indicating the end point. Perform a blank determination and make any necessary correction. Each ml of perchloric acid (0.1 mol/ml) VS is equivalent to 28.93 mg of $C_{14}H_{13}N_3O_3 \cdot H_2O$.

Category Antituberculosis.

Storage Preserve in tightly closed containers, protected from light.

Preparation Ftivazide Tablets

Ftivazide Tablets

Ftivazide Tablets contain not less than 95.0% and not more than 105.0% of the labelled amount of ftivazide ($C_{14}H_{13}N_3O_3 \cdot H_2O$).

Description pale yellow tablets.

Identification A quantity of powdered tablets equivalent to about 50 mg of ftivazide complies with the tests for Identification described under ftivazide.

Other requirement Comply with the general requirements for tablets (Appendix I A).

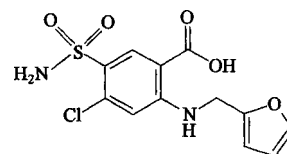
Assay Weight accurately and powder 20 tablets. Carry out the assay as described under ftivazide, using an accurately weighed quantity of the powder equivalent to about 0.2 g of ftivazide.

Category As described under ftivazide.

Strength (1) 50 mg (2) 100 mg

Storage Preserve in tightly closed containers, protected from light.

Furosemide



$C_{12}H_{11}ClN_2O_5S$ 330.75

Furosemide is 5-(aminosulfonyl)-4-chloro-2 [(2-furanylmethyl) amino]-benzoic acid. It contains not less than 99.0% of $C_{12}H_{11}ClN_2O_5S$, calculated on the dried basis.

Description A white or almost white crystalline powder; odourless; almost tasteless. Soluble in acetone; sparingly soluble in ethanol; insoluble in water.

Melting range 206-210°C, with decomposition (Appendix VI C).

Specific absorbance Dissolve an accurately weighed quantity in 0.4% sodium hydroxide solution to produce a solution of 10 µg per ml. Measure the absorbance at 271 nm (Appendix IV A), the value of A (1%, 1 cm) is 565-595.

Identification (1) To about 25 mg add 5 ml of water, add sodium hydroxide TS dropwise to just dissolved, add 1-2 drops of copper sulfate TS, a green precipitate is produced. (2) Dissolve 25 mg in 2.5 ml of ethanol in a test tube, add 2 ml of dimethylaminobenzaldehyde TS, dropwise, along the wall of test tube; a green colour is produced and becomes deep red gradually.

(3) The light absorption of a 5 µg per ml solution in 0.4% sodium hydroxide solution exhibits maxima at 228 nm and 271 nm (Appendix IV A).

(4) The infrared absorption spectrum (Appendix IV A) is concordant with the reference spectrum of furosemide (Appendix XVI).

Clarity and colour of alkaline solution Dissolve 0.50 g in 5 ml of sodium hydroxide TS, add 5 ml of water, the solution is clear and colourless. Any opalescence produced is not more pronounced than that of reference suspension II (Appendix IX B); any colour produced is not more intense than that of reference solution Y₃ (Appendix IX A, method 1).

Chlorides Shake 2.0 g with 100 ml of water thoroughly and filter. Carry out the limit test for chlorides (Appendix VIII A), using 25 ml of the filtrate. Any opalescence produced is not more pronounced than that of a reference using 7.0 ml of sodium chloride standard solution (0.014%).

Sulfates Carry out the limit test for sulfates (Appendix VIII B), using 25 ml of the filtrate obtained in the test for chlorides. Any opalescence produced is not more pronounced than that of a reference using 2.0 ml of potassium sulfate standard solution (0.04%).

Aromatic primary amine Dissolve 0.10 g in methanol in a 25 ml volumetric flask, add methanol to volume, shake thoroughly. Measure accurately 1 ml to another 25 ml

volumetric flask, add 3 ml of dimethylformamide, 12 ml of water and 1 ml of hydrochloric acid (1 mol/L) VS, mix well and cool. Add 1 ml of 0.5% sodium nitrite solution, mix well, allow to stand for 5 minutes. Add 1 ml of 2.5% sulfamic acid, mix well and allow to stand for 5 minutes. Add 1 ml of a 0.5% solution of *N*-(1-naphthyl)-ethylenediamine dihydrochloride in dilute ethanol and sufficient water to volume, mix well, allow to stand for 10 minutes. The absorbance of the resulting solution at 530 nm (Appendix IV A) is not greater than 0.12.

Loss on drying When dried at 105°C to constant weight, loses not more than 0.5% of its weight (Appendix VIII L).

Residue on ignition Not more than 0.1% (Appendix VIII N).

Heavy metals Not more than 0.002% (Appendix VIII H, method 3), using 0.50 g.

Arsenic Mix 1.0 g with 1 g of calcium hydroxide and a small quantity of water, heat gently at first, then ignite at higher temperature until cineration complete, cool, add 5 ml of hydrochloric acid and 23 ml of water. Carry out the limit test for arsenic (Appendix VIII J, method 1); complies with the requirements (0.0002%).

Assay Dissolve about 0.5 g, accurately weighed, in 30 ml of ethanol with warming, cool, add 4 drops of cresol red IS and 1 drop of bromothymol blue IS. Titrate with sodium hydroxide (0.1 mol/L) VS until a purple colour is obtained. Perform a blank determination and make any necessary correction. Each ml of sodium hydroxide (0.1 mol/L) VS is equivalent to 33.07 mg of $C_{12}H_{11}ClN_2O_5S$.

Category Diuretic agent.

Storage Preserve in tightly closed containers, protected from light.

Preparation (1) Furosemide Injection
(2) Furosemide Tablets
(3) Compound Furosemide Tablets

Furosemide Injection

Furosemide Injection is a sterile solution of furosemide in water for Injection containing sodium hydroxide and sodium chloride. It contains not less than 90.0% and not more than 110.0% of the labelled amount of furosemide ($C_{12}H_{11}ClN_2O_5S$).

Description A clear, colourless or almost colourless liquid.

Identification Complies with the tests (1), (2) and (3) for Identification described under Furosemide.

pH value 8.5-9.5 (Appendix VI H).

Other requirements Complies with the general requirements for injections (Appendix I B).

Assay Measure accurately 2 ml to a 100 ml volumetric flask, add 0.4% sodium hydroxide solution to volume, mix well. Measure accurately 5 ml of the diluted solution to another 100 ml volumetric flask, add 0.4% sodium hydroxide solution to volume, mix well. Measure the absorbance of the solution at 271 nm (Appendix IV A). Calculate the content of $C_{12}H_{11}ClN_2O_5S$, taking 580 as the value of *A* (1%, 1 cm).

Category As described under Furosemide.

Strength 2 ml:20 mg

Storage Preserve in tightly closed containers, protected from light.

Furosemide Tablets

Furosemide Tablets contain not less than 90.0% and not more than 110.0% of the labelled amount of furosemide ($C_{12}H_{11}ClN_2O_5S$).

Description White tablets.

Identification Dissolve a quantity of the powdered tablets equivalent to about 80 mg of furosemide in 10 ml of ethanol with shaking, filter and evaporate the filtrate to dryness. The residue complies with tests (1), (2) and (3) for Identification described under Furosemide.

Dissolution Carry out the dissolution test (Appendix X C, method 2), using 1000 ml of phosphate BS (pH 5.8) as the dissolution medium, adjust the rotational speed of the paddle to 50 rpm. Withdraw a quantity of the solution after exactly 30 minutes and filter, measure 5 ml of the successive filtrate and dilute with 0.8% sodium hydroxide solution to 10.0 ml, mix well. Measure the absorbance of the resulting solution at 271 nm (Appendix IV A). Calculate the dissolution of $C_{12}H_{11}ClN_2O_5S$ from each tablet, taking 580 as the value of *A* (1%, 1 cm), not less than 65% for the labelled amount is dissolved.

Other requirements Comply with the general requirements for tablets (Appendix I A).

Assay Weigh accurately and powder 20 tablets. Weigh accurately a quantity of the powdered tablets equivalent to about 20 mg of furosemide into a 100 ml volumetric flask, add about 60 ml of 0.4% sodium hydroxide solution, shake for 10 minutes. Add 0.4% sodium hydroxide solution to volume, mix well and filter, measure accurately 5 ml of successive filtrate in another 100 ml volumetric flask, dilute with 0.4% sodium hydroxide solution to volume, mix well. Measure the absorbance at 271 nm (Appendix IV A). Calculate the content of $C_{12}H_{11}ClN_2O_5S$, taking 580 as the value of *A* (1%, 1 cm).

Category As described under Furosemide.

Strength 20 mg

Storage Preserve in tightly closed containers, protected from light and stored in a dry place.

Compound Furosemide Tablets

Compound Furosemide Tablets contain 18.0-22.0 mg of furosemide ($C_{12}H_{11}ClN_2O_5S$) and 2.25-2.75 mg of Amiloride Hydrochloride ($C_6H_8ClN_7O \cdot HCl$) in each tablet.

Formula	Furosemide	20 g
	Amiloride Hydrochloride	2.5 g
	Excipient	a quantity
	to make	1000 tablets

Description Almost white to pale yellow tablets.

Identification (1) To a quantity of powdered tablets (equivalent to about 80 mg of furosemide), add 10 ml of ethanol, shake to dissolve furosemide and amiloride hydrochloride, filter, evaporate the filtrate to dryness. The

residue complies with the test; ① Dissolve about 25 mg of the residues with 2.5 ml of ethanol in the test tube, add to 2 ml of *p*-dimethylaminobenzaldehyde TS along the inner wall of the test tube, a green colour is produced, then turn to red. ② Dissolve about 20 mg of the residues with 20 ml of water, add dropwise excessive nitric acid to precipitate completely, filter, the filtrate yields the reactions characteristic of chlorides (Appendix III).

(2) The retention time of principal peaks of the furosemide and Amiloride Hydrochloride in the substance being examined in the chromatogram obtained in the Assay are identical with that the principal peaks of furosemide CRS and Amiloride Hydrochloride CRS in the chromatogram of the reference solution corresponding.

Content uniformity Comply with the requirements for content uniformity (Appendix X E). Place 1 tablet in a 100 ml volumetric flask, add 10 ml of methanol and 2 ml of hydrochloric acid (0.1 mol/L) solution, shake to dissolve furosemide and amiloride hydrochloride, dilute with mobile phase to volume, mix well and filter, use the successive filtrate as the test solution. Carry out the procedure as described under the Assay of furosemide and amiloride hydrochloride. Calculate the content of $C_{12}H_{11}ClN_2O_5S$ and $C_6H_8ClN_7O \cdot HCl$.

Dissolution Carry out the dissolution test (Appendix X C, method 2), using 900 ml of phosphate BS (pH 5.8) as the dissolution medium, adjust the rotational speed of the paddle to 50 rpm. Withdraw the solution after exact 30 minutes and filter, as the test solution. Transfer 5 ml of the reference solution as described under the assay to a 50 ml volumetric flask, accurately measured, dilute with the dissolution medium to volume, mix well. Carry out the procedure as described under the assay of furosemide and amiloride hydrochloride, calculate the dissolution of $C_{12}H_{11}ClN_2O_5S$ and $C_6H_8ClN_7O \cdot HCl$ from each tablet, Not less than 75% of the labelled amount is dissolved.

Other requirements Comply with the general requirements for tablets (Appendix I A).

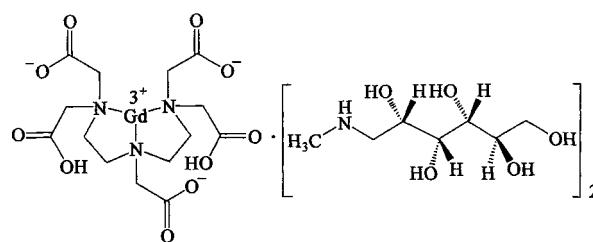
Assay Carry out the method for high performance liquid chromatography (Appendix V D), using a column packed with octadecylsilane bonded silica gel and a mixture of phosphate BS (Dissolve about 13.6 g of potassium dihydrogen phosphate with 80 ml of water in a 100 ml volumetric flask, adjust pH value to 3.0 with phosphoric acid, dilute with water to volume and mix well)-methanol-water (1:49:50) as mobile phase. Detection wavelength is 286 nm and the number of theoretical plates of the column is not less than 2000, calculated with reference to the peak of furosemide. The resolution factor between the peaks of furosemide and amiloride hydrochloride complies with the related requirements.

Procedure Weigh and powder 20 tablets. Triturate an accurately weighed quantity of powder equivalent to about 40 mg of furosemide and 5 mg of amiloride hydrochloride into a 200 ml volumetric flask, add 15 ml of methanol and 2 ml of 0.1 mol/L hydrochloric acid solution, ultrasonicate for 15 minute, cool, dilute with the mobile phase to volume, shake well, filter and inject 10 μ l of the successive filtrate into the column. Repeat the operation, using furosemide CRS and amiloride hydrochloride CRS instead of the substance being examined, calculate the content of $C_{12}H_{11}ClN_2O_5S$ and $C_6H_8ClN_7O \cdot HCl$.

Category Diuretic.

Storage Preserve in tightly closed containers, protected from light.

Gadopentetate Dimeglumine Injection



$C_{14}H_{20}GdN_3O_{10} \cdot 2C_7H_{17}NO_5$ 938.01 [86050-77-3]

Gadopentetate Dimeglumine Injection is a sterile solution of meglumine gadopentetate and an equal molecule of meglumine in water for injection. It contains not less than 95.0% and not more than 105.0% of the labeled amount of Gadopentetate Dimeglumine ($C_{14}H_{20}GdN_3O_{10} \cdot 2C_7H_{17}NO_5$).

Description A clear, colourless to pale yellow or light yellowish-green liquid.

Identification (1) The retention time of the principal peak of the substance being examined in the chromatogram of the Assay is identical with that of gadopentetate dimeglumine CRS.

(2) Dilute 5 ml with water to produce 25 ml, mix well. The light absorbance of the solution exhibits a maximum at 275 nm (Appendix IV A).

Specific optical rotation -4.7° to -5.5° (Appendix VI E).

pH value 6.5-8.0 (Appendix VI H).

Colour Not more intense than reference solution Y_4 or YG_4 (Appendix IX A, method 1).

Pentetic acid Transfer accurately 5 ml to a conical flask, add 25 ml of water, 10 ml of acetic acid-sodium acetate BS [using acetic acid-sodium acetate (pH 4.5) BS, adjust pH to 5.0 with sodium hydroxide TS], add 0.5 ml of xylenol orange IS, titrate with gadolinium chloride (0.002 mol/L) VS (dissolve about 0.53 g of gadolinium chloride accurately weighed in water and dilute to 1000 ml) until the solution turns from orange-yellow to orange-red. Perform a blank determination and make any necessary correction. Each ml of gadolinium chloride (0.002 mol/L) VS is equivalent to 0.788 mg of $C_{14}H_{23}N_3O_{10}$. It contains not less than 50 μ g and not more than 400 μ g of pentetic acid per ml.

Pyrogens Complies with the test for pyrogens (Appendix XI D), using 3 ml per kg of the rabbit's weight.

Other requirements Complies with the general requirements for injections (Appendix I B).

Assay Carry out the method for high performance liquid chromatography (Appendix V D), using a column packed with octadecylsilane bonded silica gel and a solution of tetrabutylammonium perchlorate (dissolve 1.7 g of tetrabutylammonium perchlorate in 100 ml of acetonitrile, dilute to 1000 ml with water) as mobile phase. Detection wavelength is 195 nm and the number of theoretical plates of the column is not less than 3000, calculated with reference to the peak of meglumine gadopentetate.

Procedure Measure accurately 2 ml of the injection to a 200 ml volumetric flask, dilute with water to volume, mix well, measure accurately 15 ml of the solution to a 100 ml volumetric flask, dilute with water to volume, mix well.

Inject 20 μl of the resulting solution into the column, record the chromatogram. Dissolve a quantity of meglumine gadopentetate CRS with water to produce a solution of 0.6 mg per ml. Inject 20 μl of the resulting solution into the column, calculate the content of $\text{C}_{14}\text{H}_{20}\text{GdN}_3\text{O}_{10} \cdot 2\text{C}_7\text{H}_{17}\text{NO}_5$ with respect to the peak area obtained in the chromatogram by the external standard method. Multiply the result by 1.263.

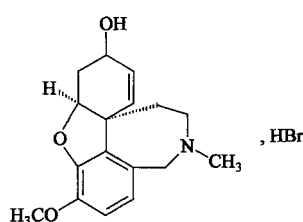
Category Diagnostic agent.

Strength Calculated as gadopentetate dimeglumine ($\text{C}_{14}\text{H}_{20}\text{GdN}_3\text{O}_{10} \cdot 2\text{C}_7\text{H}_{17}\text{NO}_5$)

- (1) 10 ml : 4.69 g (2) 12 ml : 5.63 g
(3) 15 ml : 7.04 g (4) 20 ml : 9.38 g

Storage Preserve in well closed containers, protected from light.

Galanthamine Hydrobromide



$\text{C}_{17}\text{H}_{21}\text{NO}_3 \cdot \text{HBr}$ 368.27

[1953-04-4]

Galanthamine Hydrobromide is 4 α ,5,9,10,11,12-hexahydro-3-methoxy-11-methyl-6*H*-benzofuro[3*a*,3,2-*ef*][2] benzazepin-6-ol hydrobromide. It contains not less than 98.0% of $\text{C}_{17}\text{H}_{21}\text{NO}_3 \cdot \text{HBr}$, calculated on the dried basis.

Description A white or almost white crystalline powder; odourless; taste bitter.

Soluble in water; slightly soluble in ethanol; insoluble in acetone, chloroform, ether or benzene.

Specific absorbance Measure the absorbance of a solution of 50 μg per ml in water at 289 nm (Appendix IV A), the value of *A* (1%, 1 cm) is 79.6-86.2.

Identification (1) Transfer about 1 mg to a porcelain evaporating dish, add 1 ml of 0.5% ammonium molybdate solution, evaporate to dryness on a water bath and add 1-2 drops of sulfuric acid, a bluish-green colour is produced. (2) The aqueous solution yields the reactions characteristic of bromides (Appendix III).

Clarity of solution A solution of 0.10 g in 10 ml of freshly boiled and cooled water is clear.

Acidity pH 4.5-6.5 (Appendix VI H), using the solution obtained under the test for clarity of solution.

Other alkaloids To 0.10 g each of the substance being examined and galanthamine hydrobromide CRS, add separately 2 drops of ammonia TS and a quantity of methanol to produce 10 ml as the test solution and the reference solution respectively. Carry out the method for thin-layer chromatography (Appendix V B), using aluminium oxide (alkaline, grade III-IV) as the coating substance and ether as the mobile phase. Apply separately to the plate 10 μl each of the two solutions. After developing and removal of the plate, expose it in iodine vapour. The number of spots in the chromatogram obtained with the test solution is not more than those obtained with the reference solution, and the

colour of the secondary spots is not more intense than the corresponding spots obtained with the reference solution.

Loss on drying When dried to constant weight at 105°C, loses not more than 1.0% of its weight (Appendix VIII L).

Assay Dissolve about 0.3 g, accurately weighed, in 20 ml of glacial acetic acid and 5 ml of mercuric acetate TS, add 1 drop of crystal violet IS, titrate with perchloric acid (0.1 mol/L) VS until the colour changes to bluish-green. Perform a blank determination and make any necessary correction. Each ml of perchloric acid (0.1 mol/L) VS is equivalent to 36.83 mg of $\text{C}_{17}\text{H}_{21}\text{NO}_3 \cdot \text{HBr}$.

Category Anticholinesterase agent.

Storage Preserve in tightly closed containers, protected from light.

Preparation Galanthamine Hydrobromide Injection

Galanthamine Hydrobromide Injection

Galanthamine Hydrobromide Injection is a sterile solution of galanthamine hydrobromide in Water for Injection. It contains not less than 90.0% and not more than 110.0% of the labelled amount of galanthamine hydrobromide ($\text{C}_{17}\text{H}_{21}\text{NO}_3 \cdot \text{HBr}$).

Description A clear, colourless liquid.

Identification Complies with test (1) for Identification described under Galanthamine Hydrobromide.

pH value 4.5-7.0 (Appendix VI H).

Other requirements Complies with the general requirements for injections (Appendix I B).

Assay Dilute a quantity equivalent to about 5 mg of galanthamine hydrobromide with water to produce a solution of 50 μg per ml, mix well. Measure the absorbance at 289 nm (Appendix IV A). Calculate the content of $\text{C}_{17}\text{H}_{21}\text{NO}_3 \cdot \text{HBr}$, taking 82.9 as the value of *A* (1%, 1 cm).

Category As described under Galanthamine Hydrobromide.

Strength (1) 1 ml : 1 mg (2) 1 ml : 2.5 mg
(3) 1 ml : 5 mg

Storage Preserve in well closed containers, protected from light.

Gallium [^{67}Ga] Citrate Injection

Gallium [^{67}Ga] Citrate Injection is a sterile solution of Gallium [^{67}Ga] Citrate without carrier. It contains not less than 90.0% and not more than 110.0% of the labelled amount of radioactive concentration of Gallium-67 at the date and hour stated on the label.

Description A clear, colourless liquid.

Identification (1) Carry out the γ -ray spectrum method (Appendix XIII) using sufficient of sample, the most prominent photons have energies of 0.093, 0.185 and 0.300 MeV. Carry out the determination of measurement of half-life method (Appendix XIII), 74.4-82.2 hours.

(2) The principal spot obtained in the determination of

Radiochemical purity has prominent radioactive peaks with R_f value of 0.90.

pH value 6.0-7.5 (Appendix VI H).

Bacterial endotoxin Carry out the test for bacterial endotoxin (Appendix XI E) using suitable amount of sample, diluted to at least 100 times of its original volume with water BET. It contains less than 15 EU per ml.

Sterility Complies with the test for sterility (Appendix XI H).

Radionuclidic purity Carry out the determination of radionuclidic purity (Appendix XIII), not less than 99% of the radionuclide due to Ga-67, not more than 0.2% of the radionuclide due to Ga-66.

Radiochemical purity Carry out the determination of radiochemical purity (Appendix XIII, method 1), using sodium acetate-glacial acetic acid (Dissolve 1.36 g of sodium acetate and 0.58 ml of glacial acetic acid with water in a 100 ml volumetric flask, mix well) as the mobile phase. Not less than 95% of the total radioactivity is found in the spot corresponding to gallium [^{67}Ga] citrate.

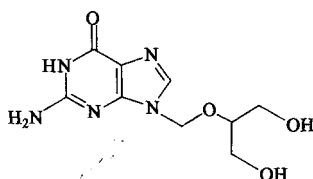
Radioactive concentration Not less than 37 MBq per ml (Appendix XIII).

Category Diagnostic agent.

Strength (1) 185 MBq (2) 370 MBq (3) 740 MBq

Storage Preserve in tightly closed lead containers, the intensity of radiation on the surface of the container complies with relevant regulation.

Ganciclovir



$\text{C}_9\text{H}_{13}\text{N}_5\text{O}_4$ 255.21

Ganciclovir is 9-[(1,3-dihydroxy-2-propyloxy)methyl] guanine. It contains not less than 99.0% of $\text{C}_9\text{H}_{13}\text{N}_5\text{O}_4$, calculated on the dried basis.

Description A white crystalline powder; odourless; tasteless, hygroscopic. Slightly soluble in water or glacial acetic acid, practically insoluble in methanol, insoluble in chloroform, sparingly soluble in hydrochloric acid solution and sodium hydroxide solution.

Specific absorbance Measure the absorbance of a solution of 10 μg per ml in water at 252 nm (Appendix IV A), the value of A (1%, 1 cm) is 516-548.

Identification (1) The light absorption of a solution of 10 μg per ml in water exhibits maximum at 252 nm, and minimum at 222 nm.

(2) The infrared absorption spectrum (Appendix IV C) is concordant with the reference spectrum of ganciclovir CRS. If necessary, dissolve a quantity of the substance being examined and ganciclovir CRS respectively in water to produce a saturated solution, filter, allow the filtrate to stand below 10°C for one night until the crystals appeared, filter and dry the crystals at 105°C, then perform the

determination (Appendix XVI)

Related substances Dissolve about 15 mg, accurately weighed, in 1 ml of 0.4% sodium hydroxide solution, dilute with the mobile phase to volume in a 50 ml volumetric flask and mix well as the test solution, transfer 1 ml of the solution into a 100 ml volumetric flask, accurately measured, dilute with the mobile phase to volume and mix well as the reference solution. Carry out the method for high performance liquid chromatography (Appendix V D), using a column packed with octadecylsilane bonded silica gel and a mixture of methanol-water (5 : 95) as the mobile phase. Detection wavelength is 252 nm and the number of theoretical plates of the column is not less than 3000, calculated with reference to the peak of ganciclovir. Inject 20 μl of the reference solution into the column, adjust the attenuation so that the principal peak height in the chromatogram is 10%-15% full scale of the chart. Inject separately 20 μl each of the solutions into the column, record the chromatograms for twice the retention time of the principal peak. In the chromatogram obtained with the test solution, the sum of the areas of all peaks other than the principal peak is not more than the area of the principle peak in the chromatogram obtained with the reference solution.

Loss on drying When dried to constant weight at 105°C, loses not more than 6.0% of its weight (Appendix VIII L).

Residue on ignition Not more than 0.1% (Appendix VIII N), using 1.0 g.

Heavy metals Carry out the limit test for heavy metals (Appendix VIII H, method 2), using the residue obtained in the test for Residue on ignition; not more than 0.001%.

Assay To about 0.15 g, accurately weighed, add 40 ml of glacial acetic acid, heat to dissolve and allow to cool, add 1 drop of crystal violet IS, titrate with perchloric acid (0.1 mol/L) VS until the colour changes to green. Perform a blank determination and make any necessary correction. Each ml of perchloric acid (0.1 mol/L) VS is equivalent to 25.52 mg of $\text{C}_9\text{H}_{13}\text{N}_5\text{O}_4$.

Category Antiviral.

Storage Preserve in tightly closed containers, protected from light.

Preparation (1) Ganciclovir and Sodium Chloride Injection
(2) Ganciclovir for Injection

Ganciclovir and Sodium Chloride Injection

Ganciclovir and Sodium Chloride Injection is a sterile solution of ganciclovir and sodium chloride in Water for Injection. It contains not less than 90.0% and not more than 110.0% of the labelled amount of $\text{C}_9\text{H}_{13}\text{N}_5\text{O}_4$, and it contains not less than 95.0% and not more than 105.0% of the labelled amount of NaCl.

Description A clear, colourless liquid.

Identification (1) Evaporate a quantity equivalent to about 20 mg of ganciclovir to dryness on a water bath, cool, add 1 ml of hydrochloric acid and 0.1 g of potassium chlorate, and evaporate to dryness on a water bath. To the residue add several drops of ammonia TS, a purple-reddish colour is produced immediately, add several drops of sodium hydroxide TS, the purple-reddish colour disappears.

(2) The retention time of the principal peak of the substance being examined in the chromatogram obtained in the Assay is

identical with that of ganciclovir CRS in the chromatogram of the reference solution.

(3) Yields the flame reaction of sodium salts and the reaction characteristic of chlorides (Appendix III).

pH value 7.0-8.0 (Appendix VI H).

Related substances Dilute a quantity with mobile phase to produce a solution containing 0.3 mg of ganciclovir per ml as the test solution. Carry out the method described under ganciclovir. In the chromatogram obtained with the test solution, the sum of the areas of all peaks other than the principal peak is not more than the area of the peak in the chromatogram obtained with reference solution.

Heavy metals Evaporate 50 ml to about 20 ml and cool, add 2 ml of acetate BS (pH 3.5) and sufficient water to produce 25 ml. Carry out the limit test for heavy metals (Appendix VIII H, method 1): not more than 0.00003%.

Bacterial endotoxin Carry out the test for bacterial endotoxin (Appendix XI E): less than 0.5 EU per ml.

Other requirements Complies with the general requirements for injections (Appendix I B).

Assay Ganciclovir Carry out the method for high performance liquid chromatography (Appendix V D), using a column packed with octadecylsilane bonded silica gel and a mixture of methanol-water (5 : 95) as the mobile phase. Detection wavelength is 252 nm and the number of theoretical plates of the column is not less than 3000, calculated with reference to the peak of ganciclovir.

Procedure Dilute an accurately measured quantity of the injection with mobile phase to produce a solution containing 40 µg of ganciclovir per ml as test solution. Transfer about 25 mg of ganciclovir CRS, accurately weighed, to a 25 ml volumetric flask, add 1 ml of 0.4% sodium hydroxide solution, dilute with the mobile phase to volume, mix well, dilute a quantity with mobile phase to produce a solution containing 40 µg of ganciclovir CRS per ml as reference solution. Inject separately 20 µl each of the reference solution and the test solution into the column. Calculate the content of $C_9H_{13}N_5O_4$ with respect to the peak area obtained in the chromatogram by the external standard method.

Sodium Chloride To 10 ml, accurately measured, add 40 ml of water, 5 ml of dextrin solution (1→50), 0.1 g of calcium carbonate and 5-8 drops of fluorescein IS and titrate with silver nitrate (0.1 mol/L) VS. Each ml of silver nitrate (0.1 mol/L) VS is equivalent to 5.844 mg of NaCl.

Category As described under Ganciclovir.

Strength (1) 100 ml : Ganciclovir 0.05 g, Sodium Chloride 0.9 g
(2) 250 ml : Ganciclovir 0.25 g, Sodium Chloride 2.25 g

Storage Preserve in well closed containers.

Ganciclovir for Injection

Ganciclovir for Injection is a sterile, lyophilized preparation of ganciclovir and a quantity of sodium hydroxide. It contains not less than 90.0% and not more than 110.0% of the labelled amount of $C_9H_{13}N_5O_4$.

Description A white, lyophilized mass or powder; hygroscopic.

Identification (1) To about 20 mg, add 2 ml of hydrochloric

acid and evaporate to dryness on a water bath, add 1 ml of hydrochloric acid and 30 mg of potassium chlorate, and evaporate to dryness on a water bath. To the residue add several drops of ammonia TS, a purple-reddish colour is produced immediately, add several drops of sodium hydroxide TS, purple-reddish colour is disappeared.

(2) The retention time of the principal peak of the substance being examined in the chromatogram obtained in the Assay is identical with that of ganciclovir CRS.

(3) Dissolve a quantity of the substance being examined in water, neutralize with dilute hydrochloric acid or ammonia TS, a white precipitate is produced, filter, the filtrate yields the flame reaction of sodium salts (Appendix III).

Alkalinity Dissolve a quantity in water to produce a solution of 12.5 mg per ml, pH 10.5-11.5 (Appendix VI H).

Water Not more than 6.0% (Appendix VIII M, method 1 A).

Clarity of solution A solution of 10 mg per ml in water is clear; any opalescence produced is not more pronounced than that of reference suspension I (Appendix IX B).

Related substances Dilute a quantity with mobile phase to produce a solution containing 0.3 mg of ganciclovir per ml as test solution. Carry out the method described under Ganciclovir. In the chromatogram obtained with the test solution, the sum of the areas of all peaks other than the principal peak is not more than the area of the principle peak in the chromatogram obtained with the reference solution.

Bacterial endotoxin Carry out the test for bacterial endotoxin (Appendix XI E): less than 0.5 EU per mg of ganciclovir.

Sterility Complies with test for Sterility (Appendix XI H, membrane filtration method), dissolving in suitable volume of 0.9% sterile sodium chloride solution.

Other requirements Complies with the general requirements for injections (Appendix I B).

Assay Dissolve the contents of 5 containers with mobile phase, combine the solution and mix well. Dilute with mobile phase to produce a solution containing 40 µg of ganciclovir per ml as test solution. Carry out the Assay described under Ganciclovir and Sodium Chloride Injection.

Category As described under Ganciclovir.

Strength (1) 0.05 g (2) 0.15 g (3) 0.25 g (4) 0.5 g

Storage Preserve in tightly closed containers, protected from light.

Gelatin

Gelatin is obtained by the partial hydrolysis of animal collagen in the skin, bone, tendon and ligament.

Description Pale yellow to yellow, translucent and faintly lustrous granules or thin sheets; odourless. Easily decomposed by microorganisms when moistened. Swells and softens when immersed in water for a long duration, its weight increases gradually five to ten times due to the absorption of water.

Soluble in hot water, acetic acid or a hot mixture of glycerol and water; insoluble in ethanol, chloroform or ether.

Identification (1) Dissolve 0.5 g in 50 ml of water by heating. To 5 ml of the solution add a few drops of a mixture of potassium dichromate TS and dilute hydrochloric acid (4 : 1), an orange flocculent precipitate is produced.

(2) To 1 ml of the solution obtained in Identification (1), add 100 ml of water, mix well, add a few drops of tannic acid TS, an opalescence is produced.

(3) Heat with soda lime, an ammoniacal odour is perceptible.

Acidity Shake to dissolve 1.0 g in 100 ml of hot water, cool to 35°C, pH 3.6-7.6 (Appendix VI H).

Transparency Soak 5.0 g in 90 ml of water, allow to swell and heat in a water bath at 65-70°C, cool and add water to produce 100 ml. Transfer 5 ml to a 25 ml Nessler cylinder, any opalescence produced is not more pronounced than that of the same volume of reference solution (Transfer accurately 30 ml of standard sodium chloride solution to a 50 ml volumetric flask, add 1 ml each of nitric acid and silver nitrate TS, dilute to volume with water, allow to stand in the dark for 5 minutes, match the colour with caramel solution if necessary), compare immediately.

Sulfite Soak 20 g in a long neck round-bottomed flask in 50 ml of water and allow to swell. Add 50 ml of dilute sulfuric acid, connect a condenser immediately and distill with steam. Receive the distillate in 20 ml of hydrogen peroxide TS (previously neutralized to methyl red-methylene blue IS), until 80 ml are collected. Stop distillation, to the distillate add a few drops of methyl red-methylene blue IS, not more than 1.0 ml of sodium hydroxide (0.1 mol/L) VS is required to change the colour to grass green. Perform a blank determination and make any necessary correction.

Loss on drying Transfer about 1 g to a stainless steel or aluminium vessel (about 75 mm in diameter) previously dried to constant weight at 105°C, weigh accurately. Add 10 ml of water and allow to swell. Heat on a water bath and evaporate to dryness, dry to constant weight at 105°C, loses not more than 16.0% of its weight (Appendix VIII L).

Ash Ignite gently 1.0 g, accurately weighed, in a crucible (previously ignited to constant weight) until completely charred, raise the temperature gradually to 600-700°C, incinerate completely to constant weight, the residue is not more than 2.0%.

Heavy metals To the residue obtained in the determination of Ash add 2 ml of hydrochloric acid and 0.5 ml of nitric acid, evaporate to dryness on a water bath. Add 5 ml of acetate BS (pH 3.5) and 20 ml of water, warm for a few minutes, add water to produce 50 ml. To 20 ml of the solution, add 5 ml of water. Carry out the limit test for heavy metals (Appendix VIII H, method 1): not more than 0.002%.

Arsenic To 1.0 g add 0.5 g of starch, 1.0 g of calcium hydroxide and a small quantity of water, mix well. Dry and ignite slowly until completely charred, incinerate to carbon-free at 500-600°C, allow to cool, dissolve the residue in 8 ml of hydrochloric acid and 20 ml of water. Carry out the limit test for arsenic (Appendix VIII J, method 1): not more than 0.0002%.

Gel strength Transfer 1.10 g to a tared conical flask, add 80 ml of water, allow to stand for 2 hours at 15-18°C to swell completely. Heat in a 60°C water bath to dissolve. Allow the solution to cool and add a quantity of water to produce 100 g. Transfer 10 ml of the solution to a test tube of 13 mm in internal diameter, freeze for 6 hours in an ice bath at 0°C. Allow the tube to be inverted for 10 seconds, nothing falls out of the tube.

Microbial limit Carry out the microbial limit test (Appendix XI J), besides that number of bacterial is not more than 1000 and that of yeasts is not more than 100 per g, *Escherichia coli* is absence.

Category Absorbable hemostatic.

Storage Preserve in well closed containers and stored in a dry place.

Preparation Absorbable Gelatin Sponge

Absorbable Gelatin Sponge

Absorbable Gelatin Sponge is obtained by dissolving gelatin in water and the solution is lyophilized and finally sterilized.

Description A white or pale yellow, light, soft, spongy material, water absorbable. Not damaged even on fairly hard kneading.
Insoluble in water.

Absorptivity Immerse a cube (1 cm × 1 cm × 0.5 cm) of the sponge, accurately weighed, in water at 20°C, knead gently until enough water is absorbed, take care not to damage the cube, withdraw from the water by means of small forceps, allow to drain for one minute while lightly held in the forceps, and then weigh accurately. The increase in weight is not less than 35 times of its original weight.

Residue on ignition Not more than 2.0%, using 0.1 g (Appendix VIII N).

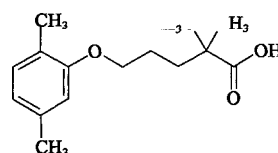
Sterility Comply with the requirement for sterility (Appendix XI H).

Category As described under Gelatin.

Strength (1) 2 cm × 2 cm × 0.5 cm
(2) 6 cm × 2 cm × 0.5 cm
(3) 6 cm × 6 cm × 1 cm
(4) 8 cm × 6 cm × 0.5 cm

Storage Preserve in hermetically sealed containers.

Gemfibrozil



$C_{15}H_{22}O_3$ 250.34

[25812-30-0]

Gemfibrozil is 2,2-dimethyl-5-(2,5-xylyloxy) valeric acid. It contains not less than 98.0% and not more than 102.0% of $C_{15}H_{22}O_3$, calculated on the anhydrous basis.

Description A white crystalline powder; odourless; tasteless. Very soluble in chloroform; freely soluble in methanol, ethanol, acetone or hexane; insoluble in water; freely soluble in sodium hydroxide TS.

Melting range 58-61°C (Appendix VI C).

Identification (1) Dissolve about 50 mg in 3 ml of ethanol. To 5 drops of the solution, add 2 drops of each of a 2% potassium iodide solution and a 4% potassium iodate solution, heat on a water bath for 1 minute, cool and add 2 drops of starch IS; a blue colour is produced.

(2) The infrared absorption spectrum (Appendix IV C) is concordant with the reference spectrum of gemfibrozil

(Appendix XVI).

Related substances Carry out the method as described under the Assay. Dissolve a quantity of the substance being examined in the mobile phase to produce a solution containing 10 mg per ml and use this solution as a test solution. Dilute a quantity of the solution, accurately measured, with the mobile phase to produce a solution containing 0.2 mg per ml and use this solution as a reference solution. Inject 50 μ l of each of the two solutions, accurately measured, into the column, and record the chromatogram for twice of the retention time of the principal peak. The sum of the areas of all peaks other than the principal peak in the chromatogram obtained with the test solution is not greater than the area of the principal peak in the chromatogram obtained with the reference solution; the maximum area of all the peaks other than the principal peak in the chromatogram obtained with the test solution is not greater than 10% of the area of the principal peak in the chromatogram obtained with the reference solution.

Water Not more than 0.25% (Appendix VIII M, method 1 A).

Residue on ignition Not more than 0.1% (Appendix VIII N), using 1.0 g.

Heavy metals Carry out the limit test for heavy metals (Appendix VIII H method 2), using the residue obtained in the test for Residue on ignition; not more than 0.002%.

Assay Carry out the method for high performance liquid chromatography (Appendix V D), using a column packed with octadecylsilane bonded silica gel and a mixture of methanol-water-glacial acetic acid (75 : 24 : 1) as the mobile phase. Detection wavelength is 276 nm and the number of the theoretical plates of the column is not less than 1500, calculated with reference to the peak of gemfibrozil.

Procedure Dissolve a quantity, accurately weighed, in the mobile phase to produce a solution containing 0.2 mg per ml. Inject 10 μ l of the resulting solution, accurately measured, into the column, and record the peak area correspondingly obtained in the chromatogram. Repeat the operation using gemfibrozil CRS instead. Calculate the content of $C_{15}H_{22}O_3$ with respect to the peak area obtained in the chromatogram by the external standard method.

Category Hypolipidaemic.

Storage Preserve in tightly closed containers.

Preparation Gemfibrozil Capsules

Gemfibrozil Capsules

Gemfibrozil Capsules contain not less than 90.0% and not more than 110.0% of the labelled amount of Gemfibrozil ($C_{15}H_{22}O_3$).

Description Capsules containing a white powder.

Identification (1) Shake a quantity of the contents, equivalent to about 60 mg of Gemfibrozil, with 3 ml of ethanol and filter. The filtrate complies with the test (1) for the Identification described under Gemfibrozil.

(2) Shake a quantity of the contents, equivalent to about 100 mg of Gemfibrozil, with 10 ml of 0.1 mol/L sodium hydroxide solution and filter. Transfer the filtrate to a centrifuge tube, acidify with dilute sulfuric acid until a precipitate is formed, centrifuge and discard the supernatant liquid. Wash the precipitate with a small quantity of water in portions and filter under reduced pressure. Dry the

precipitate over silica gel for 12 hours. The infrared absorption spectrum of the residue (Appendix IV C) is concordant with the reference spectrum of gemfibrozil (Appendix XVI).

Dissolution Carry out the dissolution test (Appendix X C, method 2), using 900 ml of phosphate buffer (dissolve 27.22 g of potassium dihydrogen phosphate and 5.52 g of sodium hydroxide in water to produce 1000 ml, adjust to pH 7.5 and shake thoroughly) as the dissolution medium, adjust the rotational speed of the paddle to 50 rpm. Withdraw a quantity of the solution after exactly 45 minutes and filter. Dilute a quantity of successive filtrate, accurately measured, with 1 mol/L sodium hydroxide solution to produce a solution containing about 70 μ g per ml. Dissolve a quantity of gemfibrozil CRS, accurately weighed, in 1 mol/L sodium hydroxide solution to produce a solution containing 70 μ g per ml. Measure the absorbances of the resulting solutions at 276 nm (Appendix IV A). Calculate the dissolution of $C_{15}H_{22}O_3$ from each capsule. Not less than 80% of the labelled amount is dissolved.

Other requirements Comply with the general requirements for capsules (Appendix I E).

Assay To an accurately weighed quantity of the mixed contents in the test for Weight variation, equivalent to about 50 mg of Gemfibrozil, in a 50 ml volumetric flask, add the mobile phase described in the Assay under Gemfibrozil to dissolve gemfibrozil and dilute with the mobile phase to volume, mix well and filter. Transfer 5 ml of the successive filtrate, accurately measured, to a 25 ml volumetric flask, dilute with the mobile phase to volume. Carry out the Assay described under gemfibrozil beginning at the words "Inject 10 μ l of the resulting solution, accurately measured, into the column...". Calculate the content of $C_{15}H_{22}O_3$.

Category As described under Gemfibrozil.

Strength (1) 0.15 g (2) 0.3 g

Storage Preserve in tightly closed containers, stored in a cool and dry place.

Gentamycin Sulfate

[1405-41-0]

Gentamycin Sulfate has a potency of not less than 590 Gentamycin Units per mg, calculated on the anhydrous basis.

Description A white or almost white powder; odourless; hygroscopic. Freely soluble in water; insoluble in ethanol, acetone, chloroform or ether.

Specific optical rotation $+107^\circ$ to $+121^\circ$, in a solution of 50 mg per ml in water (Appendix VI E).

Identification (1) Dissolve 5 mg in 1 ml of water, add 1 ml of 0.1% ninhydrin in *n*-butanol saturated with water and 0.5 ml of pyridine, heat in a water bath for 5 minutes; a purplish-blue is immediately produced.

(2) Carry out the method for thin layer chromatography (Appendix V B), using silica gel G as the coating substance and the lower layer of a mixture of chloroform-methanol-ammonia solution (1 : 1 : 1) (stand for 1 hour) as the mobile phase. Activate the plate at 105°C for 2 hours, apply separately to the plate 2 μ l each of two solutions in water containing (1) 20 mg per ml of the substance being examined and (2) 20 mg per ml of gentamicin RS. After developing and removal of the plate, allow to dry at $20-25^\circ\text{C}$

and expose it to iodine vapor. The colour and position of the principal spots in the chromatogram obtained with solution (1) correspond to that of principal spots obtained with solution (2).

(3) The infrared absorption spectrum (Appendix IV C) is concordant with the reference spectrum of gentamycin sulfate (Appendix XVI).

(4) The aqueous solution yields the reactions characteristic of sulfates (Appendix III).

Acidity An aqueous solution of 40 mg per ml, pH 4.0-6.0 (Appendix VI H).

Clarity and colour of solution To 5 portions add water respectively to produce solutions of 80 mg per ml, the solutions are clear and colourless. Any opalescence produced is not more pronounced than that of reference suspension 1 (Appendix IX B); any colour produced is not more intense than that of reference solution Y₂ or YG₂ (Appendix IX A, method 1).

Sulfates Dissolve 0.125 g, accurately weighed, in 100 ml of water and adjust the solution to pH 11 with concentrated ammonia solution. Add accurately 10.0 ml of 0.1 mol/L barium chloride VS and five drops of phthalein purple IS. Titrate with 0.05 mol/L disodium edetate (Notice: keep the pH value at 11 during the titration) until the colour of the solution begins to change, add 50 ml of alcohol and continue the titration until the violet-blue colour disappear. Perform a blank determination and make any necessary correction. Each ml of barium chloride (0.1 mol/L) VS is equivalent to 9.606 mg of SO₄, not less than 32.0% and not more than 35.0%, calculated on the anhydrous basis.

Water Not more than 15.0% (Appendix VIII M A, method 1).

Residue on ignition Not more than 0.5% (Appendix VIII N).

Bacterial endotoxin Carry out the test for bacterial endotoxin (Appendix XI E), less than 0.5 EU per 1000 Gentamycin Units.

Gentamicin C components Carry out the method for high-performance liquid chromatography (Appendix V D), using a column packed with octadecylsilane bonded silica gel (pH adaptive value is within 0.8-8.0) and a mixture of 0.2 mol/L trifluoroacetic acid-methanol (92 : 8) as the mobile phase. The flow rate is 0.6 ml per minute. The temperature of the drift tube of evaporative light-scattering detector (ELSD) is at 110°C, the flow rate of the carrier gas is 2.8 L per minute and impactor is off (these parameters can be adjusted if necessary). Dissolve an amount of gentamycin CRS and micronomicin CRS in water to obtain a solution containing 0.2 mg each of the two substances per ml. Inject 10 µl of the solution into the column. The elution order of the five major components in the chromatogram from the second peak is C_{1a}, C₂, micronomicin, C_{2a}, C₁ respectively. The resolution factors among the peaks of C₂, micronomicin and C_{2a} comply the related requirements. The relative standard deviation (RSD) of the areas of micronomicin for replicate injections is less than 2.0%.

Procedure Dissolve about 20, 50, 100 mg of micronomicin CRS, accurately weighted, with the mobile phase to volume in three 100 ml volumetric flasks respectively as reference solution (1), (2), (3). Inject 20 µl each of the three solutions into the column. Based on the corresponding concentrations (C) and areas (A) of micronomicin in reference solution (1), (2), (3), the linear regression equation of logA versus logC can be determined. The correlation coefficient (r) of the regression equation should be greater than 0.99. Dissolve a quantity of the substance

being examined, accurately weighted, in the mobile phase to produce solutions of 2.5 mg of gentamycin per ml. Inject 20 µl of the solution into the column. Calculate the corresponding concentrations of gentamycin C components (X_{C_{1a}}, X_{C₂}, X_{C_{2a}}, X_{C₁}) with respect to the regression equation of micronomicin and the corresponding peak areas of C_{1a}, C₂, C_{2a}, C₁ in the chromatogram of the substance being examined. The ratio of gentamycin C components was calculated based on the following formula:

$$C_x(\%) = \frac{X_{C_x}}{X_{C_{1a}} + X_{C_2} + X_{C_{2a}} + X_{C_1}} \times 100\%$$

where C_x (%) is the ratio of gentamycin C_x (C_{1a}, C₂, C_{2a}, C₁);

X_{C_x} is the corresponding concentrations of C_{1a}, C₂, C_{2a}, C₁.

C₁ is 25%-50%, C_{1a} is 15%-40%, C₂+C_{2a} is 20%-50%.

Assay Dissolve an accurately weighed quantity in sterile water to produce a solution of 1000 Units per ml and carry out the method for microbiological assay of antibiotics (Appendix XI A). The confidence-limit rate is not more than 7%. 1000 Units is equivalent to 1 mg of gentamycin.

Category Aminoglycoside antibiotics.

Storage Preserve in tightly closed containers, stored in a dry place.

Preparation (1) Gentamycin Sulfate Eye Drops
(2) Gentamycin Sulfate Granules
(3) Gentamycin Sulfate Injection
(4) Gentamycin Sulfate Sustained-release Tablets
(5) Gentamycin Sulfate Tablets

Gentamycin Sulfate Eye Drops

Gentamycin Sulfate Eye Drops contain not less than 90.0% and not more than 110.0% of the labelled potency of Gentamycin. It may contain suitable preservatives.

Description A clear, colourless liquid.

Identification Comply with the tests (1), (2) and (4) for Identification described under Gentamycin Sulfate.

pH value 5.0-7.0 (Appendix VI H).

Colour of solution The eye drops are colourless; any colour produced is not more intense than that of reference solution Y₁ (Appendix IX A, method 1).

Other requirements Comply with the general requirements for eye preparations (Appendix I G).

Assay Measure accurately a quantity and carry out the Assay described under Gentamycin Sulfate.

Category As described under Gentamycin Sulfate.

Strength 8 ml : 40000 Units

Storage Preserve in tightly closed containers, stored in a cool and dark place.

Gentamycin Sulfate Granules

Gentamycin Sulfate Granules contain not less than 90.0% and not more than 110.0% of the labelled amount of gentamycin.

Description Soluble granules.

Identification (1) To a quantity of the powder add water to produce a solution of about 1 mg of gentamycin per ml. The solution complies with the test (1) for Identification described under Gentamycin Sulfate, using 1 ml.

(2) Carry out the method for thin layer chromatography (Appendix V B), using silica gel G as the coating substance and the lower layer of a mixture of chloroform-methanol-ammonia solution (1 : 1 : 1) as the mobile phase. Activate the plate at 105°C for 2 hours, apply separately to the plate 5 µl each of three solutions in water containing (1) 1 mg of gentamycin of the substance being examined per ml, (2) 1 mg of gentamycin of gentamycin RS per ml and (3) 1 mg of gentamycin each of the substance being examined and gentamycin sulfate RS per ml. After developing and removal of the plate, allow to dry at 20-25°C and expose it to iodine vapor. The number of the principal spots in the chromatogram obtained with solution (3) correspond to that of the principal spots obtained with solution (2); the number, colour and position of the principal spots in the chromatogram obtained with solution (1) correspond to that of the principal spots obtained with solution (3).
(3) Comply with test (3) for Identification described under Gentamycin Sulfate.

Loss on drying When dried in vacuum over phosphorous pentoxide to constant weight at 60°C, loses not more than 2.0% of its weight (Appendix VIII L).

Other requirements Comply with the general requirements for granules (Appendix I N).

Assay Dissolve an accurately weighed quantity of the mixed contents obtained in weight variation in sterile water to produce a solution of 100 Units per ml and carry out the Assay described under Gentamycin Sulfate.

Category As described under Gentamycin Sulfate.

Strength (1) 10 mg (10000 Units)
(2) 40 mg (40000 Units)

Storage Preserve in tightly closed containers, stored in a cool, dark and dry place.

Gentamycin Sulfate Injection

Gentamycin Sulfate Injection is a sterile aqueous solution of gentamycin sulfate. It contains not less than 90.0% and not more than 110.0% of the labelled amount of Gentamycin.

Description A clear, colourless or almost colourless liquid.

Identification Comply with the tests (1), (2) and (4) for Identification described under Gentamycin Sulfate.

pH value 3.5-6.0 (Appendix VI H).

Colour of solution The solution is colourless; any colour produced is not more intense than that of reference solution Y₂ or YG₂ (Appendix IX A, Method 1).

Sterility Transfer the samples to not less than 500 ml of 0.9% sterile sodium chloride solution. Carry out the test for sterility (Appendix XI H, membrane filtration method).

Bacterial endotoxin Comply with the corresponding requirements described under Gentamycin Sulfate.

Other requirements Complies with the general requirements for injections (Appendix I B).

Gentamicin C components Dilute an accurately measured

volume of the mixed sample solution ($n \geq 10$) with water to obtain a solution of 1.5 mg per ml, carry out the method described under Gentamycin sulfate, C_1 is 25%-50%, C_{1a} is 15%-40%, $C_{2a} + C_2$ is 20%-50%.

Assay Measure accurately a quantity and carry out the Assay described under Gentamycin Sulfate.

Category As described under Gentamycin Sulfate.

Strength (1) 1 ml : 20000 Units
(2) 1 ml : 40000 Units
(3) 2 ml : 80000 Units

Storage Preserve in tightly closed containers, stored in a cool and dark place.

Gentamycin Sulfate Sustained-release Tablets

Gentamycin Sulfate Sustained-release Tablets contain not less than 90.0% and not more than 110.0% of the labelled amount of gentamycin.

Description White or almost white tablets.

Identification To a quantity of powdered tablets equivalent to about 40 mg of gentamycin, add 4 ml of water, shake thoroughly to dissolve and filter. The filtrate complies with the tests (1), (2) and (4) for Identification described under Gentamycin Sulfate.

Drug release Carry out the method for drug release (Appendix X D, method 1), using the equipment described under the dissolution test (Appendix X C, method 1) using 0.1 mol/L hydrochloric acid solution as the release medium, adjust the rotational speed of the basket to 100 rpm. Withdraw 5 ml of the solution at exactly 2, 4 and 6 hours respectively, filter and supply 5 ml of the same release medium accordingly in the vessel immediately. Measure accurately 3 ml of the successive filtrate to a test tube with stopper, add 2.2 ml of isopropanol, 0.8 ml of phthalaldehyde TS, stopper tightly, mix well. Heat in a water bath at 60°C for 15 minutes and cool. Determine the absorption spectra of the resulting solution within the range of 300-400 nm (Appendix IV A) and transform it into first derivative spectra (a plot of the gradient of the absorption curve (rate of change of the absorbance with wavelength)). Measure the absorbance of first derivative spectra at the maximum peak valley within 350-360 nm. Dissolve an accurately weighed quantity of the 10 powdered tablets equivalent to about the average weight of one tablet in a quantity of 0.1 mol/L hydrochloric acid solution in a 500 ml volumetric flask, shake thoroughly, dilute to volume and mix well. Measure accurately 25 ml of the supernatant liquid to a 50 ml volumetric flask, dilute with 0.1 mol/L hydrochloric acid solution to volume, and mix well. Filter, measure accurately 3 ml of the successive filtrate to a test tube with stopper as a reference solution, measure the absorbance in the same manner as the test solution. Calculate the content of gentamycin sulfate dissolved from each tablet at 2, 4 and 6 hours separately with respect to the absorption of first derivative spectra of the test solutions and that of the reference solution. The dissolution of gentamycin sulfate complies with the requirement; the quantity dissolved from each tablet is 45%-70%, 60%-80% and over 80% of the labelled amount at 2, 4 and 6 hour, respectively. If 1 tablet in 6 tablets at each test time fails to pass the test, but the average quantity dissolved lies in the specified range, it still complies with the requirement. If the amount of gentamycin sulfate dissolved from 1 tablet at last test time is less than

10% of the specified quantity, repeat the test with 6 further tablets. The average quantity dissolved from 12 tablets at each test time all lie in the specified range and not more than 2 of 12 tablets is less than 10% of the specified quantity at the last test time, it complies with the requirement.

Other requirements Comply with the general requirements for tablets (Appendix I A).

Assay Weigh accurately and powder 10 tablets. Weigh accurately a quantity of the powder equivalent to about 0.1 g of gentamycin. Add a quantity of sterile water, shake thoroughly to dissolve gentamycin sulfate, dilute to produce a suspension of about 1000 Units per ml, mix well and allow it to stand. Filter, measure accurately a quantity of the successive filtrate and carry out the Assay described under Gentamycin Sulfate.

Category As described under Gentamycin sulfate.

Strength 40 mg (40000 Units)

Storage Preserve in tightly closed containers, Stored in a dry place.

Gentamycin Sulfate Tablets

Gentamycin Sulfate Tablets contain not less than 90.0% and not more than 110.0% of the labelled amount of gentamycin.

Description White tablets or sugar coated tablets.

Identification To a quantity of powdered tablets (equivalent to about 40 mg of gentamycin, with coating removed) add 2 ml of water, shake well and filter. The filtrate complies with the tests (1), (2) and (4) for Identification described under Gentamycin Sulfate.

Other requirements Comply with the general requirements for tablets (Appendix I A).

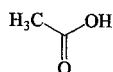
Assay Weigh accurately and powder 10 tablets. Weigh accurately a quantity of the powder equivalent to about 0.1 g of gentamycin; or triturate 4 sugar coated tablets with sterile water, shake thoroughly. Dilute with sterile water to produce a suspension of about 1000 Units per ml, mix well and allow it to stand. Measure accurately a quantity of the supernatant and carry out the Assay described under Gentamycin Sulfate.

Category As described under Gentamycin Sulfate.

Strength (1) 20 mg (20000 Units)
(2) 40 mg (40000 Units)

Storage Preserve in tightly closed containers, protected from light and stored in a cool and dry place.

Glacial Acetic Acid



$C_2H_4O_2$ 60.05

[64-19-7]

Glacial Acetic Acid contains not less than 99.0% (g/g) of $C_2H_4O_2$.

Description A clear colourless liquid or colourless crystalline mass; odour, strong and characteristic.

Miscible with water, ethanol, glycerin or most of the volatile oils and fatty oils.

Congeeing point Not less than 14.8°C (Appendix VI D).

Identification (1) Mix 1 ml with 1 ml of water, neutralize with sodium hydroxide TS, add ferric chloride TS, a deep red colour is produced. Boil, a reddish-brown precipitate is produced which dissolves in hydrochloric acid to form a yellow solution.

(2) Heat a small quantity with a few ml of sulfuric acid and ethanol, an odour of ethyl acetate is produced.

Chloride Dilute 10 ml with 20 ml of water. Carry out the limit test for chlorides (Appendix VIII A), any opalescence produced is not more pronounced than that of a reference using 4.0 ml of sodium chloride standard solution (0.0004%).

Sulfate To 20 ml add 1 ml of 1% anhydrous sodium carbonate solution, evaporate to dryness on a water bath. Carry out the limit test for sulfates (Appendix VIII B). Any opalescence produced is not more pronounced than that of a reference using 1.0 ml of potassium sulfate standard solution (0.0005%).

Formic acid and readily oxidizable substances Dilute 5 ml with 10 ml of water. To 5 ml of the resulting solution add 2.5 ml of potassium dichromate (0.01667 mol/L) VS and 6 ml of sulfuric acid, allow to stand for 1 minute, add 20 ml of water, cool to 15°C, add 1 ml of potassium iodide TS, a deep yellow or brown colour is produced immediately.

Reducing substances To 2 ml add 10 ml of water and 0.10 ml of potassium permanganate (0.02 mol/L) VS, mix well, allow to stand for 30 minutes, the pink colour is not entirely discharged.

Non-volatile substances Evaporate 20 ml in a tared evaporating dish to dryness on a water bath, dry at 105°C to constant weight, the residue is not more than 1 mg.

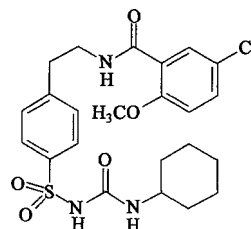
Heavy metals Evaporate 10 ml to dryness on a water bath, add 2 ml of acetate BS (pH 3.5) and 15 ml of water, heat gently to dissolve, add a quantity of water to 25 ml. Carry out the limit test for heavy metals (Appendix VIII H, method 1); not more than 0.0002%.

Assay Transfer about 2 ml to a tared conical flask with stopper. Weigh accurately, add 40 ml of freshly boiled and cooled water and 3 drops of phenolphthalein IS, titrate with sodium hydroxide (1 mol/L) VS. Each ml of sodium hydroxide (1 mol/L) VS is equivalent to 60.05 mg of $C_2H_4O_2$.

Category Corrosive.

Storage Preserve in tightly closed containers.

Glibenclamide



$C_{23}H_{28}ClN_3O_5S$ 494.01

[10238-21-8]

Glibenclamide is 1-{ 4-[2-(5-chloro-2-methoxybenzamido) ethyl] benzenesulfonyl}-3-cyclohexylurea.

It contains not less than 99.0% of $C_{23}H_{28}ClN_3O_5S$ calculated on the dried basis.

Description A white crystalline powder; almost odourless; tasteless.

Sparingly soluble in chloroform; slightly soluble in methanol or ethanol; insoluble in water or ether.

Melting range 170-174°C, with decomposition (Appendix VI C).

Identification (1) The light absorption of a 0.10 mg per ml solution in ethanol exhibits maxima at 274 and 300 nm, minima at 272 nm and 278 nm (Appendix IV A).

(2) The infrared absorption spectrum (Appendix IV C) is concordant with the reference spectrum of glibenclamide (Appendix XVI).

(3) Mix 0.1 g with 0.2 g of potassium nitrate. Heat gently until it is thoroughly charred and then ignite until the incineration is complete, cool, add 10 ml of water to dissolve the residue and filter. The filtrate yields the reactions characteristic of chlorides and of sulfates (Appendix III).

Chloride Boil 1.0 g with 50 ml of water, cool rapidly, filter, add water to make the filtrate 50 ml. Carry out the limit test for chlorides (Appendix VIII A), using 25 ml of the solution. Any opalescence produced is not more pronounced than that of a reference using 7.0 ml of sodium chloride standard solution (0.014%).

Sulfate Carry out the limit test for sulfates (Appendix VIII B), using 25 ml of the solution obtained in the test for chloride. Any opalescence produced is not more pronounced than that of a reference using 2.0 ml of potassium sulfate standard solution (0.040%).

Related substances Dissolve 25 mg, weighed accurately, in a 25 ml volumetric flask with methanol with ultrasonication and dilute to volume with methanol, mix well. Measure accurately 5 ml to a 10 ml volumetric flask, dilute to volume with mobile phase, mix well as the test solution. Measure accurately 1 ml to a 200 ml volumetric flask; dilute to volume with mobile phase as the reference solution (1). Dissolve 15 mg of each of 4-[2-(5-chloro-2-methoxy-benzamido) ethyl] benzenesulfonamide CRS and 4-[2-(5-chloro-2-methoxy-benzamido) ethyl] benzenesulfonyl-*N*-methyl carbamate CRS, weighed accurately, in 10 ml methanol with ultrasonicate respectively, dilute with mobile phase to produce each of a solution of 3 µg per ml as reference solution (2) and (3). Detection wavelength is 300 nm. Carry out the method described under Assay, inject 20 µl of reference solution (2) into the column, adjust the attenuation so that the principal peak height in the chromatogram is 10%-15% of the full scale of the chart. Inject 20 µl of reference solution (1), (3) and test solution separately, record the chromatogram. Record the chromatogram of test solution for twice the retention time of the principal peak. The area of the peak obtained with test solution corresponding to the principal peak of reference solution (2) and (3) is not greater than the area of the principal peak in the chromatogram obtained with reference solution (2) and (3). The sum of the areas of all peaks other than the principal peak obtained with test solution is not greater than the area of the principal peak in the chromatogram obtained with reference solution (1).

Loss on drying When dried to constant weight at 105°C, loses not more than 0.5% of its weight (Appendix VIII L).

Residue on ignition Not more than 0.1% (Appendix VIII N), using 1.0 g.

Heavy metals Carry out the limit test for heavy metals

(Appendix VIII H, method 2), using the residue obtained in the test for Residue on ignition, not more than 0.001%.

Assay Carry out the method for high Performance liquid chromatography (Appendix V D), using a column packed with octadecylsilane bonded silica gel. The mobile phase is methanol-ammonium dihydrogen phosphate solution (Dissolve 1.725 g of ammonium dihydrogen phosphate with water in a 300 ml volumetric flask, adjust pH 3.5 ± 0.05 with phosphate) (5 : 3). Detection wavelength is 274 nm, and the number of theoretical plates of the column is not less than 5000, calculated with reference to the peak of glibenclamide and the resolution factor between peaks of glibenclamide and internal standard complies with the related requirements.

Internal standard solution Dissolve 10 mg of butyl *p*-hydroxybenzoate in 6 ml methanol in a 100 ml volumetric flask with ultrasonication, dilute to volume with mobile phase, mix well.

Procedure Dissolve about 20 mg of glibenclamide CRS, weighed accurately, in 12 ml of methanol in a 50 ml volumetric flask with ultrasonication, dilute to volume with mobile phase, mix well. Measure accurately 25 ml and 5 ml of the internal standard solution in a 50 ml volumetric flask, dilute to volume with mobile phase, mix well. Inject 20 µl into the column, record the chromatogram. Repeat the operation using 20 mg of the substance being examined instead of the glibenclamide CRS. Calculate the content of $C_{23}H_{28}ClN_3O_5S$ with respect to the peak area obtained in the chromatogram by the internal standard method.

Category Hypoglycaemic.

Storage Preserve in tightly closed containers.

Preparation Glibenclamide Tablets

Glibenclamide Tablets

Glibenclamide Tablets contain not less than 90.0% and not more than 110.0% of the labelled amount of glibenclamide ($C_{23}H_{28}ClN_3O_5S$).

Description White tablets.

Identification (1) To a quantity of the powdered tablets equivalent to about 10 mg of glibenclamide add a quantity of ethanol to dissolve glibenclamide and filter, dilute the filtrate with ethanol to 100 ml. The solution complies with test (1) for Identification described under Glibenclamide.

(2) A quantity of the powdered tablets equivalent to about 0.1 g of glibenclamide, complies with test (3) for Identification described under Glibenclamide.

Related substances Weigh accurately a quantity of the powdered tablets, equivalent to about 25 mg of glibenclamide, to a 25 ml volumetric flask, add a quantity of methanol, ultrasonicate to dissolve, dilute to volume with methanol and mix well. Filter, measure accurately 5 ml of the successive filtrate to a 10 ml volumetric flask, dilute to volume with mobile phase, mix well as the test solution. Measure accurately 1 ml in 100 ml volumetric flask, dilute to volume with mobile phase, mix well, carry out the test of related substances described under Glibenclamide, beginning at the words "as the reference solution (1)..."

Content uniformity Comply with the requirement (Appendix X E). Triturate 1 tablet with 40 ml of ethanol in portions and transfer to a 50 ml volumetric flask. Heat on a water bath for 10 minutes and shake to dissolve glibenclamide, cool to room temperature, dilute to volume with ethanol, mix well

and filter. Measure separately the absorbances of the successive filtrate at 300 nm and 340 nm (Appendix IV A), calculate the difference of the two absorbances as ΔA . Dissolve a quantity of glibenclamide CRS, measured accurately, in ethanol to produce a solution of about 50 μg per ml, and take the same operation above to get the ΔA , calculate the content of $\text{C}_{22}\text{H}_{29}\text{FO}_5$.

Dissolution Carry out the dissolution test (Appendix X C, method 3), using 250 ml of 0.02% trometamol as the dissolution medium, adjust the rotational speed of the paddle to 75 rpm. Withdraw 10 ml of the solution after exactly 45 minutes and filter, using the successive filtrate as the test solution. Weigh accurately about 10 mg of glibenclamide CRS in a 100 ml volumetric flask, add 10 ml of ethanol, ultrasonicate to dissolve, dilute to volume with the dissolution medium and mix well. Measure accurately 5 ml to a 50 ml volumetric flask, dilute to volume with dissolution medium, mix well as the reference solution. Measure the absorbances of the resulting solutions at 225 nm (Appendix IV A), calculate the dissolution of $\text{C}_{23}\text{H}_{28}\text{ClN}_3\text{O}_5\text{S}$ from each tablet. Not less than 75% of the labelled amount is dissolved.

Other requirements Comply with the general requirements for tablets (Appendix I A).

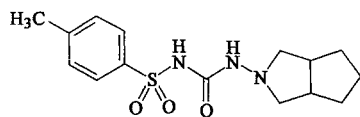
Assay Weigh accurately and powder 20 tablets. Transfer an accurately weighed quantity of the powder equivalent to about 20 mg of glibenclamide to a 50 ml volumetric flask, add 12 ml of ethanol, sonicate to dissolve, add mobile phase and dilute to volume, mix well, filter, transfer 25 ml of successive filtrate and 5 ml of the internal standard in 50 ml volumetric flask with mobile phase and dilute to volume, mix well, Inject about 20 μl into the column, carry out the test for Assay described under Glibenclamide.

Category As described under Glibenclamide.

Strength 2.5 mg

Storage Preserve in well closed containers.

Gliclazide



$\text{C}_{15}\text{H}_{21}\text{N}_3\text{O}_3\text{S}$ 323.41

[21187-98-4]

Gliclazide is 1-(3-Azabicyclo [3.3.0]-oct-3-yl)-3-(p-tolylsulfonyl) urea. It contains not less than 98.5% of $\text{C}_{15}\text{H}_{21}\text{N}_3\text{O}_3\text{S}$, calculated on the dried basis.

Description White crystals or a crystalline powder; odourless; tasteless.

Soluble in chloroform; sparingly soluble in methanol; slightly soluble in ethanol; insoluble in water.

Melting range 162-166°C (Appendix VI C).

Identification (1) To a small quantity add pyridine dropwise until it almost dissolves, and then add 5 drops of cupric sulfate TS, shake; a bluish violet colour is produced. (2) The light absorption of a solution of 10 μg per ml in ethanol exhibits a maximum at 228 nm (Appendix IV A). (3) The infrared absorption spectrum (Appendix IV C) is concordant with the reference spectrum of gliclazide (Appendix XVI).

Related substances Carry out the method for thin-layer chromatography (Appendix V B), using silica gel G as the coating substance and a mixture of ethyl acetate-chloroform-methanol (6 : 4 : 2) as the mobile phase. Apply separately to the plate 10 μl each of two solutions in chloroform containing (1) 20 mg per ml and (2) 0.2 mg per ml of the substance being examined. After developing and removal of the plate, dry in air and spray with a solution of ninhydrin and stannous chloride in ethanol (to 0.4 g of ninhydrin and 40 mg of stannous chloride add 20 ml of ethanol, shake to dissolve, prepare the solution freshly before use), after drying, spray with the same solution again, heat at 120°C for 30 minutes. Any spot, other than the principal spot in the chromatogram, obtained with solution (1) is not more intense than the principal spot obtained with solution (2).

Loss on drying When dried to constant weight at 105°C, loses not more than 1.0% of its weight (Appendix VIII L).

Residue on ignition Not more than 0.1% (Appendix VIII N).

Heavy metals Carry out the limit test for heavy metals (Appendix VIII H, method 2), using the residue obtained in the test for Residue on ignition; not more than 0.001%.

Assay Dissolve about 0.2 g, accurately weighed, in 50 ml of glacial acetic acid. Carry out method for potentiometric titration (Appendix VII A), titrate with perchloric acid (0.1 mol/L) VS. Perform a blank determination and make any necessary correction. Each ml of perchloric acid (0.1 mol/L) VS is equivalent to 32.34 mg of $\text{C}_{15}\text{H}_{21}\text{N}_3\text{O}_3\text{S}$.

Category Hypoglycaemic.

Storage Preserve in tightly closed containers, protected from light.

Preparation Gliclazide Tablets (II)

Gliclazide Tablets (II)

Gliclazide Tablets (II) contain not less than 93.0% and not more than 107.0% of the labelled amount of gliclazide ($\text{C}_{15}\text{H}_{21}\text{N}_3\text{O}_3\text{S}$).

Description White tablets.

Identification (1) Shake and extract a quantity of powdered tablets equivalent to about 0.4 g of gliclazide with two 10 ml portions of chloroform, filter and evaporate to dryness on a water bath. The residue, after drying at 105°C, complies with test (1) for Identification described under Gliclazide. (2) Dissolve a quantity of the residue obtained above in ethanol to produce a solution containing 10 μg per ml. The light absorption of the resulting solution exhibits a maximum at 228 nm (Appendix IV A).

Dissolution Carry out the method for dissolution test (Appendix X C, method 1), using 1000 ml of phosphate buffer (pH 8.6) (Dissolve 42.0 g of sodium hydroxide in 5000 ml of carbon dioxide-free water and shake thoroughly as solution A. Dissolve 136.0 g of potassium dihydrogen phosphate in 5000 ml of carbon dioxide-free water and shake thoroughly as solution B. To the mixture of 2300 ml of solution A and 2500 ml of solution B add 3150 ml of ethanol (3000 ml of dehydrated ethanol), mix well, dilute with carbon dioxide-free water to 10000 ml and mix well. The pH of the resulting solution is 8.60 ± 0.05) as the dissolution medium and adjust the rotation speed of the basket to 150 rpm. Withdraw a sample of 8 ml of the solution at exactly 60 and 180 minutes respectively, filter, use the successive filtrate as the test solution, and supply with 8 ml of

phosphate buffer (pH 8.6) accordingly in the vessel immediately. Weigh accurately 20 mg of gliclazide CRS into a 250 ml volumetric flask, add a quantity of dissolution medium, shake to dissolve it in a warm water bath. Cool, dilute with dissolution medium to volume and mix well as the reference solution. Transfer 5 ml each of the above solutions, accurately measured, to two 25 ml volumetric flasks respectively, dilute with dissolution medium to volume and mix well. Measure the absorbances of the resulting solutions at 226 nm. Calculate the content of $C_{15}H_{21}N_3O_4S$ dissolved from each tablet at 60 and 180 minutes separately. Not more than 50% and not less than 75% of the labelled amount is dissolved in 60 and 180 minutes respectively.

Other requirements Comply with the general requirements for tablets (Appendix I A).

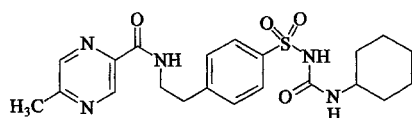
Assay Weigh accurately and powder 10 tablets. To an accurately weighed quantity of the powdered tablets equivalent to about 80 mg of gliclazide add 50 ml of chloroform, shake for 30 minutes to dissolve gliclazide. Filter through a sintered-glass filter (No. 4), wash the filter with 25 ml of chloroform in portions, combine the filtrate and washings, and evaporate to dryness in vacuum at a temperature below 40°C. Dissolve the residue in 40 ml of glacial acetic acid, carry out the method for potentiometric titration (Appendix VII A), titrate with perchloric acid (0.1 mol/L) VS. Perform a blank determination and make any necessary correction. Each ml of perchloric acid (0.1 mol/L) VS is equivalent to 32.34 mg of $C_{15}H_{21}N_3O_4S$.

Category Hypoglycaemic.

Strength 80 mg

Storage Preserve in tightly closed containers, protected from light.

Glipizide



$C_{21}H_{27}N_5O_4S$ 445.54

Glipizide is 1-cyclohexyl-3-[[p-[2-(5-methylpyrazine-2-carboxamido) ethyl] phenyl]-sulfonyl] urea. It contains not less than 98.5% of $C_{21}H_{27}N_5O_4S$, calculated on the dried basis.

Description A white or almost white crystalline powder; odourless; almost flavourless. Slightly soluble in acetone, chloroform and dioxane; very slightly soluble in ethanol; insoluble or practically insoluble in water; freely soluble in dilute sodium hydroxide solution.

Melting range 203-208°C (Appendix VI C).

Identification (1) To 50 mg add 5 ml of dioxane, heat on water bath to dissolve it, add 1 ml of 0.5% 2,4-dinitrofluorobenzene solution in dioxane, boil it for 2 to 3 minutes, a brilliant yellow colour is produced.

(2) The light absorption of a solution of about 25 µg per ml in phosphate BS (pH 7.4) exhibits two maxima at 222 nm and 275 nm (Appendix IV A).

(3) The infrared absorption spectrum (Appendix IV C) is concordant with the reference spectrum of glipizide (Appendix XVI).

Related substances Carry out the method for high performance liquid chromatography (Appendix V D), using a column packed with octadecylsilane bonded silica gel and a mixture of 0.1 mol/L sodium dihydrogen phosphate solution (adjust pH to 6.00 ± 0.05 by 2.0 mol/L sodium hydroxide solution)-methanol (55 : 45) as the mobile phase. Detection wavelength is 225 nm. The number of the theoretical plates of the column is not less than 2000, calculated with reference to the peak of glipizide and the resolution factor between the peaks of glipizide and 4-[2-(5-methylpyrazine-2-carboxamido) ethyl] should comply with the requirement. Dissolve about 25 mg of the substance being examined, weighed accurately, in 25 ml of methanol to a 50 ml volumetric flask, dilute with 0.1 mol/L sodium dihydrogen phosphate solution to volume as solution (1). Measure accurately 1 ml of solution (1) into a 100 ml volumetric flask, dilute with mobile phase to volume, mix well as solution (2). Dissolve about 12.5 mg of 4-[2-(5-methylpyrazine-2-carboxamido) ethyl] CRS, weighed accurately, in methanol to a 50 ml volumetric flask and dilute with methanol to volume, mix well as solution (3). Measure accurately 1 ml of solution (3) into a 100 ml volumetric flask, dilute with mobile phase to volume, mix well as solution (4). Inject 20 µl of solution (2) into the column, adjust the attenuation so that the peak height in the chromatogram is 10%-25% of full scale of the chart. Inject separately accurately 20 µl each of the solution (1), (2) and (4) into the column and record the chromatogram for twice the retention time of the principal peak. If there is any peak in the chromatogram obtained with solution (1) corresponding to the principal peak in the chromatogram obtained with solution (4), its area is not greater than the area of the principal peak in the chromatogram obtained with solution (4), the area of any peak other than the principal peak and the peak mentioned above is not greater than 1/2 of the area of principal peak in the chromatogram obtained with solution (2), the sum of the areas of such peaks is not greater than the area of the principal peak obtained with solution (2).

Loss on drying When dried to constant weight at 105°C, loses not more than 0.5% of its weight (Appendix VIII L).

Residue on ignition Not more than 0.1% (Appendix VIII N), using 1.0 g.

Heavy metals Carry out the limit test for heavy metals (Appendix VIII H, method 2), using the residue obtained in the test for Residue on ignition; not more than 0.002%.

Assay Dissolve about 0.4 g, accurately weighed, in 50 ml of dimethylformamide, add 2 drops of quinaldine red IS, titrate with sodium methoxide (0.1 mol/L) VS until the colour changes from red to colourless. Perform a blank determination and make any necessary correction. Each ml of sodium methoxide (0.1 mol/L) VS is equivalent to 44.55 mg of $C_{21}H_{27}N_5O_4S$.

Category Antidiabetic.

Storage Preserve in tightly closed containers, protected from light.

Preparation (1) Glipizide Capsules (2) Glipizide Tablets

Glipizide Capsules

Glipizide Capsules contain not less than 90.0% and not more than 110.0% of the labelled amount of glipizide ($C_{21}H_{27}N_5O_4S$).

Description Capsules containing white or almost white powder.

Identification (1) The retention time of principle peak of the substance being examined in the chromatogram obtained in the Assay is identical with that of glipizide CRS.

(2) Dissolve a quantity of the contents of the capsules in methanol to produce a solution of about 10 µg per ml and filter. The light absorption of the filtrate exhibits two maxima at 226 nm and 274 nm (Appendix IV A).

Content uniformity Comply with the requirements for content uniformity (Appendix X E). Transfer the content of 1 capsule to a 100 ml volumetric flask (for strength 5 mg) or 50 ml volumetric flask (for strength 2.5 mg), wash the shell with 50 ml (for strength 5 mg) or 25 ml (for strength 2.5 mg) of methanol, transfer the washings to the volumetric flask, treated by ultrasonic for 15 minutes to dissolve glipizide, dilute with 0.1 mol/L sodium dihydrogen phosphate solution to volume, mix well and filter, use the successive filtrate as test solution. Carry out the method as described under the Assay. Calculate the content of $C_{21}H_{27}N_5O_4S$.

Dissolution Carry out the dissolution test (Appendix X C, method 3), using 250 ml (for strength 5 mg) or 125 ml (for strength 2.5 mg) of phosphate BS (pH 7.8-8.0) as the dissolution medium, adjust the rotational speed of the paddle to 100 rpm. Withdraw 10 ml of the solution after exact 45 minutes and filter. Measure the absorbance of the successive filtrate at 274 nm (Appendix IV A). Weigh accurately about 20 mg of glipizide CRS, dissolve in methanol in a 50 ml volumetric flask, add methanol to volume, mix well. Transfer 5 ml of the resulting solution to a 100 ml volumetric flask, dilute to volume with phosphate BS (pH 7.8-8.0) and mix well, measure the absorbance in the same manner. Calculate the dissolution of $C_{21}H_{27}N_5O_4S$ from each capsule. Not less than 70% of the labelled amount is dissolved.

Related substances Dissolve a quantity of the contents of the capsules equivalent to about 25 mg of glipizide in a 50 ml volumetric flask, add 25 ml methanol to dissolve glipizide, dilute with 0.1 mol/L sodium dihydrogen phosphate solution to volume, mix well, filter, use the successive filtrate as the test solution. Accurately measure 1 ml of the test solution, into a 100 ml volumetric flask, add mobile phase to volume and mix well, take the solution as the reference solution (a). Dissolve about 12.5 mg of impurity A 4-[2-(5-methylpyrazine-2-formamido) ethyl] benzene sulphonamide CRS, accurately weighed, in methanol in a 50 ml volumetric flask, dilute with methanol to volume, mix well. Dilute 1.0 ml to 100.0 ml with mobile phase and mix well as the reference solution (b). Carry out the method as described under Assay. Inject 20 µl of the reference solution (a) into the column. Adjust the attenuation so that the principle peak height in the chromatogram is 10%-25% of full scale of the chart. Inject separately 20 µl each of the test solution, the reference solution (a) and (b) into the column, and record the chromatogram for twice the retention time of the principle peak. The area of impurity A peak in the chromatogram obtained with the test solution is not greater than twice of area of the principal peak in the chromatogram obtained with the reference solution (b) (1.0%), the sum of areas of the secondary peaks other than the impurity A, and the principal peak is not greater than twice area of the principal peak in the chromatogram obtained with the reference solution (a).

Other requirements Comply with the general requirements for capsules (Appendix I E).

Assay Carry out the method for high performance liquid chromatography (Appendix V D), using a column packed with octadecylsilane bonded silica gel and a mixture of 0.1 mol/L sodium dihydrogen phosphate solution (adjust to pH 6.00 ± 0.05 with 2.0 mol/L sodium hydroxide solution)-methanol (55 : 45) as the mobile phase. Detection

wavelength is 225 nm and the number of theoretical plates of the column is not less than 2000, calculated with reference to the peak of glipizide.

Procedure Weigh accurately 20 capsules, mix well the contents of the capsules, transfer a quantity, equivalent to about 5 mg of glipizide accurately weighed, in a 100 ml volumetric flask, add 50 ml of methanol, treated by ultrasonic for 15 minutes to dissolve glipizide, dilute with 0.1 mol/L sodium dihydrogen phosphate solution to volume, shake well and filter, inject 20 µl of the successive filtrate into the column, record the chromatogram. Transfer about 25 mg of glipizide CRS, accurately weighed, to a 50 ml volumetric flask, add a quantity of methanol, shake thoroughly to dissolve glipizide and dilute to volume with methanol, mix well. Transfer 5 ml, accurately measured, to another 50 ml volumetric flask, add 20 ml methanol and dilute with 0.1 mol/L sodium dihydrogen phosphate solution to volume, mix well. Repeat the operation as described above. Calculate the content of $C_{21}H_{27}N_5O_4S$ with respect to the peak area obtained in the chromatogram by external standard method.

Category As described under Glipizide.

Strength (1) 2.5 mg (2) 5 mg

Storage Preserve in tightly closed containers, protected from light.

Glipizide Tablets

Glipizide Tablets contain not less than 90.0% and not more than 110.0% of the labelled amount of glipizide $C_{21}H_{27}N_5O_4S$.

Description White tablets or coated tablets.

Identification (1) To powder equivalent to 50 mg of glipizide add 10 ml of dioxane, heat on water bath to dissolve glipizide, add 1 ml of 0.5% 2,4-dinitro-fluorobenzene solution in dioxane, boil it for 2 to 3 minutes, a brilliant yellow colour is produced.

(2) The retention time of principal peak of the substance being examined is identical with that of principal peak of the reference solution in the chromatogram obtained in Assay.

Related substances Carry out the method as described under Assay. Dissolve a quantity of the powdered tablets containing 25 mg of glipizide, weighed accurately, in 25 ml of methanol to a 50 ml volumetric flask, dilute with 0.1 mol/L sodium dihydrogen phosphate solution to volume and filter, take the successive filtrate as solution (1). Measure accurately 1 ml of solution (1) into a 100 ml volumetric flask, dilute with mobile phase to volume, mix well as solution (2). Dissolve about 12.5 mg of impurity A 4-[2-(5-methylpyrazine-2-carboxamido) ethyl] CRS, weighed accurately, in methanol in a 50 ml volumetric flask and dilute with methanol to volume, mix well as solution (3). Measure accurately 1 ml of solution (3) into a 100 ml volumetric flask, dilute with mobile phase to volume, mix well as solution (4). Inject 20 µl of solution (2) into the column, adjust the attenuation so that the peak height in the chromatogram is 10%-25% of full scale of the chart. Inject separately accurately 20 µl each of the solution (1), (2) and (4) into the column and record the chromatogram for twice the retention time of the principal peak. In the chromatogram obtained with solution (1), the area of the peak chromatogram to impurity A is not greater than twice area of the corresponding peak in the chromatogram obtained with solution (4) (1.0%). The sum of the areas of any peak

other than the principal peak and the peak corresponding to impurity A is not greater than twice the area the principal peak of solution (2).

Content uniformity Comply with the requirements for content uniformity (Appendix X E). Take 1 tablet with phosphate BS (pH 7.4) in a mortar and transfer with phosphate BS (pH 7.4) in portions to a 50 ml (for strength 2.5 mg) or 100 ml (for strength 5 mg) volumetric flask. Carry out the method as described under Assay, beginning at the words "mix well, filter and take the successive filtrate as the test solution (1)" and calculate the content of $C_{21}H_{27}N_3O_4S$.

Dissolution Carry out the dissolution test (Appendix X C, method 1), using 500 ml of phosphate BS (pH 7.4) as the dissolution medium, adjust the rotational speed of the basket to 100 rpm. Withdraw 10 ml of the solution after exactly 30 minutes, filter and take successive filtrate as the test solution. Measure 12 mg of glipizide CRS in a 50 ml of volumetric flask, add a quantity of phosphate BS (pH 7.4), heat on water bath to dissolve glipizide and cool; dilute to volume with phosphate BS (pH 7.4) and mix well. Transfer 5 ml to a 200 ml volumetric flask, dilute to volume with phosphate BS (pH 7.4) and mix well as reference solution. Measure the absorbances of the resulting solutions at 222 nm (Appendix IV A). Calculate the dissolution of $C_{21}H_{27}N_3O_4S$ from each tablet. Not less than 80% of the labelled amount is dissolved.

Other requirements Comply with the general requirements for tablets (Appendix I A).

Assay Carry out the method for high performance liquid chromatography (Appendix V D), using a column packed with octadecylsilane bonded silica gel and a mixture of 0.1 mol/L sodium dihydrogen phosphate solution (adjust pH to 6.00 ± 0.05 by 2.0 mol/L sodium hydroxide solution)-methanol (55 : 45) as the mobile phase. Detection Wavelength is 225 nm. The number of the theoretical plates of the column is not less than 2000, calculated with reference to the peak of glipizide.

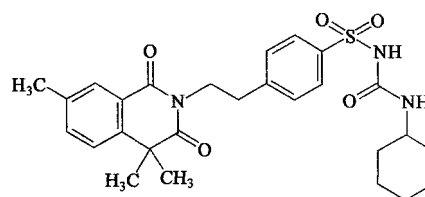
Procedure Weigh accurately and powder 20 tablets. To a quantity, weighed accurately, equivalent to about 5 mg of glipizide in a 100 ml volumetric flask, add 50 ml of methanol, for 15 minutes of ultrasonic processing until glipizide is dissolved. Dilute with 0.1 mol/L sodium dihydrogen phosphate solution to volume, mix well. Filter and take the successive filtrate as solution (1). Inject 20 μ l of solution (1) into the column and record the chromatogram. Dissolve a quantity of glipizide CRS, accurately weighed, in a quantity of methanol in a 50 ml volumetric flask with shaking and dilute to volume with methanol, mix well as solution (2). Measure accurately 5 ml of solution (2) to a 50 ml volumetric flask and add 20 ml of methanol, dilute with 0.1 mol/L sodium dihydrogen phosphate solution to volume, mix well and repeat the operation as described above, calculate the content of $C_{20}H_{24}O_2$ with respect to the peak area obtained in the chromatogram by the external standard method.

Category As described under Glipizide.

Strength (1) 2.5 mg (2) 5mg

Storage Preserve in tightly closed containers, stored in a dry place and protected from light.

Gliquidone



$C_{27}H_{33}N_3O_6S$ 527.64

33342-05-1

Gliquidone is 1-cyclohexyl-3-*p*-[2-(3,4-dihydro-7-methoxy-4,4-dimethyl-1,3-dioxo-2-(1*H*)-isoquinolyl) ethyl] phenylsulphonylurea. It contains not less than 98.0% and not more than 102.0% of $C_{27}H_{33}N_3O_6S$, calculated on the dried basis.

Description White crystals or a crystalline powder; odourless; tasteless.

Freely soluble in chloroform; sparingly soluble in acetone; slightly soluble in ethanol or methanol; practically insoluble in water.

Melting point 178-182°C (Appendix VI C).

Identification (1) To about 10 mg add 5 drops of phenylhydrazine, heat until the solution becomes clear, allow to cool and add 0.5 ml of ammonia TS, 0.5 ml of 10% nickel sulfate solution and 1 ml of chloroform, shake thoroughly, allow to stand: a violet-red colour is produced in the lower layer solution.

(2) The retention time of principal peak of gliquidone in the substance being examined in the chromatogram obtained in the Assay is identical with that of gliquidone CRS.

(3) The infrared absorption spectrum (Appendix IV C) is concordant with the reference spectrum of gliquidone (Appendix XVI).

Chloride To 2.0 g add 100 ml of water, heat to boil, cool quickly and filter, to the filtrate add a quantity of water to produce 100 ml, mix well. Carry out the limit test for chloride (Appendix VIII A), using 25 ml of the resulting solution. Any opalescence produced is not more pronounced than that of a reference solution using 7.0 ml of sodium chloride standard solution (0.014%).

Sulfate Carry out the limit test for sulfate (Appendix VIII B), using 25 ml of the filtrate obtained under the limit test for chloride. Any opalescence produced is not more pronounced than that of a reference solution using 2.0 ml of potassium sulfate standard solution (0.04%).

Related substances Dissolve a quantity of the substance being examined, accurately weighed, in mobile phase with the aid of ultrasonication, to produce solutions of 2 mg per ml (solution 1) and 20 μ g per ml (solution 2). Dissolve a quantity of isoquinoline impurity CRS, accurately weighed, in mobile phase to produce a solution of 10 μ g per ml (solution 3). Carry out the method for high performance liquid chromatography as described under Assay, inject 20 μ l of solution (2) into the column, adjust the attenuation so that the principal peak height in chromatogram is 10%-20% of the full scale of the chart. And then inject separately 20 μ l each of solutions (1), (2) and (3) into the column, and record the chromatogram for twice the retention time of the principal peak. Calculate the content of isoquinoline impurity with respect to the peak area obtained in the chromatogram by the external standard method. The isoquinoline impurity is not more than 0.75%. The sum of the areas of all peaks

other than the principal peak and the peak of isoquinoline impurity in the chromatogram obtained with solution (1) is not greater than the area of the principal peak in the chromatogram obtained with solution (2).

Loss on drying When dried to constant weight at 105°C, loses not more than 0.5% of its weight (Appendix VIII L).

Residue on ignition Not more than 0.1% (Appendix VIII N), using 1.0 g.

Heavy metals Carry out the limit test for heavy metals (Appendix VIII H, method 2), using the residue obtained in the test for Residue on ignition; not more than 0.001%.

Assay Carry out the method for high performance liquid chromatography (Appendix V D), using a column packed with octadecylsilane bonded silica gel and a mixture of ammonium dihydrogen phosphate solution (dissolve 1.725 g of ammonium dihydrogen phosphate in 300 ml of water, adjust pH to 3.5 ± 0.1 with phosphoric acid)-acetonitrile (3 : 5) as the mobile phase. Detection wavelength is 310 nm. Dissolve a quantity of gliquidone CRS and isoquinoline impurity CRS in mobile phase with the aid of ultrasonication, to produce a solution of each of 50 µg per ml, inject 20 µl into the column, record the chromatogram. The number of the theoretical plates of the column is not less than 2000, calculated with reference to the peak of gliquidone, the resolution factor between the peaks of gliquidone and isoquinoline impurity complies with the related requirements.

Procedure Dissolve a quantity of the substance being examined, accurately weighed, in mobile phase with the aid of ultrasonication to produce a solution of 0.1 mg per ml, inject 20 µl into the column and record the chromatogram. Repeat the operation, using gliquidone CRS instead of the substance being examined, calculate the content of $C_{27}H_{33}N_3O_6S$ with respect to the peak area obtained in the chromatogram by the external standard method.

Category Hypoglycaemic.

Storage Preserve in tightly closed containers.

Preparation Gliquidone Tablets

Gliquidone Tablets

Gliquidone Tablets contain not less than 90.0% and not more than 110.0% of the labelled amount of gliquidone ($C_{27}H_{33}N_3O_6S$).

Description White tablets.

Identification (1) The light absorption of a solution obtained in Assay exhibits a maximum at 310 nm and a minimum at 280 nm (Appendix IV A). Dilute the solution 10 times with methanol, the light absorption exhibits a maximum at 222 nm.

(2) Dissolve a quantity of the powdered tablets in a quantity of mobile phase with the aid of ultrasonication, to produce a solution of 0.1 mg per ml, filter and use the filtrate as the test solution. Dissolve a quantity of gliquidone CRS in a quantity of mobile phase with the aid of ultrasonication, to produce a solution of 0.1 mg per ml as the reference solution. Carry out the method for high performance liquid chromatography as described under Related substances, inject separately 20 µl of each of the solutions mentioned above into the column, and record the chromatogram. The retention time of principal peak of gliquidone in the substance being examined in the chromatogram obtained is identical with that of gliquidone CRS.

Dissolution Carry out the dissolution test (Appendix XC, method 2), using 500 ml of phosphate BS (dissolve 10 g of disodium hydrogen phosphate in 1000 ml of water, adjust the pH value to 8.5 with phosphoric acid) as the dissolution medium, adjust the rotational speed of the paddle to 75 rpm. Withdraw the solution after exactly 45 minutes and filter. Use the successive filtrate as the test solution. Dissolve about 30 mg, accurately weighed, of gliquidone CRS in 10 ml of dimethylformamide in a 100 ml volumetric flask, and dilute to volume with the dissolution medium, mix well. Measure accurately 10 ml into a 50 ml volumetric flask, dilute to volume with the dissolution medium, mix well as the reference solution. Measure the absorbances of the two resulting solutions at 314 nm (Appendix IV A), calculate the dissolution of $C_{27}H_{33}N_3O_6S$ from each tablet. Not less than 70% of the labelled amount is dissolved.

Related substances Dissolve a quantity of the powdered tablets in a quantity of mobile phase with the aid of ultrasonication, to produce a solution of 2 mg per ml, filter and use the filtrate as solution (1). Measure accurately 1 ml into a 100 ml volumetric flask, dilute to volume with mobile phase, mix well as solution (2). Dissolve a quantity of isoquinoline impurity CRS, accurately weighed, in mobile phase to produce a solution of 10 µg per ml (solution 3). Carry out the procedure described under Related substances in Gliquidone. Calculate the content of isoquinoline impurity with respect to the peak area obtained in the chromatogram by the external standard method. The isoquinoline impurity is not more than 1.0%. The sum of the areas of all peaks other than the principal peak and the peak of isoquinoline impurity in the chromatogram obtained with solution (1) is not greater than 1.5 times the area of the principal peak in the chromatogram obtained with solution (2).

Other requirements Comply with the general requirements for tablets (Appendix I A).

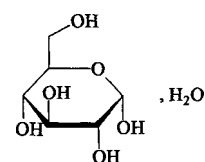
Assay Weigh accurately and powder 10 tablets. Weigh accurately a quantity of the powdered tablets, equivalent to about 50 mg of gliquidone, into a 100 ml volumetric flask, add about 70 ml of methanol, treat with the aid of ultrasonication in a water bath for 15 minutes to dissolve gliquidone, allow to cool and dilute to volume with methanol, mix well and filter. Measure accurately 10 ml of the successive filtrate, into a 50 ml volumetric flask, dilute to volume with methanol, mix well. Dissolve a quantity, accurately weighed, of gliquidone CRS, in methanol to produce a solution of 0.1 mg per ml. Measure the absorbances of the resulting solutions at 310 nm (Appendix IV A), calculate the content of $C_{27}H_{33}N_3O_6S$.

Category As described under Gliquidone.

Strength 30 mg

Storage Preserve in tightly closed containers, and protected from light.

Glucose



$C_6H_{12}O_6 \cdot H_2O$ 198.17

[77029-61-9]

Glucose is D-(+)-glucopyranose monohydrate.

Description Colourless crystals or a white crystalline or granular powder; odourless; taste, sweet. Freely soluble in water; slightly soluble in ethanol.

Specific optical rotation Dissolve about 10 g, weighed accurately, in a quantity of water and 0.2 ml of ammonia TS in a 100 ml volumetric flask and dilute with water to volume. Mix well and allow to stand for 10 minutes. The specific optical rotation of the resulting solution is $+52.5^{\circ}$ – $+53.0^{\circ}$ at 25°C (Appendix VI E).

Identification (1) Dissolve about 0.2 g in 5 ml of water, add dropwise hot alkaline cupric tartrate TS; a red precipitate of cuprous oxide is produced. (2) The infrared absorption spectrum (Appendix IV C) is concordant with the reference spectrum of glucose (Appendix XVI).

Acidity Dissolve 2.0 g in 20 ml of water, add 3 drops of phenolphthalein IS and 0.20 ml of sodium hydroxide (0.02 mol/L) VS; a pink colour is produced.

Clarity and colour of solution Dissolve 5.0 g in hot water, cool, dilute to 10 ml with water; the solution is clear and colourless. Any opalescence produced is not more pronounced than that of reference suspension 1 (Appendix IX B). Any colour produced is not more intense than that of a solution prepared by diluting 1.0 ml of a reference solution (mix 3 ml of standard cobaltous chloride CS and 3 ml of standard potassium dichromate CS with 6 ml of standard copper sulfate CS and add sufficient water to produce 50 ml) with water to 10 ml.

Clarity of ethanolic solution To 1.0 g add 30 ml of 90% ethanol and reflux on a water bath for about 10 minutes; the solution is clear.

Chloride Carry out the limit test for chlorides (Appendix VIII A), using 0.60 g. Any opalescence produced is not more pronounced than that of a reference using 6.0 ml of sodium chloride standard solution (0.01%).

Sulfate Carry out the limit test for sulfates (Appendix VIII B), using 2.0 g. Any opalescence produced is not more pronounced than that of a reference using 2.0 ml of potassium sulfate standard solution (0.01%).

Sulfites and soluble starch Dissolve 1.0 g in 10 ml of water, add 1 drop of iodine TS; a yellow colour is produced.

Loss on drying When dried to constant weight at 105°C , loses not more than 9.5% of its weight (Appendix VIII L).

Residue on ignition Not more than 0.1% (Appendix VIII N).

Protein Dissolve 1.0 g in 10 ml of water, add 3 ml of sulfosalicylic acid solution, no precipitate is produced.

Iron Dissolve 2.0 g in 20 ml of water, add 3 drops of nitric acid, boil gently for 5 minutes. Allow to cool, dilute to 45 ml with water, add 3 ml of ammonium thiocyanate solution (30→100) and mix well. Any colour produced is not more intense than that of a reference solution prepared in the same manner of iron standard solution (0.001%).

Heavy metals Dissolve 4.0 g in 23 ml of water, add 2 ml of sodium acetate BS (pH 3.5), carry out the limit test for heavy metals (Appendix VIII H, method 1); not more than 0.0005%.

Arsenic Dissolve 2.0 g in 5 ml of water, add 5 ml of dilute sulfuric acid and 0.5 ml of potassium bromide-bromine TS. Heat on a water bath for about 20 minutes and maintain the presence of excess of bromine. Add a quantity of potassium bromide-bromine TS, if necessary. Replace the evaporated water constantly and cool, then add 5 ml of hydrochloric acid and dilute with water to 28 ml. The solution complies with

the limit test for arsenic (Appendix VIII J, method 1) (0.0001%).

Microbial Limit Carry out the microbial limit test (Appendix XI J), besides that number of bacterial is not more than 1000 and that of yeasts is not more than 100 per g, escherichia coli is absence.

Category Nutrient.

Storage preserve in tightly closed containers.

Preparation (1) Glucose Injection
(2) Glucose and Sodium Chloride Injection

Glucose Injection

Glucose Injection is a sterile solution of glucose in Water for Injection. It contains not less than 95.0% and not more than 105.0% of the labelled amount of glucose ($\text{C}_6\text{H}_{12}\text{O}_6 \cdot \text{H}_2\text{O}$).

Description A clear, colourless or almost colourless liquid; taste, sweet.

Identification Add a few drops of the injection to hot alkaline cupric tartrate TS; a red precipitate of cuprous oxide is produced.

pH value 3.2–5.5 (Appendix VI H).

5-Hydroxymethylfurfural Transfer an accurately measured volume equivalent to 1.0 g of glucose to a 100 ml volumetric flask, dilute with water to volume and mix well. Measure the absorbance at 284 nm (Appendix IV A); the absorbance is not greater than 0.32.

Heavy metals Measure a volume equivalent to 3 g of glucose, evaporate to about 20 ml and cool if necessary. Add 2 ml of acetate BS (pH 3.5) and sufficient water to produce 25 ml. Carry out the limit test for heavy metals (Appendix VIII H, method 1); not more than 0.0005%, calculated with reference to the content of glucose.

Bacterial Endotoxin Comply with the test for Bacterial Endotoxin (Appendix XI E), less than 0.5 EU per ml.

Other requirements Complies with the general requirements for injections (Appendix I B).

Assay Measure accurately a volume equivalent to 10 g of glucose to a 100 ml volumetric flask, add 0.2 ml of ammonia TS dilute with water to volume and mix well (injections of 10% strength or less may be used directly with the addition of ammonia TS), allow to stand for 10 minutes. Carry out the determination of optical rotation (Appendix VI E). The observed rotation in degree multiplied by 2.0852, represents the weight in g of $\text{C}_6\text{H}_{12}\text{O}_6 \cdot \text{H}_2\text{O}$, in the volume taken for Assay.

Category As described under Glucose.

Strength

(1) 10 ml : 2 g	(2) 20 ml : 5 g
(3) 20 ml : 10 g	(4) 100 ml : 5 g
(5) 100 ml : 10 g	(6) 250 ml : 12.5 g
(7) 250 ml : 25 g	(8) 250 ml : 50 g
(9) 250 ml : 100 g	(10) 500 ml : 25 g
(11) 500 ml : 50 g	(12) 1000 ml : 50 g
(13) 1000 ml : 100 g	

Storage Preserve in tightly closed containers.

Glucose and Sodium Chloride Injection

Glucose and Sodium Chloride Injection is a sterile

solution of glucose and sodium chloride in Water for Injection. It contains not less than 95.0% and not more than 105.0% of the labelled amount of glucose ($C_6H_{12}O_6 \cdot H_2O$) and sodium chloride (NaCl).

Description A clear, colourless liquid.

Identification (1) Complies with test for Identification described under Glucose Injection.

(2) Yields the reactions characteristic of sodium salts and chlorides (Appendix III).

pH value 3.5-5.5 (Appendix VI H).

5-Hydroxymethylfurfural Dilute 2 ml, accurately measured with water to 50 ml, mix well. Measure the absorbance of the resulting solution at 284 nm (Appendix IV A); the absorbance is not greater than 0.25.

Heavy metals Evaporate 40 ml to about 20 ml, cool, add 2 ml of acetate BS (pH 3.5) and sufficient water to produce 25 ml. Carry out the limit test for heavy metals (Appendix VIII H, method 1); not more than 0.0005%.

Bacterial Endotoxin Comply with the test for Bacterial Endotoxin (Appendix XI E), less than 0.5 EU per ml.

Other requirements Complies with the general requirements for injections (Appendix I B).

Assay Glucose Carry out the determination of optical rotation (Appendix VI E). The observed rotation in degree multiplied by 2.0852 represents the weight in g of $C_6H_{12}O_6 \cdot H_2O$ of the testing volume.

Sodium chloride Measure accurately 20 ml, add 30 ml of water, 5 ml of dextrin solution (1→50), 2 ml of 2.5% borax solution and 5-8 drops of fluorescein IS, titrate with silver nitrate (0.1 mol/L) VS. Each ml of silver nitrate (0.1 mol/L) VS is equivalent to 5.844 mg of NaCl.

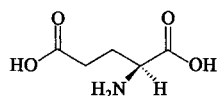
Category Body fluid supplement.

Strength

- (1) 100 ml : Glucose 5 g and Sodium Chloride 0.9 g
- (2) 100 ml : Glucose 10 g and Sodium Chloride 0.9 g
- (3) 250 ml : Glucose 12.5 g and Sodium Chloride 2.25 g
- (4) 250 ml : Glucose 25 g and Sodium Chloride 2.25 g
- (5) 500 ml : Glucose 25 g and Sodium Chloride 4.5 g
- (6) 500 ml : Glucose 50 g and Sodium Chloride 4.5 g
- (7) 1000 ml : Glucose 50 g and Sodium Chloride 9 g

Storage Preserve in tightly closed containers.

Glutamic Acid



$C_5H_9NO_4$ 147.13

[56-86-0]

Glutamic Acid is L-2-amino-pentane-1,5-dioic acid. It contains not less than 98.5% of $C_5H_9NO_4$, calculated on the dried basis.

Description White crystals or a crystalline powder; taste, slightly sour. Soluble in hot water; slightly soluble in

water; insoluble in ethanol, acetone or ether.

Specific optical rotation +31.5° to +32.5°, in a solution of 70 mg per ml 2 mol/L hydrochloric acid solution (Appendix VI E).

Identification The infrared absorption spectrum (Appendix IV C) is concordant with the reference spectrum of glutamic acid (Appendix XVI).

Transmittance of solution Dissolve 1.0 g in 20 ml of 2 mol/L hydrochloric acid solution, measure the transmittance at 430 nm (Appendix IV A), not less than 98.0%.

Chloride Carry out the limit test for chlorides (Appendix VIII A), using 0.30 g. Any opalescence produced is not more pronounced than that of a reference solution using 6.0 ml of sodium chloride standard solution (0.02%).

Sulfate Shake to dissolve 0.50 g with 2 ml of dilute hydrochloric acid TS and 5 ml of water. Carry out the limit test for sulfates (Appendix VIII B). Any opalescence produced is not more pronounced than that of a reference solution using 1 ml of potassium sulfate standard solution (0.02%).

Ammonium salt Carry out the limit test for ammonium salt (Appendix VIII K), using 0.10 g. Any opalescence produced is not more pronounced than that of a reference solution using 2.0 ml of ammonium chloride standard solution (0.02%).

Other amino acid Dissolve a quantity in 0.5 mol/L hydrochloric acid solution to produce a solution of 20 mg per ml as test solution. Dilute an accurately measured quantity with 0.5 mol/L hydrochloric acid solution to produce a solution of 0.1 mg per ml as reference solution. Carry out the method for thin-layer chromatography (Appendix V B), using silica gel G as the coating substance and a mixture of *n*-butanol-water-glacial acetic acid (2 : 1 : 1) as the mobile phase. Apply separately to the plate 5 μ l of each of two solutions. After developing and removal of the plate, dry in air, spray with ninhydrin solution in acetone (1→50) and heat at 80°C until the colour is produced. Examine the spots immediately. Any spot other than the principal spot obtained with the test solution is not more intense than the principal spot obtained with the reference solution (0.5%).

Loss on drying When dried to constant weight at 105°C, loses not more than 0.5% of its weight (Appendix VIII L).

Residue on ignition Not more than 0.1% (Appendix VIII N), using 1.0 g.

Iron To 2.0 g add 6 ml of dilute hydrochloric acid TS and a quantity of water, heat to dissolve, cool, dilute to 25 ml with water. Carry out the limit test for iron (Appendix VIII G). Any colour produced is not more intense than that of a reference solution using 1.0 ml of iron standard solution (0.0005%).

Heavy Metals Carry out the limit test for heavy metals (Appendix VIII H) using the residue obtained in the test for Residue on ignition; not more than 0.001%.

Arsenic Dissolve 2.0 g in 5 ml of hydrochloric acid and 23 ml of water. Carry out the limit test for arsenic (Appendix VIII J, method 1); not more than 0.0001%.

Pyrogens To a quantity add Sodium Chloride Injection to produce a solution of 20 mg per ml. Heat to dissolve and cool to 37°C. Complies with the test for pyrogens (Appendix XI D), using 10 ml per kg of rabbit's weight (For Parenteral Administration).

Assay Dissolve 0.25 g, weigh accurately, in 50 ml of boiling water. Cool, add 5 drops of bromothymol blue IS, titrate with sodium hydroxide (0.1 mol/L) VS until the colour changes from yellow to bluish green. Each ml of sodium hydroxide (0.1 mol/L) VS is equivalent to 14.71

mg of $C_5H_9NO_4$.

Category Amino acids.

Storage Preserve in tightly closed containers, protected from light.

Preparation (1) Glutamic Acid Tablets
(2) Sodium Glutamate Injection
(3) Potassium Glutamate Injection

Glutamic Acid Tablets

Glutamic Acid Tablets contain not less than 95.0% and not more than 105.0% of the labelled amount of glutamic acid ($C_5H_9NO_4$).

Description White tablets.

Identification (1) To a quantity of the powdered tablets equivalent to about 5 mg of glutamic acid add 5 ml of water, heat to dissolve the glutamic acid and filter. Add to the filtrate about 5 mg of ninhydrin, heat, the solution exhibits a blue to violet-blue colour.

(2) Dissolve a quantity of the powdered tablets with sodium hydroxide TS and filter, neutralize the filtrate with hydrochloric acid, filter, wash the crystals with water and dry. Dissolve the crystals and glutamic acid CRS separately in hot water to produce solutions of 2.5 mg per ml. Carry out the method for ascending paper chromatography (Appendix V A), using *n*-butanol-acetic acid-ethanol-water (4 : 1 : 1 : 2) as the mobile phase. Apply separately to the paper 5 μ l each of the two solutions. After developing and removal of the paper, dry in air, spray with ninhydrin solution (dissolve 20 mg of ninhydrin in 10 ml of acetone, add 0.4 ml of glacial acetic acid) and dry in hot air. The colour and position of the principle spot in the chromatogram obtained with the substance being examined correspond to that of the principle spot obtained with the reference substance.

Dissolution Comply with the requirements for dissolution test (Appendix X C, method 2), using 1000 ml of phosphate BS (pH 7.2) as the dissolution medium, adjust the rotational speed of the paddle to 100 rpm. Withdraw 10 ml of the solution after exactly 45 minutes and filter. Dilute the successive filtrate with phosphate BS (pH 7.2) to produce a solution of 0.3 mg per ml, as the test solution. Dissolve a quantity of glutamic acid CRS, accurately weighed, in phosphate BS (pH 7.2) to produce a reference solution of 0.3 mg per ml. Transfer 1 ml each of the two solutions to 50 ml volumetric flask, add 1 ml each of 0.5% ninhydrin solution and phosphate BS (pH 7.2), mix well, warm for 20 minutes in a water bath, cool in air, dilute with phosphate BS (pH 7.2) to volume and mix well. Measure the absorbances of the resulting solutions at 567 nm (Appendix IV A), calculate the dissolution of glutamic acid from each tablet.

Other requirements Comply with the general requirements for tablets (Appendix I A) except that the tablets disintegrate within 30 minutes.

Assay Weigh accurately and pulverize 10 tablets, dissolve an accurately weighed quantity of the powder equivalent to about 0.4 g of glutamic acid in 50 ml of boiling water. cool, add 0.5 ml of bromothymol blue IS, titrate with sodium hydroxide (0.1 mol/L) VS until the colour changes from yellow to bluish green. Each ml of sodium hydroxide (0.1 mol/L) VS is equivalent to 14.71 mg of $C_5H_9NO_4$.

Category As described under Glutamic Acid.

Strength (1) 0.3 g (2) 0.5 g

Storage Preserve in tightly closed containers, protected from light.

Strong Glutaryl Solution

Strong Glutaryl Solution is a solution of glutaryl in water. It contains not less than 95.0% and not more than 105.0% of the labelled amount of glutaryl ($C_5H_8O_2$).

Description A clear, yellowish liquid; odour, characteristic and pungent.

Freely miscible with water or ethanol.

Identification (1) Heat 1 ml in a test tube with 1 ml of ammoniated silver nitrate TS on a water bath for several minutes, a fine grey precipitate is produced or a silver mirror is produced on the tube wall.

(2) To 5 drops add a 1% solution of salicylic acid in sulfuric acid, a brownish-red colour is produced.

Clarity To 5.0 ml add water to a volume of 50 ml and shake well, the solution is clear; any opalescence produced is not more pronounced than that of reference suspension 1 (Appendix IX B).

pH value 2.5-3.5 (Appendix VI H).

Free acid To 5 ml, accurately measured, add 5 ml of water and 2 drops of phenolphthalein IS, titrate with sodium hydroxide (0.1 mol/L) VS until a pink colour is produced and persists for 15 seconds. The sodium hydroxide (0.1 mol/L) VS consumed is not more than 3.8 ml.

Assay To a quantity equivalent to about 0.2 g of glutaryl, accurately weighed, add 20 ml of 6.5% triethanolamine solution and 25 ml of a neutral solution of hydroxylamine hydrochloride (dissolve 17.5 g of hydroxylamine hydrochloride in 75 ml of water, dilute with isopropanol to 500 ml, shake well, add 15 ml of ethanolic solution of 0.04% bromophenol blue and titrate with 6.5% solution of triethanolamine until a bluish green colour is produced), shake well and allow to stand for 1 hour. Titrate with sulfuric acid (0.25 mol/L) VS until a bluish green colour is produced. Perform a blank determination and make any necessary correction. Each ml of sulfuric acid (0.25 mol/L) VS is equivalent to 25.03 mg of $C_5H_8O_2$.

Category Antiseptic and disinfectant.

Strength (1) 20% (g/g) (2) 25% (g/g)

Storage Preserve in tightly closed containers, protected from light, stored in a dark and cool place.

Preparation Dilute Glutaryl Solution

Dilute Glutaryl Solution

Dilute Glutaryl Solution is a dilution of Strong Glutaryl Solution in suitable amount of stabilizer. It contains 1.80%-2.20% (g/ml) of glutaryl ($C_5H_8O_2$).

Description A clear, colourless or slightly yellow liquid; odour, characteristic.

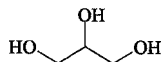
Identification Complies with the tests for Identification described under Strong Glutaryl Solution.

pH value 3.0-4.0 (Appendix VI H).

Assay Carry out the Assay described under Strong Glutaral Solution, using 10 ml, accurately measured. Each ml of sulfuric acid (0.25 mol/L) VS is equivalent to 25.03 mg of $C_5H_8O_2$.

Category, Storage As described under Strong Glutaral Solution.

Glycerol



$C_3H_8O_3$ 92.09

[56-81-5]

Glycerol is 1,2,3-propanetriol. It contains not less than 95.0% of $C_3H_8O_3$.

Description A clear, colourless, syrupy liquid; taste, sweet, followed by a warm feeling; hygroscopic; the aqueous solution (1→10) exhibits a neutral reaction. Miscible with water or ethanol; slightly soluble in acetone; insoluble in chloroform or ether.

Relative density Not less than 1.2569 at 25°C (Appendix VI A).

Identification The infrared absorption spectrum (Appendix IV C) is concordant with the reference spectrum of glycerol (Appendix XVI).

Colour Place 50 ml in a Nessler cylinder, its colour is not more intense than that of a reference solution (dilute 0.2 ml of standard potassium dichromate CS with water to 50 ml).

Chloride Carry out the limit test for chlorides (Appendix VIII A), using 5.0 g. Any opalescence produced is not more pronounced than that of a reference using 7.5 ml of sodium chloride standard solution (0.0015%).

Sulfate Carry out the limit test for sulfates (Appendix VIII B), using 10 g. Any opalescence produced is not more pronounced than that of a reference using 2.0 ml of potassium sulfate standard solution (0.002%).

Fatty acids and esters Mix 40 g with 40 ml of freshly boiled and cooled water, add accurately 10 ml of sodium hydroxide (0.1 mol/L) VS and boil the mixture for 5 minutes. Cool, add a few drops of phenolphthalein IS, and titrate the excess sodium hydroxide with hydrochloric acid (0.1 mol/L) VS. Perform a blank determination and make any necessary correction; not more than 4.0 ml of sodium hydroxide (0.1 mol/L) VS is consumed.

Acrolein, glucose and ammonium compounds Mix 5 ml with 5 ml of 10% potassium hydroxide solution; no yellow colour is produced when kept for 5 minutes at 60°C, no odour of ammonia is perceptible.

Readily carbonizable substances Carry out the limit test for readily carbonizable substance (Appendix VIII O), using 5.0 ml, allow to stand for 1 hour; any colour produced is not more intense than that of a reference solution (mix 0.2 ml of standard cobaltous chloride CS, 1.6 ml of standard potassium dichromate CS and 8.2 ml of water).

Residue on ignition Heat 20.0 g to kindling, allow to burn without further heating, cool. Carry out the test for residue on ignition; not more than 2 mg (Appendix VIII N).

Iron Carry out the limit test for iron (Appendix VIII G), using 10.0 g. Any colour produced is not more intense than that of a reference, using 2.0 ml of standard iron solution (0.0002%).

Heavy metals Dissolve 5.0 g in 2 ml of acetate BS (pH 3.5), add a quantity of water to produce 25 ml. Carry out the limit test for heavy metals (Appendix VIII H, method 1); not more than 0.0002%.

Assay Dissolve about 0.1 g, accurately weighed, in 45 ml of water, add 25 ml of 2.14% sodium periodate solution, mix well, allow to stand in dark for 15 minutes. Add 5 ml of 50% glycol solution, mix well and allow to stand in dark for 20 minutes. Add 0.5 ml of phenolphthalein IS, titrate with sodium hydroxide (0.1 mol/L) VS. Perform a blank determination and make any necessary correction. Each ml of sodium hydroxide (0.1 mol/L) VS is equivalent to 9.21 mg of $C_3H_8O_3$.

Category Lubricating laxative.

Storage Preserve in tightly closed containers, stored in a dry place.

Preparation Glycerol Suppositories

Glycerol and Fructose Injection

Glycerol and Fructose Injection is a sterile mixture of Glycerol, Fructose and Sodium Chloride in Water for Injection. It contains not less than 90.0% and not more than 110.0% of the labelled amount of glycerol ($C_3H_8O_3$); not less than 93.0% and not more than 107.0% of the labelled amount of fructose ($C_6H_{12}O_6$) and sodium chloride (NaCl), respectively.

Formula	Glycerol	100 g
	Fructose	50 g
	Sodium chloride	9 g
	Water for injection	a sufficient quantity
	To make	1000 ml

Description A clear, colourless liquid.

Identification (1) Measure 10 ml, add 0.1 g of resorcinol and 1 ml of hydrochloric acid, heat in a water bath for 3 minutes, a red colour is produced.

(2) The retention time of three principal peaks in the substance being examined in the chromatogram obtained in the Assay are identical with that of sodium chloride CRS, fructose CRS and glycerol CRS correspondingly.

(3) Yields the reactions characteristic of sodium salts and chlorides (Appendix III).

pH value 3.0-6.0 (Appendix VI H).

5-Hydroxymethylfurfural Measure 5.0 ml, add to 20.0 ml in water and mix well. Measure the absorbance at 284 nm (Appendix IV A) and the absorbance is not more than 0.30.

Heavy metals Measure 10 ml, add 2 ml of acetate BS (pH 3.5) and sufficient water to produce 25 ml. Carry out the limit test for heavy metals (Appendix VIII H, method 1); not more than 0.00025%.

Arsenic Measure 4 ml, add 5 ml of hydrochloric acid and 19 ml of water, carry out the limit test for arsenic (Appendix VIII J, method 1); not more than 0.00005%.

Pyrogens Complies with the test for pyrogens (Appendix XI D), using 10 ml per kg of the rabbit's weight.

Other requirements Complies with the general requirements for injections (Appendix I B).

Assay Carry out the method for high performance liquid

chromatography (Appendix V D), using a column packed with strong cation-exchange resin consisting of sulfonated cross-linked styrene-divinylbenzene copolymer in the hydrogen form and 0.04 mol/L phosphoric acid solution as the mobile phase. Detection wavelength is 200 nm and column temperature is 50°C. The substances are eluted in the following order: sodium chloride, fructose, glycerol and internal standard. The number of theoretical plates of the column is not less than 2500, calculated with reference to the peak of sodium chloride. The resolution factor between the peaks complies with the related requirements.

Internal standard solution Measure accurately 15 ml of 1, 2-propylene glycol in a 100 ml volumetric flask, dilute to volume with the mobile phase and mix well.

Procedure Measure accurately 5 ml and 10 ml of internal standard solution in a 100 ml volumetric flask, dilute to volume with the mobile phase and mix well. Inject 20 µl of the resulting solution, accurately measured, into the column. Dissolve a quantity of sodium chloride CRS, fructose CRS and glycerol CRS in water, accurately weighed, dilute with the mobile phase to produce a solution of 9 mg, 50 mg, and 100 mg per ml, respectively. Measure accurately 5 ml of the resulting solution and 10 ml of internal standard solution in a 100 ml volumetric flask, dilute to volume with the mobile phase, mix well, measure in the same manner. Calculate the content of $C_3H_8O_3$, $C_6H_{12}O_6$ and NaCl, respectively.

Category Dehydrant.

Strength (1) 250 ml (2) 500 ml

Storage Preserve in well closed containers.

Glycerol for Injection

$C_3H_8O_3$ 92.09 [56-81-5]

Glycerol for Injection is 1,2,3-propanetriol. It contains not less than 98.0% of $C_3H_8O_3$.

Description A clear, colourless viscous liquid; taste, sweet; hygroscopic; the aqueous solution (1 → 10) exhibits a neutral reaction.

Miscible with water or ethanol; slightly soluble in acetone; insoluble in chloroform or ether.

Relative density Not less than 1.257 at 25°C (Appendix VI A).

Refractive index 1.470-1.475 (Appendix VI F).

Identification The infrared absorption spectrum (Appendix IV C) is concordant with the reference spectrum of glycerol (Appendix XVI).

Acidity or alkalinity Dilute 25.0 g to 50 ml with water, add 0.5 ml of phenolphthalein IS, the solution is colourless. Then add 0.2 ml of 0.1 mol/L sodium hydroxide solution, the solution is pink.

Colour Transfer 50 ml to a Nessler cylinder; any colour produced is not more intense than that of a reference solution prepared by diluting 0.2 ml of potassium dichromate CS to 50 ml with water.

Chlorides Carry out the limit test for chlorides (Appendix VIII A), using 5.0 g. Any opalescence produced is not more pronounced than that of a reference solution using 3.0 ml of sodium chloride standard solution (0.0006%).

Sulfates Carry out the limit test for sulfates (Appendix VIII B), using 10 g. Any opalescence produced is not more pronounced than that of a reference solution using 2.0 ml of

potassium sulfate standard solution (0.002%).

Aldehydes and reducing substances Transfer 3.75 g to a Nessler cylinder with stopper, dilute to 15 ml with water and mix. Add 1.0 ml of decolorised pararosaniline (weigh 0.1 g of pararosaniline hydrochloride ($C_{19}H_{18}ClN_3$) into a conical flask with stopper, add 60 ml of water and 10 ml of 7.5% sodium metabisulfite solution, then add 4.5 ml of dilute hydrochloric acid with gentle stirring. Insert the stopper and shake until completely dissolved, dilute to 100 ml with water and mix, allow to stand for 12 hours before use), mix, insert the stopper, and allow to stand for 1 hour. Any colour produced is not more intense than that of a reference solution operated in the similar manner using 7.5 ml of formaldehyde solution (5.0 µg of formaldehyde (CH_2O) per ml) and 7.5 ml of water (The test is not valid unless the reference solution is red).

Fatty acids and esters To 40 g add 40 ml of freshly boiled and cooled water, add 10 ml of sodium hydroxide (0.1 mol/L) VS, accurately measured, and mix well. Boil for 5 minutes and cool. Add several drops of phenolphthalein IS, titrate with hydrochloric acid (0.1 mol/L) VS until the pink colour disappears. Perform a blank determination and make any necessary correction. Not more than 2.0 ml of sodium hydroxide (0.1 mol/L) VS is required.

Readily carbonizable substances Carry out the limit test for readily carbonizable substances (Appendix VIII O), using 5.0 ml, allow to stand for 1 hour. Any colour produced is not more intense than that of an equal volume of a reference solution prepared by mixing 0.2 ml of cobaltous chloride CS, 1.6 ml of potassium dichromate CS and 8.2 ml of water.

Sugar Mix 5.0 g with 5 ml of water, add 1 ml of dilute sulfuric acid, warm on a water bath for 5 minutes. Add 3 ml of 2 mol/L carbonate-free sodium hydroxide solution and 1 ml of cupric sulfate TS dropwise, mix well. The solution is blue and clear, continue to warm on a water bath for 5 minutes, the solution is still blue and no precipitate is produced.

Residue on ignition Heat 20.0 g. When the substance ignites, stop heating. After combustion, allow to cool; not more than 2 mg (Appendix VIII N).

Iron Carry out the limit test for iron (Appendix VIII G), using 20.0 g. Any colour produced is not more intense than that of a reference solution using 1.0 ml of iron standard solution (0.00005%).

Heavy metals Carry out the limit test for heavy metals (Appendix VIII H, method 1), using 5.0 g; not more than 0.0002%.

Arsenic Mix 6.65 g with 23 ml of water and 5 ml of hydrochloric acid. Carry out the limit test for arsenic (Appendix VIII J, method 1); not more than 0.00003%.

Assay Mix about 0.1 g, accurately weighed, with 45 ml of water, add 25 ml of 2.14% (g/ml) sodium periodate solution, accurately measured, mix well, and allow to stand in a dark place for 15 minutes. Add 5 ml of 50% (g/ml) ethylene glycol and mix well, allow to stand in a dark place for 20 minutes. Add 0.5 ml of phenolphthalein IS, titrate with sodium hydroxide (0.1 mol/L) VS. Perform a blank determination and make any necessary correction. Each ml of sodium hydroxide (0.1 mol/L) VS is equivalent to 9.21 mg of $C_3H_8O_3$.

Category Pharmaceutical aid.

Storage Preserve in well closed containers, stored in a dry place.

Glycerol Suppositories

Formula	Glycerol	1820 g
	Sodium stearate	180 g
	To make	1000 suppositories

Process Heat glycerol in a steam bath to 120°C, add powdered and dried sodium stearate and stir the mixture at a temperature of 85–95°C until sodium stearate is dissolved to form a clear solution. Filter, pour into the moulds. Allow to cool and remove the suppositories.

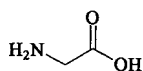
Description Colourless or almost colourless, transparent or translucent suppositories.

Other requirements Comply with the general requirements for suppositories (Appendix I D), except the disintegration test.

Category Lubricating laxative.

Storage Preserve in tightly closed containers, stored at a temperature below 30°C.

Glycine



$\text{C}_2\text{H}_5\text{NO}_2$ 75.07

[56-40-6]

Glycine is 2-aminoethanoic acid. It contains not less than 99.0% of $\text{C}_2\text{H}_5\text{NO}_2$, calculated on the dried basis.

Description A white crystalline powder; odourless; taste, sweet.

Soluble in water; practically insoluble in ethanol or ether.

Identification The infrared absorption spectrum (Appendix IV C) is concordant with the reference spectrum of glycine (Appendix XVI).

Acidity Dissolve 1.0 g in 20 ml of water, pH 5.6–6.6 (Appendix VI H).

Transmittance of solution Dissolve 1.0 g in 20 ml of water, the transmittance at 430 nm is not less than 98.0% (Appendix IV A).

Chlorides Carry out the limit test for chlorides (Appendix VIII A), using 1.0 g. Any opalescence produced is not more pronounced than that of a reference solution using 7.0 ml of sodium chloride standard solution (0.007%).

Sulfates Carry out the limit test for sulfates (Appendix VIII B), using 2.5 g. Any opalescence produced is not more pronounced than that of a reference solution using 1.5 ml of potassium sulfate standard solution (0.006%).

Ammonium Carry out the limit test for ammonium (Appendix VIII K), using 0.10 g. Any colour produced is not more intense than that of a reference solution using 2.0 ml of ammonium chloride standard solution (0.02%).

Loss on drying When dried at 105°C for 3 hours, loses not more than 0.2% of its weight (Appendix VIII L).

Residue on ignition Not more than 0.1% (Appendix VIII N).

Iron Carry out the limit test for iron (Appendix VIII G),

using 1.50 g. Any colour produced is not more intense than that of a reference solution using 1.5 ml of iron standard solution (0.001%).

Heavy metals Dissolve 2.0 g in 23 ml of water, add 2 ml of acetate BS (pH 3.5). Carry out the limit test for heavy metals (Appendix VIII H, method 1); not more than 0.001%.

Arsenic Dissolve 2.0 g in 23 ml of water, add 5 ml of hydrochloric acid. Carry out the limit test for arsenic (Appendix VIII J, method 1); not more than 0.0001%.

Bacterial endotoxin Carry out the test for bacterial endotoxin (Appendix XI E); less than 0.02 EU per mg of glycine (for parenteral administration).

Assay Dissolve about 70 mg, accurately weighed, in 1.5 ml of dehydrated formic acid, add 25 ml of glacial acetic acid. Carry out the method for potentiometric titration (Appendix VII A), titrate with perchloric acid (0.1 mol/L) VS. Perform a blank determination and make any necessary correction. Each ml of perchloric acid (0.1 mol/L) VS is equivalent to 7.507 mg of $\text{C}_2\text{H}_5\text{NO}_2$.

Category Amino acid.

Storage Preserve in tightly closed containers, protected from light.

Preparation Glycine Irrigation Solution

Glycine Irrigation Solution

Glycine Irrigation Solution is a sterile solution of glycine in Water for Irrigation. It contains not less than 95.0% and not more than 105.0% of the labelled amount of glycine ($\text{C}_2\text{H}_5\text{NO}_2$).

Description A clear, colourless liquid.

Identification (1) Evaporate 35 ml to about 5 ml on a water bath, add 1 ml of dilute hydrochloric acid and 5 drops of 50% sodium nitrite solution. Effervescence occurs.

(2) Dilute a quantity with water to produce a solution containing 2.5 mg per ml as test solution. Prepare a reference solution of 2.5 mg of glycine CRS per ml. Carry out the thin-layer chromatography (Appendix V B), using silica gel G as the coating substance and a mixture of propanol-concentrated ammonia solution (7 : 3) as the mobile phase. Apply separately to the plate 2 µl each of above two solutions, after developing and removal of the plate, dry in air, spray with ninhydrin TS, heat at 105°C for 10 minutes. The colour and position of the principal spot in the chromatogram obtained with the test solution correspond to the principal spot obtained with reference solution.

pH value 4.5–6.5 (Appendix VI H).

Bacterial endotoxin Carry out the test for bacterial endotoxin (Appendix XI E); less than 0.5 EU per ml.

Other requirements Complies with the general requirements for irrigation solutions (Appendix I S).

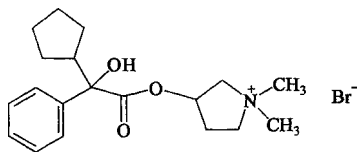
Assay Transfer accurately 10 ml to a conical flask, add 10 ml of water and 10 ml of formaldehyde solution previously adjusted to pH 9.0, mix well. Add 5 drops of a mixed indicator solution prepared by dissolving 75 mg of phenolphthalein and 25 mg of thymol blue in 100 ml of ethanol-water (1 : 1). Titrate with sodium hydroxide (0.1 mol/L) VS until the colour changes to faint violet. Each ml of sodium hydroxide (0.1 mol/L) VS is equivalent to 7.507 mg of $\text{C}_2\text{H}_5\text{NO}_2$.

Category As described under Glycine.

Strength 2000 ml : 30 g

Storage Preserve in tightly closed containers, protected from light.

Glycopyrrolate



$C_{19}H_{28}BrNO_3$ 398.34

[596-51-0]

Glycopyrrolate is 3-hydroxy-1, 1-dimethylpyrrolidinium bromide α -cyclopentylmandelate. It contains not less than 99.0% of $C_{19}H_{28}BrNO_3$, calculated on the dried basis.

Description A white crystalline powder; odourless; taste, bitter.

Freely soluble in water, methanol or ethanol; practically insoluble in chloroform or ether.

Melting range 191-195°C (Appendix VI C), melts within a range of 2°C.

Identification (1) Dissolve about 50 mg in 5 ml of dilute acetic acid, add several drops of potassium iodobismuthate TS; an orange precipitate is produced.

(2) The light absorption of a solution of 0.5 mg per ml in water exhibits two maxima at 258 nm and 264 nm, and two minima at 254 nm and 261 nm (Appendix IV A).

(3) The infrared absorption spectrum (Appendix IV C) is concordant with the reference spectrum of glycopyrrolate (Appendix XVI).

(4) Yields the reactions characteristic of bromides (Appendix III).

Related substances Carry out the method for thin-layer chromatography (Appendix V B), using silica gel G as the coating substance and a mixture of ethyl acetate-water-dehydrated methanol (74 : 16 : 10) as the mobile phase. Apply separately to the plate 5 μ l of each of two solutions in ethanol containing (1) 50 mg per ml and (2) 0.2 mg per ml of the substance being examined. After developing and removal of the plate, dry in air, spray with dilute potassium iodobismuthate TS and examine immediately. Not more than three spots, other than the principal spot in the chromatogram, obtained with solution (1) are observed. Any spot, other than the principal spot in the chromatogram, obtained with solution (1) is not more intense than the principal spot obtained with solution (2).

Loss on drying When dried to constant weight at 105°C, loses not more than 0.5% of its weight (Appendix VIII L).

Residue on ignition Not more than 0.1% (Appendix VIII N).

Assay Dissolve about 0.2 g, accurately weighed, in 25 ml of glacial acetic acid, add 5 ml of mercuric acetate TS and 1 drop of crystal violet IS, titrate with perchloric acid (0.1 mol/L) VS until the solution becomes bluish green. Perform a blank determination and make any necessary correction. Each ml of perchloric acid (0.1 mol/L) VS is equivalent to 39.83 mg of $C_{19}H_{28}BrNO_3$.

Category Anticholinergic.

Storage Preserve in well closed containers.

Preparation Glycopyrrolate Tablets

Glycopyrrolate Tablets

Glycopyrrolate Tablets contain not less than 90.0% and not more than 110.0% of the labelled amount of glycopyrrolate ($C_{19}H_{28}BrNO_3$).

Description White tablets.

Identification (1) Dissolve a quantity of the powdered tablets equivalent to about 10 mg of glycopyrrolate in methanol to produce a solution containing 0.5 mg of glycopyrrolate per ml and filter. The light absorption of the successive filtrate exhibits two maxima at 258 nm and 264 nm, and two minima at 255 nm and 262 nm.

(2) The retention time of the principal peak of the substance being examined in the chromatogram obtained in the Assay is identical with that of glycopyrrolate CRS.

Content uniformity Comply with the requirements for content uniformity (Appendix X E). Transfer 1 tablet to a 25 ml (for strength 0.5 mg) or 50 ml (for strength 1 mg) volumetric flask, add a quantity of water, shake to dissolve glycopyrrolate and dilute with water to volume. Mix well and filter through 0.8 μ m membrane. Measure the successive filtrate and carry out the procedure as described under the Assay. Calculate the content of $C_{19}H_{28}BrNO_3$.

Dissolution Comply with the requirements for dissolution test (Appendix X C, method 1), using 500 ml of water as the dissolution medium, adjust the rotational speed of the basket to 50 rpm. Withdraw 10 ml of the solution after exactly 45 minutes and filter. Use the successive filtrate as the test solution. Dissolve an accurately weighed quantity of glycopyrrolate RS in water to produce a solution of about 1 μ g (for strength 0.5 mg) or 2 μ g (for strength 1 mg) per ml as the reference solution. Carry out the procedure as described under Assay, inject accurately 20 μ l of each of the two solutions separately into the column. Calculate the dissolution of $C_{19}H_{28}BrNO_3$ from each tablet with respect to the peak area obtained in the chromatogram by the external standard method. Not less than 75% of the labelled amount is dissolved.

Other requirements Comply with the general requirements for tablets (Appendix I A).

Assay Carry out the method for high performance liquid chromatography (Appendix V D), using a column packed with octadecylsilane bonded silica gel and a mixture of sodium pentanesulfonate solution (dissolve 0.2 g of sodium pentanesulfonate and 1.0 g of anhydrous sodium sulfate in 615 ml of water, add 3.0 ml of 0.5 mol/L sulfuric acid solution)-acetonitrile-methanol (615 : 235 : 150) as the mobile phase. Detection wavelength is 222 nm and the number of the theoretical plates of the column is not less than 2000, calculated with reference to the peak of glycopyrrolate. The resolution factor between the peak of glycopyrrolate and its adjacent impurity peaks complies with the related requirements.

Procedure Weigh accurately and powder 20 tablets. Weigh accurately a quantity of the powdered tablets equivalent to 2 mg of glycopyrrolate into a 100 ml volumetric flask, add a quantity of water, shake to dissolve glycopyrrolate, dilute to volume with water and mix well. Filter through 0.8 μ m membrane and use the successive filtrate as the test solution. Dissolve an accurately weighed quantity of glycopyrrolate CRS in water to produce a solution of 20 μ g per ml as the reference solution. Inject accurately 20 μ l of each of the two solutions separately into the column and record the

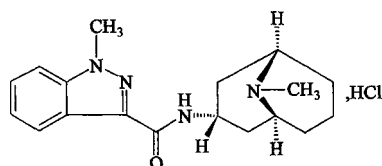
chromatogram. Calculate the content of $C_{19}H_{28}BrNO_3$ with respect to the peak area obtained in the chromatogram by the external standard method.

Category As described under Glycopyrrolate.

Strength (1) 0.5 mg (2) 1 mg

Storage Preserve in tightly closed containers.

Granisetron Hydrochloride



$C_{18}H_{24}N_4O \cdot HCl$ 348.87

[107007-99-8]

Granisetron Hydrochloride is 1-Methyl-N-(9-methyl-endo-9-azabicyclo [3.3.1] non-3-yl)-1H-indazole-3-carboxamide monohydrochloride. It contains not less than 98.0% and not more than 102.0% of granisetron hydrochloride, calculated on the dried basis.

Description White or almost white crystalline powder; odourless, taste bitter.

Freely soluble in water; sparingly soluble in methanol, slightly soluble in ethanol; sparingly soluble in 0.1 mol/L hydrochloric acid solution.

Identification (1) The retention time of principal peak of the substance being examined in the chromatogram obtained in the Assay is identical with that of granisetron hydrochloride CRS.

(2) The light absorption of a solution of 10 μg per ml in 0.1 mol/L hydrochloric acid solution exhibits a maximum at 302 nm, and a minimum at 251 nm (Appendix IV A).

(3) The infrared absorption spectrum (Appendix IV C) is concordant with the reference spectrum of granisetron hydrochloride (Appendix XVI).

(4) Yields the reactions characteristic of chlorides (Appendix III).

Acidity The solution obtained in the test for Clarity of solution, pH 4.0-6.5 (Appendix VI H).

Clarity of solution Dissolve 0.10 g in 10 ml of water, the solution is clear.

Sulfates Carry out the limit test for sulfates (Appendix VIII B), using 1.0 g. Any opalescence produced is not more pronounced than that of a reference solution using 2.0 ml of potassium sulfate standard solution (0.02%).

Related substances Carry out the method as described under Assay. Dissolve a quantity of the substance being examined, accurately weighed, in mobile phase to produce solutions of 0.5 mg per ml as test solution and 5 μg per ml as reference solution. Inject 20 μl of the reference solution into the column, adjust the attenuation so that the principal peak height in the chromatogram is about 10% of full scale of the chart. Inject separately 20 μl each of the test solution and the reference solution into the column, and record the chromatogram for twice the retention time of the principal peak. The sum of the areas of all peaks other than the principal peak is not greater than the area of the principal peak in the chromatogram obtained with the reference solution.

Loss on drying When dried to constant weight at 105°C, loses not more than 0.5% of its weight (Appendix VIII L).

Residue on ignition Not more than 0.1% (Appendix VIII N), using 1.0 g.

Heavy metals Carry out the limit test for heavy metals (Appendix VIII H, method 2), using the residue obtained in the test for Residue on ignition; not more than 0.002%.

Assay Carry out the method for high performance liquid chromatography (Appendix V D), using a column packed with cyano silane group bonded silica gel and a mixture of 0.05 mol/L sodium acetate solution containing 0.25% of triethylamine (adjust to pH 6.0 with glacial acetic acid)-methanol (50 : 50) as the mobile phase. Detection wavelength is 302 nm and the number of theoretical plates of the column is not less than 2000, calculated with reference to the peak of granisetron hydrochloride.

Procedure Dissolve an accurately weighed quantity of the substance being examined, in mobile phase to produce a solution of 0.1 mg per ml, inject 20 μl of the resulting solution into the column. Repeat the operation, using granisetron hydrochloride CRS instead of the substance being examined, calculate the content of $C_{18}H_{24}N_4O \cdot HCl$ with respect to the peak area obtained in the chromatogram by the external standard method.

Category Antiemetics for sickness caused by chemotherapy and radiotherapy.

Storage Preserve in tightly closed container, protected from light.

Preparation (1) Granisetron Hydrochloride Tablets
(2) Granisetron Hydrochloride Injection

Granisetron Hydrochloride Injection

Granisetron Hydrochloride Injection is a sterile solution of Granisetron Hydrochloride in Water for Injection. It contains not less than 95.0% and not more than 105.0% of the labelled amount of granisetron ($C_{18}H_{24}N_4O$).

Description A clear, colourless or almost colourless liquid.

Identification (1) The retention time of principal peak of the substance being examined in the chromatogram obtained in the Assay is identical with that of granisetron hydrochloride CRS.

(2) The light absorption of a solution of 10 μg per ml in 0.1 mol/L hydrochloric acid solution exhibits a maximum at 302 nm, and a minimum at 251 nm (Appendix IV A).

(3) Yields the reactions characteristic of chlorides (Appendix III).

pH value 4.5-7.0 (Appendix VI H).

Related substances Dilute the injection with mobile phase to produce a solution of about 0.5 mg per ml as the test solution. Dilute a quantity of above solution, accurately measured, with mobile phase to produce a solution of 5 μg per ml as reference solution. Carry out the method as described under Assay. Inject 20 μl of the reference solution into the column, adjust the attenuation so that the principal peak height in the chromatogram is about 10% of full scale of the chart. Inject 20 μl each of the test solution and the reference solution into the column separately, and record the chromatogram for twice the retention time of the principal peak. The sum of the secondary peak is not greater than the

area of the principal peak in the chromatogram obtained with the reference solution.

Bacterial endotoxins Carry out the test for bacterial endotoxins (Appendix XI E); less than 20 EU per mg of griseofulvin.

Other requirements Complies with the general requirements for injections (Appendix I B).

Assay Measure accurately a quantity, dilute with mobile phase to produce a solution of about 80 µg per ml. Carry out the assay as described under griseofulvin hydrochloride, and multiply the result by 0.8955.

Category As described under Griseofulvin Hydrochloride.

Strength Calculated as $C_{18}H_{24}N_4O$
(1) 1 ml : 1 mg (2) 3 ml : 3 mg

Storage Preserve in well closed container, protected from light.

Granisetrone Hydrochloride Tablets

Granisetrone Hydrochloride Tablets contain not less than 90.0% and not more than 110.0% of the labeled amount of granisetrone ($C_{18}H_{24}N_4O$).

Description White or almost white tablets.

Identification (1) The retention time of principal peak of the substance being examined in the chromatogram obtained in the Assay is identical with that of granisetrone hydrochloride CRS.

(2) The light absorption of a solution of 10 µg per ml in 0.1 mol/L hydrochloric acid solution exhibits a maximum at 302 nm, and a minimum at 251 nm (Appendix IV A).

(3) Shake a quantity of powdered tablets with water, filter. The filtrate yields the reactions characteristic of chlorides (Appendix III).

Related substance Shake a quantity of finely powdered tablets with mobile phase to dissolve granisetrone hydrochloride. Dilute with the mobile phase to produce a solution of about 0.5 mg per ml, filter, taking the successive filtrate as the test solution. Dilute a quantity of above solution, accurately measured, with mobile phase to produce a solution of 5 µg per ml as reference solution. Carry out the method as described under Assay. Inject 20 µl of the reference solution into the column, adjust the attenuation so that the principal peak height in the chromatogram is about 10% of full scale of the chart. Inject 20 µl each of the test solution and the reference solution into the column separately, and record the chromatogram for twice the retention time of the principal peak. The sum of the secondary peak is not greater than the area of the principal peak in the chromatogram obtained with reference solution.

Content uniformity Comply with the requirements for content uniformity (Appendix X E). Transfer 1 tablet to a 100 ml volumetric flask, add 50 ml of 0.1 mol/L hydrochloric acid solution, shake to disintegrate. Dissolve granisetrone hydrochloride with constant shaking for 30 minutes, dilute with 0.1 mol/L hydrochloric acid solution to volume and mix well, filter, taking the successive filtrate as test solution. Dissolve an accurately weighed quantity of granisetrone hydrochloride CRS in 0.1 mol/L hydrochloric acid solution, to produce a solution of 10 µg per ml as reference solution. Measure the absorbance of the resulting solutions at 302 nm (Appendix IV A). Calculate the content of $C_{18}H_{24}N_4O$.

Other requirements Comply with the general requirements for tablets (Appendix I A).

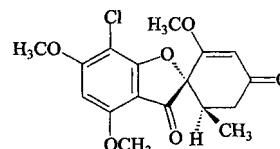
Assay Weigh accurately and powder 20 tablets. Weigh accurately a quantity of the powder equivalent to about 8 mg of granisetrone, dissolve in mobile phase to produce a solution of 80 µg per ml, and filter. Measure accurately a quantity of the successive filtrate and carry out the assay as described under griseofulvin hydrochloride, multiply the result by 0.8955.

Category As described under Griseofulvin Hydrochloride.

Strength 1 mg (calculated as $C_{18}H_{24}N_4O$)

Storage Preserve in tightly closed container, protected from light.

Griseofulvin



$C_{17}H_{17}ClO_6$ 352.77

[126-07-8]

Griseofulvin is 7-chloro-2',4,6-trimethoxy-6'-β-methylspiro [benzofuran-2 (3H), 1'-[2] cyclohexene]-3,4'-dione. It contains not less than 95.0% of $C_{17}H_{17}ClO_6$, calculated on the dried basis.

Description A white, or almost white fine powder; odourless; taste slightly bitter.

Freely soluble in dimethylformamide; slightly soluble in dehydrated ethanol; very slightly soluble in water.

Melting range 218-224°C (Appendix VI C).

Specific optical rotation +352° to +367°, in a solution of 10 mg per ml in dimethylformamide (Appendix IV E).

Identification (1) The retention time of principal peak of the substance being examined in the chromatogram obtained in the Assay is identical with that of griseofulvin CRS.

(2) The infrared absorption spectrum (Appendix IV C) is concordant with the reference spectrum of griseofulvin (Appendix XVI).

Particle size Moisten 10 mg with 2-4 drops of water, add 20 glass beads, shake for 3-5 minutes, add 10 ml of a 5% solution of acacia, shake thoroughly for 10 minutes. Withdraw the resulting solution with a dropper immediately from the bottom, wipe the outside of the dropper with filter paper; add vertically a drop on Blood Cell Counting Chamber and examine under a microscope; particles of low to 5 µm in maximum dimension are not less than 85% and particles of 50 µm may be occasionally observed, particles of up to 50 µm are not more than 5.

Related substances Dissolve an accurately weighed quantity in the mobile phase to produce a solution of 0.5 mg per ml as the test solution; measure accurately 1 ml of the above solution in a 100 ml volumetric flask and dilute with mobile phase to volume, mix well, as the reference solution. Carry out the method described under Assay, inject 10 µl of the reference solution into the column, adjust the attenuation so that the principal peak height in the chromatogram is about 20% of full scale of the chart. Inject separately 10 µl each of the test solution and the reference solution and record the chromatogram for twice the retention time of principle peak. The relative retention time for griseofulvin is 1.0 and for dechlorogriseofulvin is about 0.7. The area of dechlorogriseofulvin is not greater than 2.5 times that of the

principal peak in the chromatogram obtained with the reference solution (2.5 per cent). The relative retention time for dehydrogriseofulvin is about 1.1. The area of dehydrogriseofulvin is not greater than 0.75 times that of the principal peak in the chromatogram obtained with the reference solution (0.75 per cent). The sum of the areas of all other impurity peaks, apart from the principal peak, is not greater than the area of the principal peak in the chromatogram obtained with the reference solution (1.0 per cent). (Disregard any peak with an area less than 0.05 times that of the principal peak in the chromatogram obtained with the reference solution.)

Loss on drying When dried to constant weight at 105°C, loses not more than 0.5% of its weight (Appendix VIII L).

Residue on ignition Not more than 0.2% (Appendix VIII M).

Assay Carry out the method for high performance liquid chromatography (Appendix V D), using a column packed with octadecylsilane bonded silica gel and a mixture of 0.05 mol/L potassium dihydrogen phosphate solution-acetonitrile-methanol (57 : 38 : 5) as the mobile phase, adjust the pH to 3.7 ± 0.2 with phosphoric acid. The wavelength of the detector is 254 nm and the number of theoretical plates of the column is not less than 800, calculated with reference to the peak of griseofulvin.

Procedure Dissolve about 50 mg of the substance being examined, accurately weighed, in dehydrated ethanol and dilute to volume in a 50 ml volumetric flask, mix well. Measure accurately 5.0 ml to a 50 ml volumetric flask, dilute with dehydrated ethanol to volume and mix well, inject 10 µl into the column. Repeat the operation using griseofulvin CRS instead of the substance being examined, calculate the content of C₁₇H₁₇ClO₆.

Category Antifungus.

Storage Preserve in tightly closed containers.

Preparation Griseofulvin Tablets

Griseofulvin Tablets

Griseofulvin Tablets contain not less than 90.0% and not more than 110.0% of the labelled amount of griseofulvin (C₁₇H₁₇ClO₆).

Description White, or almost white tablets.

Identification The retention time of principal peak in the substance being examined in the chromatogram obtained in the Assay is identical with that of griseofulvin CRS.

Dissolution Carry out the dissolution test (Appendix X C, method 2), using 0.54% sodium lauryl sulfate solution as the dissolution medium, adjust the rotational speed of the paddle to 100 rpm. Withdraw 10 ml of the solution after exactly 60 minutes and filter. Measure accurately a quantity of the successive filtrate and dilute with methanol-water (4 : 1) to produce a solution of about 5.6 µg per ml. Measure the absorbance at 291 nm (Appendix IV A). Calculate the dissolution of C₁₇H₁₇ClO₆ from each tablet, taking 686 as the value of A (1%, 1 cm). Not less than 70% of the labelled amount is dissolved.

Related substances Weigh accurately and powder 10 tablets. To an accurately weighed quantity of the powder equivalent to about 50 mg of griseofulvin, in a 100 ml volumetric flask add a quantity of mobile phase, sonicate for 30 minutes, cool, dilute with mobile phase to volume, mix well, as the

test solution. Carry out the method described under Griseofulvin. The area of dechlorogriseofulvin is not greater than 2.5 times that of the principal peak in the chromatogram obtained with the reference solution (2.5%). The area of dehydrogriseofulvin is not greater than 0.75 times area of the principal peak in the chromatogram obtained with the reference solution (0.75%).

Other requirements Comply with the general requirements for tablets (Appendix I A).

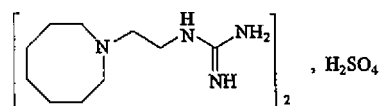
Assay Weigh accurately and powder 10 tablets. To a quantity of the powder equivalent to about 100 mg of griseofulvin, accurately weighed, in a 100 ml volumetric flask add a quantity of dehydrated ethanol, sonicate for 30 minutes, cool, dilute with dehydrated ethanol to volume and mix well. Filter with a 0.45 µm membrane, measure accurately 5.0 ml of the successive filtrate to a 50 ml volumetric flask, dilute with mobile phase to volume and mix well. Carry out the Assay described under Griseofulvin.

Category As described under Griseofulvin.

Strength (1) 0.1 g (2) 0.25 g

Storage Preserve in tightly closed containers.

Guanethidine Sulfate



(C₁₀H₂₂N₄)₂ · H₂SO₄ 494.69

[60-02-6]

Guanethidine Sulfate is 2-[hexahydro-1 (2H-azocinyl)] ethyl guanidine sulfate (2 : 1). It contains not less than 98.0% of (C₁₀H₂₂N₄)₂ · H₂SO₄, calculated on dried basis.

Description White crystals or a crystalline powder; odourless; taste, bitter.

Freely soluble in hot water; soluble in water; slightly soluble in ethanol; very slightly soluble in chloroform or ether.

Identification (1) Dissolve about 30 mg in 20 ml of water, add 2 ml of sodium hydroxide TS and 25 ml of trinitrophenol TS, a yellow precipitate is produced. Wash the precipitate with water and dry at 100°C, it melts at 156-162°C, with decomposition (Appendix VI C).

(2) Dissolve about 10 mg in 10 ml of water. Add 2 ml of an alkaline α-naphthol solution, prepared by dissolving 0.5 g of α-naphthol, 3 g of sodium hydroxide and 8 g of sodium carbonate in water to make 50 ml. Then add 1 ml of 2,3-butanedione solution (1 → 2000), mix well, and allow to stand at room temperature, a red colour develops.

(3) The aqueous solution yields the reactions characteristic of sulfates (Appendix III).

Alkalinity pH of a 0.2% solution in water is 9.0-10.0 (Appendix VI H).

Loss on drying When dried in vacuum at 60°C to constant weight, loses not more than 0.5% of its weight (Appendix VIII L).

Residue on ignition Not more than 0.1% (Appendix VIII N), using 1.0 g.

Heavy metals Carry out the limit test for heavy metals (Appendix VIII H, method 2), using the residue obtained in the test for Residue on ignition; not more than 0.001%.

Assay Dissolve about 0.1 g, accurately weighed, in 10 ml of glacial acetic acid, add 1 drop of crystal violet IS. Titrate with perchloric acid (0.1 mol/L) VS until the colour changes to bluish-green. Perform a blank determination and make any necessary correction. Each ml of perchloric acid (0.1 mol/L) VS is equivalent to 16.49 mg of $(C_{10}H_{22}N_4)_2 \cdot H_2SO_4$.

Category Antihypertensive.

Storage Preserve in tightly closed containers, protected from light.

Preparation Guanethidine Sulfate Tablets

Guanethidine Sulfate Tablets

Guanethidine Sulfate Tablets contain not less than 90.0% and not more than 110.0% of the labelled amount of guanethidine sulfate $[(C_{10}H_{22}N_4)_2 \cdot H_2SO_4]$.

Description White tablets.

Identification Add 50 ml of ethanol to a quantity of powdered tablets equivalent to 0.1 g of guanethidine sulfate, shake well. Filter and evaporate the filtrate to dryness. The residue complies with the tests for Identification described under Guanethidine Sulfate.

Other requirements Comply with the general requirements for Tablets (Appendix I A).

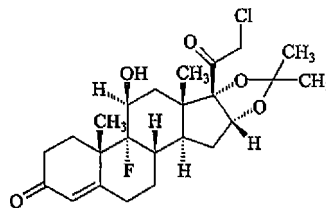
Assay Weigh accurately and powder 20 tablets. To an accurately weighed quantity, equivalent to 0.15 g of guanethidine sulfate in a Kjeldahl flask add 10 g of potassium sulfate, 0.3 g of anhydrous cupric sulfate, 0.2 g of yellow mercuric oxide and 20 ml of sulfuric acid. Heat gently until frothing subsides. Raise the temperature and boil the mixture briskly until a clear, green solution is obtained. Continue the heating for 1 hour, cool, add cautiously 300 ml of water along the inner wall of the flask, mix well and allow to cool. Add a mixture of 80 ml of sodium hydroxide solution (1→2) and 5 ml of sodium thiosulfate solution (1→2) along the inner wall of the flask to form a layer beneath the acid solution. Carry out the method for determination of nitrogen (Appendix VI D, method 1), beginning at the words "add a few pieces of Zinc granules...". Each ml of sulfuric acid (0.05 mol/L) VS is equivalent to 6.184 mg of $(C_{10}H_{22}N_4)_2 \cdot H_2SO_4$.

Category As described under Guanethidine Sulfate.

Strength (1) 10 mg (2) 25 mg

Storage Preserve in tightly closed containers, protected from light.

Halcinonide



$C_{24}H_{32}ClFO_5$ 454.97

[3093-35-4]

Halcinonide is 21-chloro-9-fluoro-11β-hydroxy-16α,17-[(1-methylethylidene) dioxy] pregn-4-ene-3,20-dione. It contains not less than 97.0% and not more than 102.0% of $C_{24}H_{32}ClFO_5$, calculated on the dried basis.

Description A white or light yellow crystalline powder; odourless.

Soluble in chloroform; slightly soluble in methanol or ethanol; insoluble in water.

Specific optical rotation $+150^\circ$ to $+159^\circ$, in a solution of 10 mg per ml in chloroform (Appendix VI E).

Identification (1) The infrared absorption spectrum (Appendix IV C) is concordant with the reference spectrum of Halcinonide (Appendix XVI).

(2) Yields the reaction characteristic of fluorinated compounds (Appendix III).

(3) Weigh about 15 mg, carry out the method for oxygen-flask combustion (Appendix VII C), using 20 ml of water as the absorbing liquid. The resulting solution yields the reactions characteristic of chlorides (Appendix III).

Fluorine content Carry out the limit test for fluorine (Appendix VIII E), the content of fluorine is not less than 3.4% and not more than 4.4%.

Related substances Carry out the method as described under Assay. Dissolve about 12.5 mg of the substance being examined, weighed accurately, in 19 ml of methanol in a 25 ml volumetric flask, dilute with water to volume and mix well as the test solution (1). Measure accurately 1 ml of solution (1) into a 100 ml volumetric flask, dilute with mobile phase to volume, mix well as the reference solution (2). Inject 20 μl of solution (2) into the column, adjust the attenuation so that the principal peak height in the chromatogram is about 50% of full scale of the chart. Inject separately accurately 20 μl each of the solution (1) and (2) into the column and record the chromatogram for 2.5 times of the retention time of the principal peak. Each peak area and the sum of the areas of all peaks other than the principal peak are not greater than 0.5 and 1.5 times the area of the principal peak in the chromatogram obtained with solution (2) respectively. Disregard any peak with an area less than 0.05 times that of the principal peak in the chromatogram obtained with solution (2).

Loss on drying When dried to constant weight at 105°C, loses not more than 0.5% of its weight (Appendix VIII L).

Residue on ignition Not more than 0.1% (Appendix VIII N).

Assay Carry out the method for high performance liquid chromatography (Appendix V D), using a column packed with octadecylsilane bonded silica gel and a mixture of methanol-water (70 : 30) as the mobile phase. Detection Wavelength is 240 nm. The number of the theoretical plates

of the column is generally 8000, calculated with reference to the peak of halcinonide. The resolution factor between the peaks of halcinonide and adjacent impurities should agree with the requirement.

Procedure Dissolve about 25 mg of the substance being examined, accurately weighed, in 74 ml of methanol in a 100 ml volumetric flask, dilute with water to volume and mix well. Measure accurately 5 ml of the solution into a 50 ml volumetric flask, dilute with mobile phase to volume, mix well as the test solution. Inject 20 μ l of solution into the column and record the chromatogram. Repeat the operation using halcinonide CRS instead of the substance being examined, calculate the content of $C_{24}H_{32}ClFO_5$ with respect to the peak area obtained in the chromatogram by the external standard method.

Category Corticosteroid.

Storage Preserve in a tightly closed containers, protected from light.

Preparation (1) Halcinonide Cream
(2) Halcinonide Film
(3) Halcinonide Ointment
(4) Halcinonide Solution

Halcinonide Cream

Halcinonide Cream contains not less than 85.0% and not more than 115.0% of the labelled amount of halcinonide ($C_{24}H_{32}ClFO_5$).

Description White cream.

Identification In the chromatograms obtained in the Assay, the principal peak of the substance being examined is identical to that of halcinonide CRS in retention time.

Other requirements Complies with the general requirements for cream (Appendix I F).

Assay Carry out the method for high performance liquid chromatography (Appendix V D), using a column packed with octadecylsilane bonded silica gel and a mixture of methanol-water (70 : 30) as the mobile phase. Detection wavelength is 240 nm and the number of theoretical plates of the column is not less than 2000. The resolution factor between the peaks of halcinonide and internal standard complies with the related requirements.

Internal standard solution Dissolve a quantity of progesterone in mobile phase to produce a solution of 0.15 mg per ml.

Procedure Dissolve a quantity of the cream, equivalent to about 1.25 mg of halcinonide, accurately weighed, in about 30 ml of methanol in a 50 ml volumetric flask and put on an 80°C water bath for 2 minutes and shake until halcinonide is dissolved, cool to room temperature, add accurately 5 ml of internal standard solution, dilute with methanol to volume, mix well and put in a ice water bath for at least 2 hours. Filter immediately and cool to room temperature, take the successive filtrate as the test solution. Inject 20 μ l into the column and record the chromatogram. Dissolve about 12.5 mg of halcinonide CRS, accurately weighed, in methanol in a 100 ml volumetric flask and dilute with methanol to volume, mix well. Measure accurately 10 ml of the solution and 5 ml of internal standard solution into a 50 ml volumetric flask, dilute with methanol to volume, mix well as the reference solution. Repeat the operation using the reference solution, calculate the content of $C_{24}H_{32}ClFO_5$ with respect to the peak area obtained in the chromatogram by the internal standard method.

Category As described under Halcinonide.

Strength 10 g : 10 mg

Storage Preserve in tightly closed containers, protected from light and stored in cool place.

Halcinonide Film

Halcinonide film contains not less than 90.0% and not more than 110.0% of the labelled amount of halcinonide ($C_{24}H_{32}ClFO_5$).

Description A clear, colourless, slightly viscous liquid.

Identification The retention time of principal peak of the substance being examined in the chromatogram obtained in the Assay is identical with that of halcinonide CRS.

Other requirements Comply with the general requirements for Films (Appendix I T).

Assay Dissolve a quantity of films equivalent to about 2.5 mg of halcinonide in the mobile phase in a 100 ml volumetric flask, dilute with the mobile phase to volume, mix well. Carry out the Assay described under Halcinonide. Inject 20 μ l of the resulting solution into the column and record the chromatogram. Dissolve about 25 mg of halcinonide CRS, accurately weighed, in 74 ml of methanol in a 100 ml volumetric flask, dilute with water to volume, mix well. Measure accurately 5 ml of the solution into a 50 ml volumetric flask, dilute with the mobile phase to volume, mix well. Measure in the same manner, calculate the content of $C_{24}H_{32}ClFO_5$.

Category As described under Halcinonide.

Strength 10 g : 10 mg

Storage Preserve in tightly closed containers and stored in a cool place.

Halcinonide Ointment

Halcinonide Ointment contains not less than 90.0% and not more than 110.0% of the labelled amount of halcinonide ($C_{24}H_{32}ClFO_5$).

Description A white creamy ointment.

Identification (1) Dissolve a quantity equivalent to 2 mg of halcinonide with 50 ml of cyclohexane and 25 ml of methanol in a separator with shaking. Separate the lower layer into another separator containing 50 ml of 5% potassium aluminum sulfate solution. Extract the upper layer twice with 15 ml and 10 ml of a mixture of methanol-10% sodium chloride solution (5 : 1). Combine the lower layer into the above separator, extract with chloroform (50, 25, 5, 5 ml) for four times. Combine the chloroform extracts, filter through a funnel containing about 10 g of anhydrous sodium sulfate, collect the filtrate in a beaker, evaporate to dryness on a water bath. Dissolve the residue in 1 ml of chloroform-methanol (9 : 1) and use the resulting solution as the test solution. Dissolve a quantity of halcinonide CRS in chloroform-methanol (9 : 1) to make a solution of 2 mg per ml as the reference solution. Carry out the method of thin-layer chromatography (Appendix V B), using silica gel G as coating substance and chloroform-methanol (3 : 1) as the mobile phase. Apply 10 μ l each of above two solutions separately on the same plate. After developing and removal

of the plate, dry in air and heat at 105°C for 10 minutes, spray with alkaline tetrazolium blue TS and examine immediately. The colour and position of the principal spot of the two solutions should be identical in the chromatogram.

(2) The retention time of principal peak of the substance being examined in the chromatogram obtained in the Assay is identical with that of halcinonide CRS.

Test (1) or (2) can be used alternatively.

Other requirements Complies with the general requirements for ointments (Appendix I F).

Assay Carry out the method for high performance liquid chromatography (Appendix V D), using a column packed with octadecylsilane bonded silica gel and a mixture of methanol-water (70 : 30) as the mobile phase. Detection wavelength is 240 nm and the number of theoretical plates of the column is not less than 2000. The resolution factor between the peaks of halcinonide and internal standard complies with the related requirements.

Internal standard solution Dissolve a quantity of progesterone in mobile phase to produce a solution of 0.15 mg per ml.

Procedure Dissolve a quantity of the cream, equivalent to about 1.25 mg of halcinonide, accurately weighed, in about 30 ml of methanol in a 50 ml volumetric flask and put on an 80°C water bath for 2 minutes and shake until halcinonide is dissolved, cool to room temperature, add accurately 5 ml of internal standard solution, dilute with methanol to volume, mix well and put in a ice water bath for at least 2 hours. Filter immediately and cool to room temperature, take the successive filtrate as the test solution. Inject 20 µl into the column and record the chromatogram. Dissolve about 12.5 mg of halcinonide CRS, accurately weighed, in methanol in a 100 ml volumetric flask and dilute with methanol to volume, mix well. Measure accurately 10 ml of the solution and 5 ml of internal standard solution into a 50 ml volumetric flask, dilute with methanol to volume, mix well as the reference solution. Repeat the operation using the reference solution, calculate the content of $C_{24}H_{32}ClFO_5$ with respect to the peak area obtained in the chromatogram by the internal standard method.

Category As described under Halcinonide.

Strength 10 g : 10 mg

Storage Preserve in tightly closed containers, stored in cool place.

Halcinonide Solution

Halcinonide Solution contains not less than 90.0% and not more than 110.0% of the labelled amount of halcinonide ($C_{24}H_{32}ClFO_5$).

Description A colourless, clear, slightly viscous liquid.

Identification The retention time of principal peak of the substance being examined in the chromatogram obtained in the Assay is identical with that of halcinonide CRS.

Content Complies with the requirement of limit test for content (Appendix X F).

Microbial limit Complies with the requirements of microbial limit tests (Appendix XI J).

Assay Carry out the method for high performance liquid chromatography (Appendix V D), using a column packed with octadecylsilanized silica gel and a mixture of methanol-water-ether (76 : 24 : 4) as the mobile phase. The detection wavelength is 238 nm. The theoretical plate should be not

lower than 2500, calculated with the reference to halcinonide. The resolution of halcinonide and the internal standard complies with the requirement. Dissolve a quantity of progesterone, accurately weighed, in methanol to make a solution of about 0.15 mg per ml as the internal standard solution.

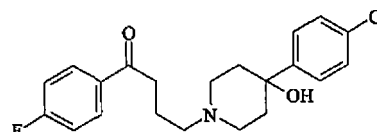
Procedure Dissolve a quantity, accurately weighed of halcinonide CRS in methanol to make a solution of about 0.1 mg per ml. Measure accurately 10 ml of the solution and 5 ml of internal standard solution into a 50 ml volumetric flask and dilute to volume with methanol, shake well. Inject 20 µl into the column, record the chromatogram. Repeat the operation using a quantity of the substance being examined instead of Halcinonide CRS. Calculate the content of $C_{24}H_{32}ClFO_5$ correspondingly.

Category As described under Halcinonide.

Strength (1) 0.1% (2) 0.025%

Storage Preserved in tightly closed containers, protected from light.

Haloperidol



$C_{21}H_{23}ClFNO_2$ 375.87

[52-86-8]

Haloperidol is 4-[4-(4-chlorophenyl)-4-hydroxy-1-piperidinyl]-1-(4-fluorophenyl)-1-butanone. It contains not less than 98.5% of $C_{21}H_{23}ClFNO_2$, calculated on the dried basis.

Description A white or almost white crystalline powder; odourless; tasteless.

Soluble in chloroform; sparingly soluble in ethanol; slightly soluble in ether; practically insoluble in water.

Melting range 149-153°C (Appendix VI C).

Specific absorbance Protect from light throughout the procedure. Measure the absorbance of a solution of 15 µg per ml in a mixture of hydrochloric acid solution (9→100)-methanol (1 : 99) at 244 nm (Appendix IV A), the value of A (1%, 1 cm) is 338-360.

Identification (1) Rotate the test tube containing about 1 ml of saturated solution of chromium trioxide in sulfuric acid, the solution is spread evenly on the wall; add 2 mg of the substance being examined, heat gently, rotate the test tube, the solution can no longer be spread evenly on the wall, but attached to the wall with greasiness.

(2) The infrared absorption spectrum (Appendix IV C) is concordant with the reference spectrum of haloperidol (Appendix XVI).

(3) Weigh about 20 mg, carry out the method for oxygen flask combustion (Appendix VII C), using 5 ml of sodium hydroxide TS as the absorbing liquid. When the absorption is complete, acidify the liquid with dilute nitric acid, boil gently for 2 minutes, the resulting solution yields the reactions characteristic of chlorides (Appendix III).

Clarity of acidic solution Dissolve, with heating, 50 mg in 10 ml of lactic acid solution (0.5→100), the resulting solution is clear.

Related substances Carry out the method for thin-layer chromatography (Appendix V B), using silica gel G as the

coating substance and a mixture of chloroform-ethanol (8 : 1) as the mobile phase. Apply separately to the plate 10 μ l each of two solutions in chloroform containing (1) 10 mg per ml and (2) 0.10 mg per ml of the substance being examined. After developing and removal of the plate, dry in air and spray with dilute potassium iodobismuthate TS. examine immediately. Any spot other than the principal spot in the chromatogram obtained with solution (1) is not more intense than the principal spot in the chromatogram obtained with solution (2).

Loss on drying When dried in vacuum to constant weight at 60°C, loses not more than 0.5% of its weight (Appendix VIII L).

Residue on ignition Not more than 0.1% (Appendix VIII N).

Assay To about 0.2 g, accurately weighed, add 20 ml of glacial acetic acid and heat gently to dissolve. Allow to cool, add 2 drops of naphtholbenzein IS, titrate with perchloric acid (0.1 mol/L) VS until the solution becomes green. Perform a blank determination and make any necessary correction. Each ml of perchloric acid (0.1 mol/L) VS is equivalent to 37.59 mg of $C_{21}H_{23}ClFNO_2$.

Category Antipsychotic.

Storage Preserve in tightly closed containers, protected from light.

Preparation (1) Haloperidol Tablets
(2) Haloperidol Injection

Haloperidol Injection

Haloperidol Injection is a sterile solution of Haloperidol in Water for Injection containing a quantity of lactic acid. It contains not less than 90.0% and not more than 110.0% of the labelled amount of haloperidol ($C_{21}H_{23}ClFNO_2$).

Description A clear, colourless solution.

Identification (1) Complies with test (1) for Identification described under Haloperidol, using 3 drops.
(2) Protect from light throughout the procedure. The light absorption of the solution obtained in the Assay exhibits a maximum at 244 nm and a minimum at 232 nm (Appendix IV A).

pH value 2.8-3.6 (Appendix VI H).

Other requirements Complies with the general requirements for injections (Appendix I B).

Assay Protect from light throughout the procedure. Dilute a quantity, accurately measured, with a mixture of hydrochloric acid solution (9→100)-methanol (1 : 99) to produce a solution of 10 μ g of haloperidol per ml. Measure the absorbance of the resulting solution at 244 nm (Appendix IV A). Calculate the content of $C_{21}H_{23}ClFNO_2$, taking 353 as the value of A (1%, 1 cm).

Category As described under Haloperidol.

Strength 1 ml : 5 mg

Storage Preserve in well closed containers, protected from light.

Haloperidol Tablets

Haloperidol Tablets contain not less than 90.0%

and not more than 110.0% of the labelled amount of haloperidol ($C_{21}H_{23}ClFNO_2$).

Description Sugar-coated tablets with white cores.

Identification (1) Add 2 ml of chloroform to a quantity of powdered tablets equivalent to about 2 mg of haloperidol, shake, filter. Evaporate the filtrate to dryness. The residue complies with test (1) for Identification described under Haloperidol.

(2) The light absorption of the solution obtained in the Assay exhibits a maximum at 244 nm and a minimum at 232 nm (Appendix IV A).

Related substances Carry out the method for thin-layer chromatography (Appendix V B), using silica gel G as the coating substance and a mixture of chloroform-ethanol (8 : 1) as the mobile phase. Apply separately to the plate 10 μ l each of the following solutions: shake an accurately weighed quantity of the powdered tablets equivalent to about 10 mg of haloperidol with 10 ml of chloroform, filter, evaporate the filtrate to dryness and dissolve the residue in 1.0 ml of chloroform (solution 1); dilute a quantity of solution (1) with chloroform to produce a solution of 0.20 mg per ml (solution 2). After developing and removal of the plate, dry in air and spray with dilute potassium iodobismuthate TS, examine immediately. Any spot other than the principal spot in the chromatogram obtained with solution (1) is not more intense than the principal spot obtained with solution (2).

Content uniformity Protect from light throughout the procedure. Comply the requirements (Appendix X E), triturate 1 tablet with the coating removed with 1 ml of hydrochloric acid solution (9→100) for 2 minutes. Transfer in portions with the aid of 30 ml of methanol to a 50 ml volumetric flask, heat on a water bath with shaking to dissolve haloperidol, cool, add methanol to volume and mix well, filter. Measure accurately 5 ml of the successive filtrate to a 20 ml volumetric flask, add a mixture of hydrochloric acid solution (9→100)-methanol (1 : 99) to volume and mix well. Proceed as directed in the Assay and calculate the content of $C_{21}H_{23}ClFNO_2$.

Dissolution Protect from light throughout the procedure. Carry out the dissolution test (Appendix X C, method 3), using 200 ml of hydrochloric acid (9→1000) as the dissolution medium, adjust the rotational speed of the paddle to 75 rpm. Withdraw 10 ml of the solution after exactly 45 minutes and filter. Dilute a quantity of the successive filtrate (for strength 4 mg) with the same volume of dissolution medium. Dissolve 25 mg of haloperidol CRS, accurately weighed, in a mixture solution of hydrochloric acid (9→100)-methanol (1 : 99) and dilute to volume in a 100 ml volume flask, mix well. Transfer 2 ml, accurately measured, to a 50 ml volume flask, dilute with hydrochloric acid (9→1000) to volume and mix well. Measure the absorbances of the resulting solutions at 248 nm (Appendix IV A), calculate the dissolution of $C_{21}H_{23}ClFNO_2$ from each tablet. Not less than 70% of the labelled amount is dissolved.

Other requirements Comply with the general requirements for tablets (Appendix I A).

Assay Protect from light throughout the procedure. Weigh accurately and powder 20 tablets with coatings removed, weigh accurately a quantity of the powder equivalent to about 10 mg of haloperidol to a 100 ml volumetric flask, add 1 ml of hydrochloric acid solution (9→100), shake for 2 minutes and add 60 ml of methanol. Heat on a water bath with shaking to dissolve haloperidol, cool, add methanol to volume and mix well. Filter, measure accurately 10 ml of the successive filtrate to a 100 ml volumetric flask, add a mixture of hydrochloric acid solution (9→100)-methanol (1 : 99) to volume and mix well. Measure the absorbance of

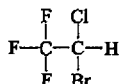
the resulting solution at 244 nm (Appendix IV A). Calculate the content of $C_{21}H_{23}ClFNO_2$, taking 353 as the value of A (1%, 1 cm).

Category As described under Haloperidol.

Strength (1) 2 mg (2) 4 mg

Storage Preserve in tightly closed containers, protected from light.

Halothane



$C_2HBrClF_3$ 197.38 [151-67-7]

Halothane is 2-bromo-2-chloro-1,1,1-trifluoro ethane. It contains 0.01% (g/g) of thymol as stabilizer.

Description A clear, colourless, mobile, dense liquid; odour similar to chloroform; taste sweet. Miscible with ethanol, chloroform, ether or fixed oil; slightly soluble in water.

Relative density 1.871-1.875 (Appendix VI A).

Identification (1) To 1 ml in a test tube add 2 ml of sulfuric acid, the sample forms a layer under the acid (distinction from Methoxyflurane).

(2) Yields the reactions characteristic of organic fluoride compound (Appendix III).

Acidity Shake 20 ml with 20 ml of water for 3 minutes. Separate the water layer, add 2 drops of bromocresol purple IS and 0.10 ml of sodium hydroxide (0.01 mol/L) VS, a purple colour is produced.

Halides and free halogens Shake 15 ml with 30 ml of freshly boiled and cooled water for 3 minutes, then carry out the following tests.

(1) To 5 ml of the water layer add 5 ml of water, 1 drop of nitric acid and 0.2 ml of silver nitrate TS. Any opalescence produced is not more pronounced than that of the reference solution (to 5 ml of the water layer add 5 ml of water and 1 drop of nitric acid).

(2) To 10 ml of the water layer add 1 ml of cadmium iodide TS and 2 drops of starch IS, no blue colour is produced.

Thymol Dilute 1 ml, accurately measured, of a solution of 0.225% thymol in carbon tetrachloride to 10 ml with carbon tetrachloride and measure accurately 0.5 ml of this solution to a 25 ml stoppered Nessler cylinder (1). Dilute 1 ml, accurately measured, of a solution of 0.225% thymol in carbon tetrachloride to 15 ml with carbon tetrachloride and measure accurately 0.5 ml of this solution to a second 25 ml stoppered Nessler cylinder (2). Measure accurately 0.5 ml of the substance being examined to a third 25 ml stoppered Nessler cylinder (3). To each of the three cylinders add 5 ml of carbon tetrachloride and 5 ml of titanium sulfate TS, shake vigorously for 30 seconds, and allow to stand until the layers have separated. The intensity of the yellowish-brown colour of the lower layer in cylinder (3) lies between those produced in cylinders (1) and (2) (0.008%-0.0012%).

Non-volatile substances Evaporate 50 ml on a water bath and dry the residue at 105°C for 2 hours, the residue weighs not more than 1 mg.

Volatile impurities Carry out the method for gas chromatography (Appendix V E), using the substance being

examined and that containing 0.010% (ml/ml) of dichloromethane (internal standard), use trioctyl phosphate (25%) as the stationary phase. The number of theoretical plates of the column is not less than 750. Maintain the column temperature at 48-50°C. Record the peaks until the principal peak appears in the chromatogram. The results comply with the requirements.

Category Inhalant anaesthetic.

Strength (1) 20 ml (2) 100 ml

Storage Preserve in tightly closed containers, protected from light and stored in a cool place.

Heavy Magnesium Carbonate

Heavy Magnesium Carbonate is a hydrated basic magnesium carbonate. It contains not less than 40.0% and not more than 43.5% of MgO .

Description A white, granular powder; odourless; almost tasteless.

Practically insoluble in water or ethanol; the aqueous solution exhibits weak alkaline reaction and dissolves in dilute acids with effervescence.

Identification It dissolves in dilute hydrochloric acid with effervescence; the solution yields the reactions characteristic of magnesium salts (Appendix III).

Chlorides Dissolve 0.2 g in 0.4 ml of nitric acid and quantity of water to produce 25 ml. Carry out the limit test for chlorides (Appendix VIII A). Any opalescence produced is not more pronounced than that of a reference using 7.0 ml of sodium chloride standard solution (0.035%).

Sulfates Dissolve 0.10 g in 1 ml of hydrochloric acid and a quantity of water, dilute to 25 ml with water. Carry out the limit test for sulfates (Appendix VIII B), using 10 ml of the resulting solution. Any opalescence produced is not more pronounced than that of a reference using 2.0 ml of potassium sulfate standard solution (0.5%).

Calcium oxide Weigh accurately about 0.5 g and carry out the test for calcium oxide described under magnesium oxide, not more than 0.6%.

Soluble salts Boil 1.0 g in 50 ml of water for 5 minutes, filter, evaporate the filtrate to dryness on a water bath, and dry for 1 hour at 105°C, the residue is not more than 10 mg (1.0%).

Acid-insoluble substances To 5 g add 75 ml of water, and add a small amount of hydrochloric acid in portions with stirring until no more is dissolved. Boil for 5 minutes and filter, wash the residue with water until the washing is free from chloride. Ignite the residue to constant weight; not more than 2.5 mg (0.05%).

Iron Boil 0.25 g in 5 ml of dilute nitric acid for 1 minute, allow to cool, dilute to 35 ml with water. Carry out the limit test for Iron (Appendix VIII G). Any colour produced is not more intense than that of a reference using 5.0 ml of iron standard solution (0.02%).

Heavy metals Boil 0.50 g in 5 ml of dilute hydrochloric acid and 10 ml of water for 5 minutes, cool and filter. To the filtrate add 1 drop of phenolphthalein IS and a quantity of ammonia TS until the solution is pale red; add 2 ml of acetate BS (pH 3.5) and a quantity of water to produce 25 ml. To the resulting solution add 0.5 g of ascorbic acid. Carry out the limit test for Heavy metals (Appendix VIII H, method 1), compare the colour of the two solutions after 5

minutes; not more than 0.003%.

Arsenic To 1.0 g add a quantity of water and hydrochloric acid dropwise to dissolve the substance being examined. add 5 ml of hydrochloric acid in excess and a quantity of water to produce 28 ml. Complies with the limit test for Arsenic (Appendix VIII J, method 1) (0.0002%).

Assay Dissolve about 1 g accurately weighed and moistened with 5 ml of water in 30 ml of sulfuric acid (0.5 mol/L) VS, accurately measured. Add 1 drop of methyl orange IS, titrate with sodium hydroxide (1 mol/L) VS. Each ml of sulfuric acid (0.5 mol/L) /VS is equivalent to 20.15 mg of MgO and 28.04 mg of CaO, calculate the difference between the total volume (ml) of sulfuric acid (0.5 mol/L) VS and the volume consumed by calcium oxide.

Category Antacid.

Storage Preserve in tightly closed containers.

Heparin Sodium

Heparin Sodium is the sodium salt of a sulfated glycosaminoglycan prepared from the intestinal mucosa of pigs, or oxen. It has a potency of not less than 150 Units per mg, calculated on the dried basis.

Description A white or almost white powder; hygroscopic. Freely soluble in water.

Specific optical rotation Not less than +35., in a solution of 40 mg per ml in water (Appendix VI E).

Identification (1) Dissolve separately the substance being examined and Heparin RS in water to produce a solution of 2.5 mg per ml. Carry out the method for electrophoresis (Appendix V F, method 3). The ratio of the distance migrated by the principal band obtained with substance being examined to the distance migrated by the principal band obtained with Heparin RS is 0.9-1.1.

(2) The aqueous solution yields the reactions characteristic of sodium salts (Appendix III).

Acidity or alkalinity Dissolve 0.10 g in 10 ml of water, pH 5.0-7.5 (Appendix VI H).

Clarity and colour of solution A solution of 0.50 g in 10 ml of water is clear and colourless, any colour produced is not more intense than that of reference solution Y₁ (Appendix IX A, method 1). The absorbance of the solution at 640 nm (Appendix IV A) is not more than 0.018.

Light absorption The light absorption of a solution of 4 mg per ml in water exhibits maxima at 260 nm and 280 nm; the absorbance is not more than 0.20 and 0.15 respectively (Appendix IV A).

Viscosity Triturate an accurately weighed quantity equivalent to about 400000 Units with water, transfer the liquid to a previously dried and weighed 10 ml volumetric flask, wash the mortar with water and add the washings to the flask. Place the flask in a water bath at 25°C, add water (25°C) to volume and mix well. Weigh accurately and calculate the density of the solution. Filter the solution if necessary, through a 0.45 µm filter membrane. The kinetic viscosity of the solution at 25°C ± 0.1°C (Appendix VI G, method 1) is not more than 0.030 Pa · s.

Nitrogen content Carry out the method for determination of nitrogen (Appendix VII D, method 2): The total nitrogen content is not less than 1.3% and not more than 2.5%, calculated on the dried basis.

Sulfur Carry out the method for oxygen flask combustion (Appendix VII C), using a 1000 ml combustion flask and 0.1 ml of concentrated hydrogen peroxide solution and 10 ml of water as the absorbing liquid. When the combustion is complete, cool on ice bath for 15 minutes, heat gently to boil for 2 minutes and cool. Add 50 ml of ethanol-ammonium acetate buffer solution (pH 3.7), 30 ml of ethanol and 0.3 ml of 0.1% alizarin red solution as indicator solution. Titrate with barium perchlorate (0.05 mol/L) VS until the colour changes to orange-red. Each of barium perchlorate (0.05 mol/L) VS is equivalent to 1.603 mg of S. It contains not less than 10.0%.

Loss on drying When dried in vacuum to constant weight at 60°C, loses not more than 5.0% of its weight (Appendix VIII L).

Residue on ignition Not less than 28.0% and not more than 41.0% (Appendix VIII N), using 0.50 g.

Potassium salt Test preparation (B): Dissolve 0.10 g in a 100 ml volumetric flask with water and dilute to volume, mix well.

Reference Preparation (A): Dissolve 191 mg of potassium chloride (AR), previously dried at 150°C for 1 hour and accurately weighed in a 1000 ml volumetric flask with water and dilute to volume, mix well. Transfer 5.0 ml of the solution to a 50 ml volumetric flask, add test preparation (B) to volume and mix well. Carry out the method for atomic absorption spectrophotometry (test for impurities) (Appendix IV A), the absorbance of the solutions, measured at 766.5 nm, complies with the requirement.

Heavy metals Carry out the limit test for heavy metals (Appendix VIII H, method 2), using the substance obtained in the test for Residue on ignition; not more than 0.003%.

Bacterial endotoxin Carry out the test for bacterial endotoxin (Appendix XI E); less than 0.015 EU per Unit of heparin.

Assay Carry out the biological assay of heparin (Appendix XII D), the estimated potency is not less than 91% and not more than 110% of the labelled potency.

Category Anticoagulant.

Storage Preserve in tightly closed containers, stored in a cool place and protected from light.

Preparation (1) Heparin Sodium Injection
(2) Heparin Sodium Cream

Heparin Sodium Cream

Heparin Sodium Cream contains not less than 86% and not more than 116% of the labelled amount of heparin sodium.

Description A white cream.

Identification (1) Dissolve a quantity equivalent to about 700 Units of heparin sodium in 10 ml of 60% ethanol by warming on a water bath and cool in a refrigerator at 4°C for 5 hours. Filter, use the filtrate as the test solution. Dissolve a quantity of heparin sodium RS in water to produce a reference solution containing 1.25 mg per ml. Apply separately to a gel plate 2 µl each of above two solutions. Carry out the method for electrophoresis (Appendix V F, method 3). The ratio of the mobility of the principal spot in the electrophoretogram obtained with the test solution to that in the electrophoretogram obtained with the reference solution is 0.9 to 1.1.

(2) The test solution obtained in identification test (1) yields the flame reaction characteristic of sodium salts

(Appendix III).

Acidity or alkalinity Dissolve 1 g in 10 ml of water, mix well. pH 6.5-8.5 (Appendix VI H).

Other requirements Complies with the general requirements for creams (Appendix I F).

Assay Dissolve about 2 g, accurately weighed, in 30 ml of dehydrated ethanol by warming on a water bath, allow to cool. Transfer the solution to a 100 ml volumetric flask, dilute with 0.9% sodium chloride solution to volume, mix well, cool in a refrigerator at 4°C overnight and filter. Evaporate 50 ml of the successive filtrate, accurately measured, on a water bath until no smell of ethanol. Transfer the remaining solution to a 50 ml volumetric flask, dilute with 0.9% sodium chloride solution to volume and mix well. Carry out the biological assay of Heparin (Appendix XI D), it complies with the requirement for potency.

Category Anticoagulant.

Strength (1) 20 g : 5000 Units of heparin sodium
(2) 20 g : 7000 Units of heparin sodium
(3) 25 g : 8750 Units of heparin sodium

Storage Preserve in tightly closed containers, stored in a cool place.

Heparin Sodium Injection

Heparin Sodium Injection is a sterile solution of Heparin Sodium in Water for Injections. It has a potency of not less than 86% and not more than 116% of the labelled potency.

Description A clear, colourless or pale yellow liquid.

Identification Yields the reactions characteristic of sodium salts (Appendix III).

pH value 5.5-8.5 (Appendix VI H).

Bacterial endotoxin Complies with the test for Bacterial endotoxin described under Heparin Sodium.

Other requirements Complies with the general requirements for injections (Appendix I B).

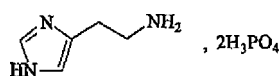
Assay Carry out the biological assay of heparin (Appendix XI D), it complies with the requirement.

Category As described under Heparin Sodium.

Strength (1) 2 ml : 1000 Units (2) 2 ml : 5000 Units
(3) 2 ml : 12500 Units

Storage Preserve in well closed containers, stored in a cool place, protected from light.

Histamine Phosphate



$C_5H_9N_3 \cdot 2H_3PO_4$ 307.14

[51-74-1]

Histamine Phosphate is 1*H*-imidazole-4-ethanamine phosphate. It contains not less than 98.0% of $C_5H_9N_3 \cdot 2H_3PO_4$, calculated on the dried basis.

Description Long prismatic crystals; odourless; deteriorated

on exposure to light; the aqueous solution yields an acidic reaction.

Freely soluble in water; slightly soluble in ethanol.

Melting range 126-132°C (Appendix VI C).

Identification (1) Dissolve 50 mg in 5 ml of hot water, add 10 ml of hot picronic acid solution (50 mg of picronic acid in 10 ml of hot ethanol), allow to stand until the crystallization is complete. Filter, wash the crystals with a small quantity of ice water and dry at 105°C for 1 hour; the melting range is 250-254°C, with decomposition (Appendix VI C).

(2) Dissolve about 5 mg in 7 ml of water and 3 ml of sodium hydroxide TS, add 50 mg of sulfanilic acid, 10 ml of water, and a mixture of 2 drops of hydrochloric acid and 2 drops of sodium nitrite solution (1→10), a red colour is produced.

(3) The aqueous solution yields the reactions characteristic of phosphates (Appendix III).

Loss on drying When dried to constant weight at 105°C, loses not more than 3.0% of its weight (Appendix VIII L).

Assay Dissolve about 0.1 g, accurately weighed, in 10 ml of water. Add 5 ml of chloroform, 25 ml of ethanol and 10 drops of thymolphthalein IS, titrate with sodium hydroxide (0.1mol/L) VS. Each ml of sodium hydroxide (0.1mol/L) VS is equivalent to 7.68 mg of $C_5H_9N_3 \cdot 2H_3PO_4$.

Category Diagnostic agent.

Storage Preserve in tightly closed containers, protected from light.

Preparation Histamine Phosphate Injection

Histamine Phosphate Injection

Histamine Phosphate Injection is a sterile solution of Histamine Phosphate in Water for Injection. It contains not less than 90.0% and not more than 110.0% of the labelled amount of histamine phosphate ($C_5H_9N_3 \cdot 2H_3PO_4$).

Description A clear, colourless liquid; deteriorated on exposure to light.

Identification (1) Evaporate a quantity of the injection, equivalent to about 2 mg of histamine phosphate, on a water bath to dryness, the residue complies with test (2) for Identification described under Histamine Phosphate.

(2) Evaporate a quantity of the injection, equivalent to about 1 mg of histamine phosphate, on a water bath to about 1 ml, add dropwise ammonium molybdate TS; a yellow precipitate is produced and dissolved on adding ammonia TS.

pH value 3.0-6.0 (Appendix VI H).

Other requirements Complies with the general requirements for injections (Appendix I B).

Assay *Reference preparation* Dissolve an accurately weighed amount of histamine phosphate CRS, in water to produce a solution of about 50 µg per ml.

Test preparation Measure accurately a quantity of the injection, equivalent to about 2.5 mg of histamine phosphate, to a 50 ml volumetric flask, dilute with water to volume, mix well.

Procedure Measure accurately 5 ml of each of two solutions to two 10 ml volumetric flasks, respectively, to each flask add 1 ml of 1% sodium borate solution and 1 ml of freshly prepared 0.5% β-naphthoquinone-4-sodium sulfonate solution,

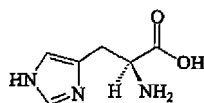
both accurately measured. Place the flasks in boiling water bath immediately for 10 minutes. Then immerse them in ice-water bath (5-10°C) for 5 minutes. To each flask add 1 ml of acidic formaldehyde solution [to 45 ml of 1 mol/L hydrochloric acid solution, add 10 ml of glacial acetic acid and 0.5 ml of formaldehyde solution, dilute with water to 80 ml], mix well, add 1 ml of 0.1 mol/L sodium thiosulfate solution, dilute with water to volume and mix well. Measure the absorbances of the two solutions at 460 nm (Appendix IV B) immediately, calculate the content of $C_6H_9N_3O_2 \cdot 2H_3PO_4$.

Category As described under Histamine Phosphate.

Strength (1) 1 ml : 1 mg (2) 1 ml : 0.5 mg
(3) 5 ml : 0.2 mg

Storage Preserve in well closed containers, protected from light.

Histidine



$C_6H_9N_3O_2$ 155.16

Histidine is (S)-2-amino-3-(imidazol-4-yl) propanoic acid. It contains not less than 99.0% and not more than 101.0% of $C_6H_9N_3O_2$, calculated on the dried basis.

Description White crystals or crystalline powder; odourless; taste, slightly bitter. Soluble in water, very slightly soluble in ethanol, insoluble in ether.

Specific optical rotation +12.0° to +12.8°, in a solution of 0.11 g per ml in 6 mol/L hydrochloric acid solution (Appendix VI E).

Identification The infrared absorption spectrum is (Appendix IV C) is concordant with the spectrum of Histidine CRS (Appendix IV C).

Acidity or alkalinity Dissolve 1.0 g in 50 ml of water, pH 7.0-8.5 (Appendix VI H).

Transmittance of solution Dissolve 0.60 g in 20 ml of water, the transmittance at 430 nm is not less than 98.0% (Appendix IV A).

Chlorides Carry out the limit test for chlorides (Appendix VIII A), using 0.25 g. Any opalescence produced is not more pronounced than that of a reference solution using 5.0 ml of sodium chloride standard solution (0.02%).

Sulfates Carry out the limit test for sulfates (Appendix VIII B), using 1.0 g. Any opalescence produced is not more pronounced than that of a reference solution using 2.0 ml of potassium sulfate standard solution (0.02%).

Ammonium Carry out the limit test for ammonium (Appendix VIII K), using 0.10 g. Any colour produced is not more intense than that of a reference solution using 2.0 ml of ammonium chloride standard solution (0.02%).

Other amino acids Carry out the method for thin-layer chromatography (Appendix V B), using silica gel G as the coating substance and *n*-propyl alcohol-concentrated ammonia solution (67 : 33) as the mobile phase. Apply separately to

the plate 5 µl of each of two solutions in water containing (1) 10 mg per ml, (2) 50 µg per ml of the substance being examined. After developing and removal of the plate, dry in air, spray with ninhydrin acetone solution (1→50), heat at 80°C until the colour is produced and examine immediately. Any spot, other than the principal spot in the chromatogram, obtained with solution (1) is not more intense than the principal spot obtained with solution (2) (0.5%).

Loss on drying When dried at 105°C for 3 hours, loses not more than 0.2% of its weight (Appendix VIII L).

Residue on ignition Not more than 0.1% (Appendix VIII N).

Iron Carry out the limit test for iron (Appendix VIII G), using 1.0 g. Any colour produced is not more intense than that of a reference solution using 1.0 ml of iron standard solution (0.001%).

Heavy metals Carry out the limit test for heavy metals (Appendix VIII H, method 1), using 1.0 g; not more than 0.001%.

Arsenic Dissolve 2.0 g in 23 ml of water, add 5 ml of hydrochloric acid, carry out the limit test for arsenic (Appendix VIII J, method 1); not more than 0.001%.

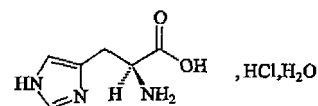
Pyrogens Complies with the test for pyrogens (Appendix XI D), using 10 ml of a solution of 30 mg per ml in Sodium chloride Injection per kg of the rabbit's weight.

Assay Dissolve about 0.15 g, accurately weighed, in 2 ml of dehydrated formic acid, add 50 ml of glacial acetic acid. Carry out the method for potentiometric titration (Appendix VII A), titrate with perchloric acid (0.1 mol/L) VS. Perform a blank determination and make any necessary correction. Each ml of perchloric acid (0.1 mol/L) VS is equivalent to 15.52 mg of $C_6H_9N_3O_2$.

Category Amino acid.

Storage Preserve in tightly closed containers, protected from light.

Histidine Hydrochloride



$C_6H_9N_3O_2 \cdot HCl \cdot H_2O$ 209.63

Histidine hydrochloride is (S)-2-amino-3-(imidazol-4-yl) propanoic acid hydrochloride monohydrate. It contains not less than 98.5% of $C_6H_9N_3O_2 \cdot HCl \cdot H_2O$, calculated on the dried basis.

Description A white crystalline powder; odourless; taste, slightly sour and bitter. Freely soluble in water, insoluble in ethanol, chloroform or ether.

Specific optical rotation +8.5° to +10.5°, in a solution of about 0.11 g per ml in 6 mol/L hydrochloric acid solution (Appendix VI E).

Identification The infrared absorption spectrum (Appendix IV C) is concordant with the reference spectrum of histidine hydrochloride monohydrate (Appendix XVI).

Acidity Dissolve 1.0 g in 10 ml of water, pH 3.5-4.5 (Appendix VI H).

Transmittance of solution Dissolve 1.0 g in 10 ml of water, the transmittance at 430 nm is not less than 98.0% (Appendix IV A).

Chlorine Content Dissolve about 0.4 g, accurately weighed, in 50 ml of water, add 2 ml of dilute nitric acid. Carry out the method for potentiometric titration (Appendix VI A), titrate with silver nitrate (0.1 mol/L) VS. Perform a blank determination and make any necessary correction. Each ml of silver nitrate (0.1 mol/L) VS is equivalent to 3.545 mg of chlorine. It contains not less than 16.7% and not more than 17.1% of chlorine, calculated on the dried basis.

Sulfates Carry out the limit test for sulfates (Appendix VII B), using 1.0 g. Any opalescence produced is not more pronounced than that of a reference solution using 2.0 ml of potassium sulfate standard solution (0.02%).

Ammonium Carry out the limit test for ammonium (Appendix VIII K), using 0.10 g. Any colour produced is not more intense than that of a reference solution using 2.0 ml of ammonium chloride standard solution (0.02%).

Other amino acids Carry out the method for thin-layer chromatography (Appendix V B), using silica gel G as the coating substance and *n*-butanol-acetone-concentrated ammonia solution-water (10 : 10 : 5 : 2) as the mobile phase. Apply separately to the plate 2 μ l of each of the two solutions in water containing (1) 50 mg per ml and (2) 0.1 mg per ml of the substance being examined. After developing and removal of the plate, dry in air and spray with ninhydrin acetone solution (1 \rightarrow 50), heat at 80°C until the colour is produced and examine immediately. Any spot, other than the principal spot in the chromatogram, obtained with solution (1) is not more intense than the principal spot obtained with solution (2) (0.2%).

Loss on drying When dried at 105°C for 3 hours, loses not more than 0.2% of its weight (Appendix VIII L).

Residue on ignition Not more than 0.1% (Appendix VIII N).

Iron Carry out the limit test for iron (Appendix VIII G), using 1.0 g. Any colour produced is not more intense than that of a reference solution using 1.0 ml of iron standard solution (0.001%).

Heavy metals Dissolve 2.0 g in 23 ml of water, add 2 ml of acetate BS (pH 3.5). Carry out the limit test for heavy metals (Appendix VIII H, method 1); not more than 0.001%.

Arsenic Dissolve 2.0 g in 23 ml of water, add 5 ml of hydrochloric acid, carry out the limit test for arsenic (Appendix VIII J, method 1); not more than 0.0001%.

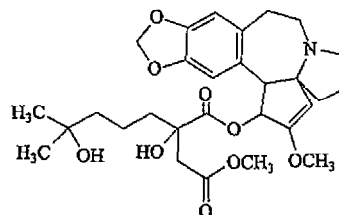
Pyrogens Complies with the test for pyrogens (Appendix XI-D), using 10 ml of a solution of 35 mg per ml in Sodium Chloride Injection, per kg of the rabbit's weight.

Assay Dissolve about 0.2 g, accurately weighed, in 5 ml of water, add a mixture of 1 ml of formaldehyde TS and 20 ml of ethanol (neutralized to phenolphthalein), add several drops of phenolphthalein IS. Titrate with sodium hydroxide (0.1 mol/L) VS. Each ml of sodium hydroxide (0.1 mol/L) VS is equivalent to 10.48 mg of $C_{29}H_{39}NO_9 \cdot HCl \cdot H_2O$.

Category Amino acid.

Storage Preserve in tightly closed containers, protected from light.

Homoharringtonine



$C_{29}H_{39}NO_9$ 545.63

Homoharringtonine is an alkaloid extracted from *Cephalotaxus fortunei* Hook. f. or other plants of the same genus. It contains not less than 95.0% and not more than 103.0% of $C_{29}H_{39}NO_9$, calculated on the dried basis.

Description An almost white or pale yellow, crystalline powder or amorphous friable solid; hygroscopic; darkens on exposure to light.

Freely soluble in chloroform, ethanol or methanol; slightly soluble in ether or water.

Melting range 143-147°C (Appendix VI C).

Identification (1) Dissolve about 0.5 mg in 1 ml of water, add 1 drop of potassium iodobismuthate TS, an orangish-red precipitate is produced.

(2) To about 1 mg, add about 1 mg of chromotropic acid and 5-10 drops of sulfuric acid. Heat in a water bath at 50-60°C for a few minutes, a reddish-violet colour is produced.

(3) Dissolve about 2 mg in 1 ml of dehydrated ethanol, add a few drops each of an ethanol solution saturated with hydroxylamine hydrochloride and an ethanol solution saturated with potassium hydroxide. Heat gently until bubbles are produced, cool, acidify with dilute hydrochloric acid. Add 1 drop of ferric chloride TS, a reddish-brown colour is produced.

(4) The light absorption of the solution obtained in the Assay exhibits maxima at 240 nm and 291 nm (Appendix IV A).

(5) The infrared absorption spectrum (Appendix IV C) is concordant with the reference spectrum of homoharringtonine (Appendix XI).

Clarity of solution A solution of 10 mg in 10 ml of 0.1% tartaric acid solution is clear.

Related substances Dissolve a quantity of the substance being examined in the mobile phase to produce solutions of 1 mg per ml (solution 1) and 10 μ g per ml (solution 2). Carry out the method for high performance liquid chromatography (Appendix V D), using a column packed with octadecylsilane bonded silica gel and a mixture of methanol-0.01 mol/L potassium dihydrogen phosphate solution (40 : 60) as the mobile phase, adjust pH to 2.5 with phosphoric acid. Detection wavelength is 288 nm and the number of theoretical plates of the column is not less than 1500, calculated with reference to peak of homoharringtonine. Inject 20 μ l of solution (2) into the column, adjust the attenuation so that the principal peak height in the chromatogram is 20%-25% of the full scale of the chart. Inject separately 20 μ l of solution (1) and solution (2) into the column and record the chromatogram for twice the retention time of the principal peak. The sum of the areas of all peaks in the chromatogram obtained with solution (1) other than the principal peak is not greater than the area of the principal peak in the chromatogram obtained with solution (2).

Loss on drying When dried to constant weight in vacuum over phosphorus pentoxide, loses not more than 2.0% of its weight (Appendix VIII L).

Assay Dissolve an accurately weighed quantity of the substance being examined in dehydrated ethanol to produce a solution of about 60 µg per ml. Measure the absorbance at 291 nm (Appendix IV A) and calculate the content of $C_{29}H_{39}NO_9$, taking 76 as the value of A (1%, 1 cm).

Category Antineoplastic.

Storage Preserve in tightly closed containers, protected from light, stored in a cool place.

Preparation Homoharringtonine Injection

Homoharringtonine Injection

Homoharringtonine Injection is a sterile solution of Homoharringtonine in Water for Injections. It contains not less than 90.0% and not more than 110.0% of the labelled amount of homoharringtonine ($C_{29}H_{39}NO_9$).

Description A clear, colourless liquid.

Identification (1) To 1 ml, add 1 drop of potassium iodobismuthate TS, an orangish-red precipitate is produced. (2) The light absorption of the solution obtained in the Assay exhibits maxima at 242 nm and 288 nm (Appendix IV A).

pH value 3.5-4.5 (Appendix VI H).

Related substance Take the substance being examined as solution (1) and dilute a quantity of solution (1) with the mobile phase to produce a solution of 30 µg per ml as solution (2). Carry out the Related Substance as described under Homoharringtonine. The sum of the areas of all peaks in the chromatogram obtained with solution (1) other than the principal peak is not greater than the area of the principal peak in the chromatogram obtained with solution (2).

Bacterial endotoxin Carry out the test for bacterial endotoxin (Appendix XI E); less than 25 EU per mg of homoharringtonine.

Other requirements Complies with the general requirements for injections (Appendix I B).

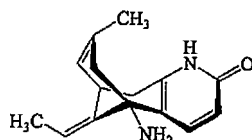
Assay To an accurately measured quantity add 0.01 mol/L hydrochloric acid solution to produce a solution containing 50 µg of homoharringtonine per ml. Measure the absorbance at 288 nm (Appendix IV A) and calculate the content of $C_{29}H_{39}NO_9$, taking 65 as the value of A (1%, 1 cm).

Category As described under Homoharringtonine.

Strength (1) 1 ml : 1 mg (2) 2 ml : 2 mg

Storage Preserve in tightly closed containers, protected from light, stored in a cool place.

Huperzine A



$C_{15}H_{18}N_2O$ 242.32

Huperzine A is (5R,9R,11E)-5-amino-11 ethylidene-5,8,9,10-tetrahydro-7-methyl-5,9 methanocyclooctatetraene [b] pyridine-2 (1H)-one. It contains not less than 97.0% and not more than 102.0% of $C_{15}H_{18}N_2O$, calculated on the dried basis.

Description A white or almost white crystalline powder; odourless; taste, slightly bitter; hygroscopic. Freely soluble in methanol; soluble in ethanol; insoluble in water; slightly soluble in 0.01 mol/L hydrochloric acid solution.

Identification (1) To about 0.2 mg, add 5 drops of ethanol to dissolve huperzine A, add 2 drops of potassium iodobismuthate TS, an orange yellow precipitate is produced. (2) The retention time of principal peak of the substance being examined in the chromatogram obtained in the Assay is identical with that of the principal peak of huperzine A CRS. (3) The infrared absorption spectrum (Appendix IV C) is concordant with the reference spectrum of huperzine A (Appendix XVI).

Clarity of acidic solution Dissolve 5 mg in 5 ml of 0.1 mol/L hydrochloric acid solution, the solution is clear.

Related substances Dissolve a quantity of the substance being examined in 0.01 mol/L hydrochloric acid solution, to produce a solution of 0.1 mg per ml as test solution. Dilute a quantity of the test solution, accurately measured, with 0.01 mol/L hydrochloric acid solution to produce a solution of 2.5 µg per ml as reference solution. Carry out the method as described under Assay. Inject 20 µl of the reference solution into the column. Adjust the attenuation so that the principal peak height in the chromatogram is about 10% of full scale of the chart. Inject 20 µl each of the test solution and the reference solution into the column separately, and record the chromatograms for twice the retention time of the principal peak. The sum of the areas of all peaks other than the principal peak is not greater than the area of the principal peak in the chromatogram obtained with the reference solution.

Loss on drying when dried in vacuum to constant weight at 80°C, loses not more than 4.0% of its weight (Appendix VIII L), using 0.3 g.

Assay Carry out the method for high performance liquid chromatography (Appendix V D), using a column packed with octadecylsilane bonded silica gel and a mixture of acetonitrile-phosphate buffer (dissolve potassium dihydrogen phosphate 2.72 g in 1000 ml of water, adjust to pH 2.5 with phosphoric acid) (14 : 86) as the mobile phase. Detection wavelength is 310 nm and the number of theoretical plates of the column is not less than 2000, calculated with reference to the peak of huperzine A.

procedure Weigh accurately a quantity of the substance being examined, dissolve in 0.01 mol/L hydrochloric acid solution to produce a solution of 40 µg per ml. Inject 20 µl of the resulting solution into the column and record the peak area. Repeat the operation, using the huperzine A CRS instead of the substance being examined. Calculate the content of $C_{15}H_{18}N_2O$ with respect to the peak area obtained in the chromatogram by the external standard method.

Category Cholinesterase inhibitor.

Storage Preserve in tightly closed containers, protected from light.

Preparation (1) Huperzine A Tablets
(2) Huperzine A Injection
(3) Huperzine A Capsules

cool and dry place, protected from light.

Huperzine A Capsules

Huperzine A capsules contain not less than 90.0% and not more than 110.0% of the labelled amount of huperzine A ($C_{15}H_{18}N_2O$).

Description Capsules containing white or almost white granules or powder.

Identification (1) Shake a quantity of the contents, equivalent to about 0.1 mg of huperzine A, with 3 ml anhydrous ethanol, treated with aid of ultrasonicator to dissolve huperzine, centrifuge. To the supernatant add 2 drops of potassium iodobismuthate TS, an orange yellow precipitate is produced.

(2) The retention time of principal peak of the substance being examined in the chromatogram obtained in the Assay is identical with that of the principal peak of huperzine A CRS.

Related substances To a quantity of the contents, add 0.01 mol/L hydrochloric acid solution to produce a solution of about 20 μ g per ml, filter, taking the successive filtrate as test solution. Measure accurately a quantity of the resulting solution, dilute with the same solvent to produce a solution of 0.8 μ g per ml as reference solution. Carry out the method as described under Assay. Inject 50 μ l of the reference solution into the column, adjust the attenuation so that the principal peak height in the chromatogram is about 10% full scale of the chart. Inject 20 μ l each of the test solution and the reference solution into the column separately, and record the chromatogram for twice the retention time of the principal peak. The sum of the areas of all peaks other than the principal peak, the solvent peak, and the ingredient peaks (the relative retention time of ingredient to principal peak is equal or less than 0.2) is not greater than the area of the principal peak in the chromatogram obtained with the reference solution.

Content uniformity Comply with the requirements for content uniformity (Appendix X E). Transfer the content of 1 capsule to a 10 ml volumetric flask, wash the shell with 0.01 mol/L hydrochloric acid solution in divided portions, transfer the washings to the same volumetric flask, add a quantity of 0.01 mol/L hydrochloric acid solution, treated with aid of ultrasonicator to dissolve huperzine A, dilute with 0.01 mol/L hydrochloric acid solution to volume and shake thoroughly, filter, taking the successive filtrate as test solution. Carry out the method as described under Assay and calculate the content of $C_{15}H_{18}N_2O$.

Other requirements Comply with the general requirements for capsules (Appendix I E).

Assay Weigh accurately and powder the contents of 20 capsules. Weigh accurately a quantity of the powder, equivalent to about 100 μ g of huperzine A, into a 20 ml volumetric flask, add a quantity of 0.01 mol/L hydrochloric acid solution, treated with aid of ultrasonicator to dissolve huperzine A, dilute with 0.01 mol/L hydrochloric acid solution to volume, shake thoroughly and filter. Carry out the method for Assay as described under Huperzine A. Inject 50 μ l of successive filtrate into the column and record the peak area. Repeat the operation, using huperzine A CRS instead of the substance being examined. Calculate the content of $C_{15}H_{18}N_2O$ with respect to the peak area obtained in the chromatogram by the external standard method.

Category As described under Huperzine A.

Strength 50 μ g

Storage Preserve in tightly closed containers, stored in a

Huperzine A Injection

Huperzine A injection is a sterile solution of Huperzine A in water for injection. It contains not less than 90.0% and not more than 110.0% of the labelled amount of huperzine A ($C_{15}H_{18}N_2O$).

Description A clear, colourless liquid.

Identification (1) To about 1 ml add 2 drops of potassium iodobismuthate TS, an orange yellow precipitate is produced.

(2) The retention time of principal peak of the substance being examined in the chromatogram obtained in the Assay is identical with that of the principal peak of huperzine A CRS.

pH value 3.5-6.5 (Appendix VI H)

Related substances To a quantity, dilute with 0.01 mol/L hydrochloric acid solution to produce a solution of 0.1 mg per ml as test solution. Measure accurately a quantity of the resulting solution, dilute with the same solvent to produce a solution of 4 μ g per ml as reference solution. Carry out the method as described under Assay. Inject 20 μ l of the reference solution into the column, adjust the attenuation so that the principal peak height in the chromatogram is about 10% of full scale of the chart. Inject 20 μ l each of the test solution and the reference solution into the column separately, and record the chromatogram for twice the retention time of the principal peak. The sum of the secondary peak other than the principal peak is not greater than the area of the principal peak in the chromatogram obtained with the reference solution.

Other requirements Complies with the general requirements for injections (Appendix I B).

Assay Measure accurately a quantity of the injection, add 0.01 mol/L hydrochloric acid solution to produce a solution of 40 μ g per ml as test solution. Carry out the method as described under Huperzine A, calculate the content of $C_{15}H_{18}N_2O$.

Category As described under Huperzine A.

Strength 1 ml : 0.2 mg

Storage Preserve in well closed containers, protected from light.

Huperzine A Tablets

Huperzine A Tablets contain not less than 90.0% and not more than 110.0% of the labelled amount of huperzine A ($C_{15}H_{18}N_2O$).

Description White tablets.

Identification (1) Shake a quantity of the powdered tablets, equivalent to about 0.1 mg of huperzine A, with 3 ml anhydrous ethanol, treated with aid of ultrasonicator to dissolve huperzine, centrifuge. To the supernatant liquid add 2 drops of potassium iodobismuthate TS, an orange yellow precipitate is produced.

(2) The retention time of principal peak of the substance being examined in the chromatogram obtained in the Assay is identical with that of the principal peak of huperzine A CRS.

Related substances To a quantity of powdered tablets add

0.01 mol/L hydrochloric acid solution to produce a solution of about 20 µg per ml, filter, taking the successive filtrate as test solution. Measure accurately a quantity of the resulting solution, dilute with the same solvent to produce a solution of 0.8 µg per ml as reference solution. Carry out the method as described under Assay. Inject 50 µl of the reference solution into the column, adjust the attenuation so that the principal peak height in the chromatogram is about 10% of full scale of the chart. Inject 50 µl each of the test solution and the reference solution into the column separately, and record the chromatogram for twice the retention time of principal peak. The sum of the areas of all peaks other than the principal peak, the solvent peak, and the ingredient peaks (the relative retention time of ingredient to principal peak is equal or less than 0.2) is not greater than the area of the principal peak in the chromatogram obtained with the reference solution.

Content uniformity Comply with the requirements for content uniformity (Appendix X E). Transfer 1 tablet to a 10 ml volumetric flask, add a quantity of 0.01 mol/L hydrochloric acid solution, treated with aid of ultrasonicator to dissolve huperzine A, dilute with 0.01 mol/L hydrochloric acid solution to volume and shake thoroughly filter, taking the successive filtrate as test solution. Carry out the method as described under Assay and calculate the content of $C_{15}H_{18}N_2O$.

Other requirements Comply with the general requirements for tablets (Appendix I A).

Assay Weigh accurately and powder 20 tablets. Weigh accurately a quantity of the powdered tablets, equivalent to about 100 µg of huperzine A, into a 20 ml volumetric flask, add a quantity of 0.01 mol/L hydrochloric acid solution and treated with aid of ultrasonicator to dissolve huperzine A, dilute with 0.01 mol/L hydrochloric acid solution to volume, shake thoroughly and filter. Carry out the method as described under Huperzine A. Inject 50 µl of successive filtrate into the column and record the peak area. Repeat the operation, using the huperzine A CRS instead of the substance being examined. Calculate the content of $C_{15}H_{18}N_2O$ with respect to the peak area obtained in the chromatogram by the external standard method.

Category As described under Huperzine A.

Strength 50 µg

Storage Preserve in tightly closed containers, stored in a cool and dry place and protected from light.

Hyaluronidase

Hyaluronidase is an enzyme, prepared from the mammalian testes and capable of hydrolyzing mucopolysaccharide of the type of hyaluronic acid. It contains not less than 300 Units per mg.

Description A white to slightly yellow powder; odourless. Freely soluble in water; insoluble in ethanol, acetone or ether.

Identification (1) Dissolve a quantity in phosphate BS (Appendix XIII C) to produce a solution of 500-1000 Units per ml. Add 1 ml of the resulting solution to each of two test tubes, boil one of them and cool. To each test tube add 1 ml of potassium hyaluronate stock solution (Appendix XIII C), mix well. Place the tubes in a water bath maintained at 37°C for 30 minutes, remove the tubes from the water bath and add 1 ml of serum solution (Appendix XIII C) to each tube,

mix well. The solution has not been boiled is clearer.

(2) Inject intracutaneously 0.1 ml of sodium chloride injection containing 0.25% of methylene blue into each of two spots on the back of a healthy guinea pig as control. Inject intracutaneously 0.1 ml of the same solution with further addition of 10 Units of hyaluronidase into each of another two spots crossed over to the above control spots on the back of the same guinea pig as the test spots. The distance between any two of the four spots should be more than 3 cm. Kill and skin the guinea pig 5 minutes after the injections were completed. Examine the diffusion of methylene blue on the peeled skin from the back surface, the size of the test spots should be larger than that of the control spots.

Acidity or alkalinity pH 4.5-7.5, using a solution of 3 mg per ml in water (Appendix VI H).

Clarity and colour of solution A solution of 0.1 g in 10 ml of water is clear; any colour produced is not more intense than that of reference solution Y₄ (Appendix IX A, method 1).

Light absorption The light absorbance of a solution of 300 Units per ml in freshly boiled and cooled water is not greater than 0.6 at 280 nm and not greater than 0.42 at 260 nm (Appendix IV A).

Tyrosine Evaporate, at 105°C, 1 ml of a solution containing 5 mg of hyaluronidase in a centrifuge tube to dryness. Add 0.2 ml of 6 mol/L sodium hydroxide solution and heat in saturated steam at 121°C for 3 hours or in a water bath for 4-5 hours. Cool and add 0.3 ml of 3.5 mol/L sulfuric acid; 1.5 ml of water and 1.5 ml of 15% mercuric sulfate solution in 2.5 mol/L sulfuric acid. Heat in a water bath for 10 minutes, cool to room temperature and add 1 ml of 3.5 mol/L sulfuric acid solution and 1 ml of 0.2% sodium nitrite solution, shake. Add water immediately to produce 6 ml, shake and centrifuge. Pipet the supernatant liquid at twenty minutes after the addition of water and measure its absorbance at 540 nm (Appendix IV A). Repeat the operation, replacing the substance being examined by 1 ml of water; use 1.5 ml of a 30 µg per ml solution of tyrosine CRS in 0.2 mol/L sulfuric acid solution in place of 1.5 ml of water. The content of tyrosine is not more than 0.1 µg per Unit;

$$\text{Content of tyrosine } (\mu\text{g/Unit}) = \frac{(T/S) \times 45}{W (\text{mg}) \times U}$$

Where *T* is absorbance of the test solution;
S is absorbance of the reference solution;
W is weight of the substance being examined;
U is Units per mg.

Undue toxicity Inject subcutaneously 0.25 ml of a solution of 10000 Units per ml in sodium chloride injection into each of five healthy mice with body weight between 17-22 g, no necrosis of the skin or death is observed within 48 hours. If one of the mice develops necrosis or dies, repeat the test and the sample complies with the requirements if none of the second group of five mice develops necrosis or dies within 48 hours.

Bacterial endotoxin Carry out the test for bacterial endotoxin (Appendix XII E); less than 0.2 EU per Unit of hyaluronidase.

Assay Carry out the assay of hyaluronidase (Appendix IX C).

Category Proteolytic enzyme.

Storage Preserve in tightly closed containers, stored in a cool and dry place.

Preparation Hyaluronidase for Injection

Hyaluronidase for Injection

Hyaluronidase for Injection is a sterile lyophilized product with the addition of a suitable excipient. It contains not less than 90.0% and not more than 120.0% of the labelled potency.

Description A white or almost white lyophilized mass or powder.

Identification Complies with the tests for Identification as described under Hyaluronidase.

Acidity or alkalinity Dissolve each container in 2 ml of water, pH 6.0-7.5 (Appendix VI H).

Loss on drying When dried in vacuum over phosphorus pentoxide to constant weight, loses not more than 5.0% of its weight (Appendix VIII L).

Bacterial endotoxin Complies with the test for bacterial endotoxin described under Hyaluronidase.

Other requirements Complies with the general requirements for injections (Appendix I B), except the weight variation of contents.

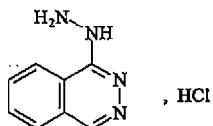
Assay Dissolve the contents of 3 containers separately in cold dilute solution of hydrolyzed gelatin to produce a solution containing 1.5 Units per ml, carry out the assay of hyaluronidase (Appendix XIII C). The potency of the contents of each container complies with the requirement. If the content of one of the three containers fails to pass the test, repeat the assay with another 3 containers. The potency of each container of the second group complies with the requirement.

Category As described under Hyaluronidase.

Strength (1) 150 Units (2) 1500 Units

Storage Preserve in well closed containers, stored in a dry and cool place.

Hydralazine Hydrochloride



$C_8H_8N_4 \cdot HCl$ 196.64

[304-20-1]

Hydralazine Hydrochloride is 1-hydrazinophthalazine monohydrochloride. It contains not less than 98.0% and not more than 102.0% of $C_8H_8N_4 \cdot HCl$, calculated on the dried basis.

Description A white to pale yellow crystalline powder; odourless.

Soluble in water; slightly soluble in ethanol; very slightly soluble in ether.

Identification (1) Dissolve about 10 mg in 2 ml of water in test tube, add 1 ml of ammoniated silver nitrate TS, bubbles and a black turbidity are produced immediately, and a silver mirror is formed on the wall of the tube.

(2) To 10 mg add 5 ml of water, 2 drops of dilute hydrochloric acid and a few drops of ferric chloride TS,

neutralize with sodium hydroxide TS, the colour of the solution becomes red and then changes to blue.

(3) The light absorption of a solution of 10 μ g per ml in water exhibits maxima at 260 nm, 303 nm and 315 nm.

(4) The infrared absorption spectrum (Appendix IV C) is concordant with the reference spectrum of hydralazine hydrochloride (Appendix XVI).

(5) The aqueous solution yields the reactions characteristic of chlorides (Appendix III).

Acidity Dissolve 0.50 g in 25 ml of water, pH 3.5-4.5 (Appendix VI H).

Clarity and colour of solution A solution of 0.20 g in 10 ml of water is clear and colourless; any colour produced is not more intense than that of reference solution Y4 (Appendix IX A, method 1).

Sulfates Carry out the limit test for sulfates (Appendix VIII B), using 0.50 g. Any opalescence produced is not more pronounced than that of a reference solution using 2 ml of potassium sulfate standard solution (0.04%).

Free hydrazine To 0.10 g add 5 ml of water and 0.1 ml of a solution of salicylaldehyde in ethanol (1→20); no turbidity is produced within 1 minute.

Water insoluble substances To 2.0 g add 100 ml of water, shake for 30 minutes to dissolve hydralazine hydrochloride. Filter with a No. 5 sintered glass filtering crucible previously dried to constant weight. Wash the residue with 10 ml each of water for three times, dry it to constant weight at 105°C; the residue does not exceed 10 mg (0.5%).

Loss on drying When dried to constant weight at 105°C, loses not more than 2.0% of its weight (Appendix VIII L).

Residue on ignition Not more than 0.1% (Appendix VIII N), using 1.0 g.

Heavy metals Carry out the limit test for heavy metals (Appendix VIII H, method 2), using the residue obtained in the test for Residue on ignition; not more than 0.002%.

Assay Dissolve about 0.2 g, accurately weighed, in water in a 100 ml volumetric flask, dilute to volume and mix well. Measure accurately 25 ml of the resulting solution to an iodine flask, add 25 ml of bromine (0.05 mol/L) VS, accurately measured, and 5 ml of hydrochloric acid, stopper immediately and mix well, allow to stand in the dark place for 15 minutes. Add 7 ml of potassium iodide TS, stopper the flask immediately, mix well. Titrate with sodium thiosulfate (0.1 mol/L) VS, add 2 ml of starch TS as the end point and continue the titration until the blue colour disappears. Perform a blank determination and make any necessary correction. Each ml of bromine (0.05 mol/L) VS is equivalent to 4.916 mg of $C_8H_8N_4 \cdot HCl$.

Category Antihypertensive.

Storage Preserve in tightly closed containers, stored in a dry place and protected from light.

Preparation Hydralazine Hydrochloride Tablets

Hydralazine Hydrochloride Tablets

Hydralazine Hydrochloride Tablets contain not less than 90.0% and not more than 110.0% of the labelled amount of hydralazine hydrochloride ($C_8H_8N_4 \cdot HCl$).

Description White or almost white tablets, or sugar coated tablets with white or almost white core.

Identification Shake a quantity of the powdered tablets equivalent to about 30 mg of hydralazine hydrochloride with 10 ml of water, filter. The filtrate complies with test (1) and (2) for Identification described under Hydralazine Hydrochloride.

Dissolution Carry out dissolution test (Appendix X C, method 1), using 900 ml of hydrochloric acid solution (9→1000) as the dissolution medium, adjust the rotational speed of the basket to 100 rpm. Withdraw 10 ml of the solution at 30 minutes (60 minutes for sugar coated tablets) and filter. Dilute a quantity of the successive filtrate, accurately measured, to produce a solution of 10-20 µg per ml. Dissolve hydralazine hydrochloride CRS previously dried to constant weight at 105°C in hydrochloric acid solution (9→1000) to produce a solution of 10-20 µg per ml. Measure the absorbances of the resulting solutions at 260 nm (Appendix IV A). Calculate the dissolution of $C_8H_8N_4 \cdot HCl$ from each tablet. Not less than 65% of the labelled amount is dissolved.

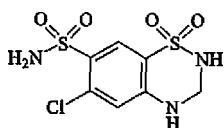
Other requirements Comply with the general requirements for tablets (Appendix I A).

Assay Weigh accurately and powder (Sugar tablets with coating removed) 25 tablets (10 mg) or 10 tablets (25 mg or 50 mg). Triturate an accurately weighed quantity of the powder equivalent to about 0.1 g of hydralazine hydrochloride in a mortar with a small quantity of water and transfer to a 50 ml volumetric flask, wash the mortar with water in portions, add washings to the volumetric flask, dilute with water to volume and mix well. Filter with dry filter paper. Measure accurately 25 ml of the successive filtrate, proceed as described under Hydralazine Hydrochloride beginning at the words "to an iodine flask, add 25.0 ml of bromine (0.05 mol/L) VS...". Each ml of bromine (0.05 mol/L) VS is equivalent to 4.916 mg of $C_8H_8N_4 \cdot HCl$.

Category, Storage As described under Hydralazine Hydrochloride.

Strength (1) 10 mg (2) 25 mg (3) 50 mg

Hydrochlorothiazide



$C_7H_8ClN_3O_4S_2$ 297.74

[58-93-5]

Hydrochlorothiazide is 6-chloro-3,4-dihydro-2H-1,2,4-benzothiazine-7-sulfonamide-1,1-dioxide. It contains not less than 98.5% and not more than 101.5% of $C_7H_8ClN_3O_4S_2$, calculated on the dried basis.

Description A white, crystalline powder; odourless; taste, slightly bitter. Soluble in acetone; slightly soluble in ethanol; insoluble in water, chloroform or ether; soluble in sodium hydroxides solution.

Melting range 265-273°C, with decomposition (Appendix VI C).

Identification (1) Boil about 20 mg with 3 ml of sodium hydroxide TS for 5 minutes and cool. Acidify one half of the resulting solution with hydrochloric acid, add 0.25 ml of 4% sodium nitrite solution, mix well, add 0.2 ml of 10% ammonium sulphamate solution and again mix well. Add 1 ml of freshly prepared 0.5% chromotropic acid solution and

5 ml of sodium acetate TS, a red colour is produced. To the other half of the resulting solution add 5 ml of chromotropic acid TS, warm on a water bath, a bluish-violet colour is produced.

(2) Mix about 50 mg with 0.2 g of sodium carbonate and heat on a flame until it carbonizes completely. Allow to cool, add 5 ml of water, boil, cool and filter. The filtrate yields the reactions characteristic of chlorides (Appendix III).

Chlorides To 0.50 g add 20 ml of water, shake and filter. Carry out the limit test for chlorides (Appendix VIII A), using 10 ml of the filtrate. Any opalescence produced is not more pronounced than that of a reference using 5.0 ml of sodium chloride standard solution (0.02%).

Primary aromatic amine Dissolve 80 mg in acetone in a 100 ml volumetric flask, add acetone to volume, mix well. To 1 ml, accurately measured, of this solution add 9 ml of 1 mol/L hydrochloric acid solution and 0.1 ml of 4% sodium nitrite solution, mix well and allow to stand for 1 minute. Add 0.2 ml of 10% ammonium sulphamate solution, mix well and allow to stand for 3 minutes. Add 0.8 ml of 2% N-(1-naphthyl)-ethylenediamine dihydrochloride solution in dilute ethanol, mix well and allow to stand for 2 minutes. Measure immediately the absorbance of the resulting solution at 518 nm (Appendix IV A); not greater than 0.10.

Loss on drying When dried to constant weight at 105°C, loses not more than 0.5% of its weight (Appendix VIII L).

Residue on ignition Not more than 0.15% (Appendix VIII N).

Heavy metals Dissolve 1.0 g in 7 ml of sodium hydroxide TS, add water to produce 25 ml, carry out the limit test for heavy metals (Appendix VIII H, method 3); not more than 0.0015%.

Assay Weigh accurately about 0.12 g, carry out the Assay described under Bendroflumethiazide. Each ml of sodium methoxide (0.1 mol/L) VS is equivalent to 14.89 mg of $C_7H_8ClN_3O_4S_2$.

Category Diuretic and antihypertensive.

Storage Preserve in tightly closed containers, protected from light.

Preparation Hydrochlorothiazide Tablets

Hydrochlorothiazide Tablets

Hydrochlorothiazide Tablets contain not less than 93.0% and not more than 107.0% of the labelled amount of hydrochlorothiazide ($C_7H_8ClN_3O_4S_2$).

Description White tablets.

Identification To a quantity of the powdered tablets equivalent to about 50 mg of hydrochlorothiazide add 10 ml of sodium hydroxide TS, shake to dissolve hydrochlorothiazide and filter, comply with test (1) for Identification described under Hydrochlorothiazide using 3 ml beginning at the words "boil for 5 minutes...".

Dissolution Comply with the dissolution test (Appendix X C, method 1), using 1000 ml of hydrochloric acid solution (to 24 ml of dilute hydrochloric acid add water to produce 1000 ml) as the dissolution medium, adjust the rotational speed of the basket to 150 rpm. Withdraw 10 ml of the solution after exactly 30 minutes and filter. Dilute a quantity of the successive filtrate with the same dissolution medium to produce a solution of 5-10 µg per ml. Measure the absorbance of the resulting solution at 272 nm (Appendix IV A). Calculate the dissolution of $C_7H_8ClN_3O_4S_2$ from each

tablet, taking 640 as the value of A (1%, 1 cm): not less than 60% of the labelled amount is dissolved.

Other requirements Comply with the general requirements for tablets (Appendix I A).

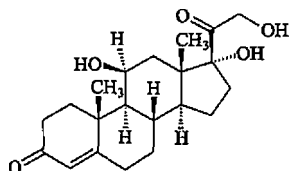
Assay Weigh accurately and powder 20 tablets. To a quantity of the powder equivalent to about 20 mg of hydrochlorothiazide, accurately weighed, into a 100 ml volumetric flask add a quantity of hydrochloric acid solution (add water to 24 ml of dilute hydrochloric acid to produce 1000 ml) and shake in a warm water bath to dissolve, allow it to cool, dilute with the same solvent to volume, shake well and filter. Measure accurately 5 ml of the successive filtrate to a 100 ml volumetric flask, dilute to volume with the same solvent and mix well. Measure the absorbance at 272 nm (Appendix IV A). Calculate the content of $C_{17}H_{25}ClN_2O_4S_2$, taking 640 as the value of A (1%, 1 cm).

Category As described under Hydrochlorothiazide.

Strength (1) 10 mg (2) 25 mg

Storage Preserve in tightly closed containers, protected from light.

Hydrocortisone



$C_{21}H_{30}O_5$ 362.47

[50-23-7]

Hydrocortisone is $11\beta,17\alpha,21$ -trihydroxypregn-4-ene-3,20-dione. It contains not less than 97.0% and not more than 103.0% of $C_{21}H_{30}O_5$, calculated on the dried basis.

Description A white or almost white crystalline powder; odourless; tasteless at first but subsequently a bitter taste persists; deteriorates gradually on exposure to light. Sparingly soluble in ethanol or acetone; slightly soluble in chloroform; practically insoluble in ether; insoluble in water.

Specific optical rotation $+162^\circ$ to $+169^\circ$, in a solution of 10 mg per ml in dehydrated ethanol (Appendix VI E).

Specific absorbance Measure the absorbance of a solution of 10 μ g per ml in dehydrated ethanol at 242 nm (Appendix IV A), the value of A (1%, 1 cm) is 422-448.

Identification (1) Dissolve about 0.1 mg in 1 ml of ethanol, add 8 ml of freshly prepared phenylhydrazine sulfate TS, heat at 70°C for 15 minutes, a yellow colour is produced.

(2) Dissolve about 2 mg in 2 ml of sulfuric acid, allow the solution to stand for 5 minutes; a brownish-yellow or red colour is produced with green fluorescence. Pour the solution into 10 ml of water, the colour changes to yellow or orangish-yellow with a faint green fluorescence and a small amount of flocculent precipitate.

(3) The infrared absorption spectrum (Appendix IV C) is concordant with the reference spectrum of hydrocortisone (Appendix XVI).

Related substances Carry out the method for high performance liquid chromatography (Appendix V D), using a column packed with octadecylsilane bonded silica gel and a mixture of tetrahydrofuran-water (19 : 81) as the mobile phase.

Detection wavelength is 254 nm. The resolution factor between the peaks of prednisolone and hydrocortisone should be greater than 2.4.

Procedure Dissolve about 12.5 mg of the substance being examined, weighed accurately, in 5 ml of tetrahydrofuran to a 25 ml volumetric flask and dilute with water to volume, mix well as solution (1). Dissolve about 12.5 mg of prednisolone CRS, weighed accurately, in 10 ml of tetrahydrofuran in a 50 ml volumetric flask and dilute with water to volume, mix well as solution (2). Measure accurately 1 ml each of solution (1) and (2) into a 100 ml volumetric flask, dilute with mobile phase to volume, mix well as solution (3). Inject 20 μ l of solution (3) into the column, adjust the attenuation so that the peak height of hydrocortisone in the chromatogram is about 30% of full scale of the chart and the resolution factor between the peaks of prednisolone and hydrocortisone should be greater than 2.4. Inject separately accurately 20 μ l each of the solution (1) and (3) into the column and record the chromatogram for 3.5 times the retention time of the peak of hydrocortisone. If there is any other peak except the peak of hydrocortisone in the chromatogram obtained with solution (1), its area corresponding to the peak of prednisolone in the chromatogram obtained with solution (3) is not greater than 0.5%, calculated by the external standard method. The area of any other simple impurity peak is not larger than 1/2 of the area of the peak of hydrocortisone in the chromatogram obtained with solution (3), the sum of the areas of any impurity peaks is not greater than 1.5 times of the area of the peak of hydrocortisone in the chromatogram obtained with solution (3).

Loss on drying When dried to constant weight at 105°C , loses not more than 0.5% of its weight (Appendix VIII L).

Assay Carry out the method for high performance liquid chromatography (Appendix V D), using a column packed with octadecylsilane bonded silica gel and a mixture of methanol-water (70 : 30) as the mobile phase. Detection wavelength is 240 nm and the number of theoretical plates of the column is not less than 2000, calculated with reference to the peak of hydrocortisone. The resolution factor between the peaks of hydrocortisone and internal standard complies with related requirements.

Internal Standard Solution Dissolve norethisterone in methanol to produce a solution of 0.40 mg per ml.

Procedure Dissolve an accurately weighed quantity of hydrocortisone CRS in methanol to produce a solution of about 0.50 mg per ml, as the reference solution. Measure accurately 5 ml each of reference solution and internal standard solution to a 25 ml volumetric flask, dilute with methanol to volume, mix well. Inject 5-10 μ l of the resulting solution into the column and record the chromatogram. Repeat the operation using a quantity of the substance being examined instead of hydrocortisone CRS, accurately weighed. Calculate the content of $C_{21}H_{30}O_5$ with respect to the peak area obtained in the chromatogram by the external standard method.

Category Corticosteroid.

Storage Preserve in tightly closed containers, protected from light.

Preparation (1) Hydrocortisone Cream
(2) Hydrocortisone Injection
(3) Hydrocortisone Tablets

Hydrocortisone Cream

Hydrocortisone Ointment contains not less than

90.0% and not more than 110.0% of the labelled amount of hydrocortisone ($C_{21}H_{30}O_5$).

Description Creamy white cream.

Identification To about 5 g of the ointment in a beaker, add 30 ml of dehydrated ethanol and warm on a water bath by heating, allow to cool in an ice bath, filter and evaporate the filtrate to dryness. The residue complies with following tests.

(1) To a quantity of the residue, add 1 ml of ethanol, and 8 ml of phenylhydrazine sulfate, freshly prepared; then heat for 15 minutes at 70°C, a yellow colour is produced.

(2) To a quantity of the residue, add 2 ml of sulfuric acid and mix well, allow to stand for 5 minutes, and a yellow or brownish-yellow colour with green fluorescence is produced.

Other requirements Complies with the general requirements for cream (Appendix I F).

Assay *Reference preparation* Dissolve 20 mg of hydrocortisone CRS, accurately weighed, in a 100 ml volumetric flask in dehydrated ethanol, and dilute to volume with the same solvent, mix well.

Test preparation To a quantity of the cream, equivalent to 20 mg of hydrocortisone, accurately weighed, in a beaker, add 30 ml of dehydrated ethanol, Heat on a water bath and effect the dissolution of hydrocortisone acetate, cool in an ice bath and filter into a 100 ml volumetric flask. Repeat the extraction for 3 times, combine all filtrates, dilute with dehydrated ethanol to volume and mix well.

Procedure To 1 ml each of the two preparations, accurately measured, in separate stoppered test tubes, add accurately 9 ml of dehydrated ethanol and 1 ml of triphenyltetrazolium chloride TS and mix well; then add accurately 1 ml of tetramethylammonium hydroxide TS and mix well. Allow to stand in the dark place at 25°C for 40-45 minutes and measure the absorbances at 485 nm (Appendix IV A). Calculate the content of $C_{21}H_{30}O_5$.

Category As described under Hydrocortisone.

Strength (1) 10 g : 25 mg (2) 10 g : 50 mg
(3) 10 g : 100 mg

Storage Preserve in tightly closed containers, protected from light.

Hydrocortisone Injection

Hydrocortisone Injection is a sterile solution of Hydrocortisone in dilute ethanol. It contains not less than 93.0% and not more than 107.0% of the labelled amount of hydrocortisone ($C_{21}H_{30}O_5$).

Description A clear, colourless liquid.

Identification Evaporate 1 ml to dryness on a water bath, the residue complies with tests (1) and (2) for Identification described under Hydrocortisone.

Ethanol Not less than 47% and not more than 55% (Appendix VII E).

Bacterial endotoxin Carry out the test for bacterial endotoxin (Appendix XI E); less than 1 EU per ml.

Other requirements Complies with the general requirements for injections (Appendix I B).

Assay To 5 ml of the injection, accurately measured, in a 100 ml volumetric flask add dehydrated ethanol to volume and mix well. Transfer 5 ml of the solution, accurately measured, into another 100 ml volumetric flask, add

dehydrated ethanol to volume and mix well. Measure the absorbance of the resulting solution at 242 nm (Appendix VIII A). Calculate the content of $C_{21}H_{30}O_5$, taking 435 as the value of A (1%, 1 cm).

Category Corticosteroid.

Strength (1) 2 ml : 10 mg (2) 5 ml : 25 mg
(3) 10 ml : 50 mg (4) 20 ml : 100 mg

Storage Preserve in tightly closed containers, protected from light.

Hydrocortisone Tablets

Hydrocortisone Tablets contain not less than 90.0% and not more than 110.0% of the labelled amount of hydrocortisone ($C_{21}H_{30}O_5$).

Description White tablets.

Identification Triturate a quantity of powdered tablets equivalent to 5 mg of hydrocortisone with 5 ml of dehydrated ethanol and filter. Evaporate the filtrate to dryness on a water bath, the residue complies with tests (1) and (2) for Identification described under Hydrocortisone.

Dissolution Carry out the dissolution test (Appendix X C, method 2), using 900 ml of water as the dissolution medium, adjust the rotation speed of the paddle to 50 rpm. Withdraw proper quantities of the solution at 30 minutes and filter. Dilute 5 ml of the successive filtrate, accurately measured, with water to 10 ml and mix well. Measure the absorbance at 248 nm (Appendix IV A). Calculate the dissolution of $C_{21}H_{30}O_5$ from each tablet, taking 449.3 as the value of A (1%, 1 cm). Not less than 70% of the labelled amount is dissolved.

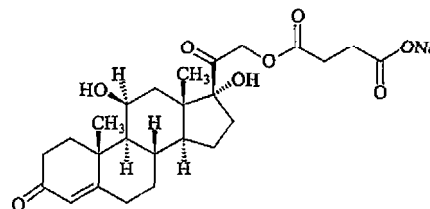
Other requirements Comply with the general requirements for tablets (Appendix I A).

Assay Weigh accurately and powder 20 tablets. Transfer an accurately weighed amount of the powder equivalent to 20 mg of hydrocortisone into a 100 ml volumetric flask. Add 75 ml of dehydrated ethanol, shake for 1 hour, add dehydrated ethanol to volume and mix well. Filter, transfer 5 ml of the successive filtrate, accurately measured, into another 100 ml volumetric flask, add dehydrated ethanol to volume and mix well. Measure the absorbance of the resulting solution at 242 nm (Appendix IV A). Calculate the content of $C_{21}H_{30}O_5$, taking 435 as the value of A (1%, 1 cm).

Strength (1) 10 mg (2) 20 mg

Storage Preserve in tightly closed containers, protected from light.

Hydrocortisone Sodium Succinate



$C_{25}H_{32}NaO_8$ 484.52

Hydrocortisone sodium succinate is monosodium 11 β ,17,21-trihydroxypreg-4-ene-3,20-dione-21-succinate. It contains not less than 97.0% and not more than 102.0% of $C_{25}H_{33}NaO_8$, calculated on the dried basis.

Description A white or almost white powder; odourless; hygroscopic. Freely soluble in water, sparingly soluble in ethanol, practically insoluble in chloroform.

Specific optical rotation $+135^\circ$ to $+145^\circ$, in a solution of 10 mg per ml in ethanol (Appendix VI E).

Identification (1) To a quantity of 1% solution, add equal volume of alkaline cupric tartrate TS, a red precipitate is produced immediately by heating.

(2) The infrared absorption spectrum (Appendix IV C) is concordant with the reference spectrum of hydrocortisone sodium succinate (Appendix XVI).

(3) The aqueous solution yields the reactions characteristic of sodium salts (Appendix III).

Loss on drying When dried at 105°C for 3 hours, loses not more than 2.0% of its weight (Appendix VIII L).

Sodium content Dissolve about 1.0 g, weigh accurately, in 75 ml of glacial acetic acid by gentle heating, add 20 ml of dioxane, then add 1 drop of crystal violet IS, titrate with perchloric acid (0.1 mol/L) VS until the colour changes to bluish violet. Each ml of perchloric acid (0.1 mol/L) VS is equivalent to 2.299 mg of Na. It contains not less than 4.60% and not more than 4.84% of Na, calculated on the dried basis.

Assay Carry out the method for high performance liquid chromatography (Appendix V D), using a column packed with octadecylsilane bonded silica gel and a mixture of methanol-phosphate BS freshly prepared (8 mmol/L potassium dihydrogen phosphate solution, adjust pH value to 5.0 ± 0.1 with 8 mmol/L dipotassium hydrogen phosphate solution) (43 : 57) as the mobile phase. Detection wavelength is 242 nm and the number of the theoretical plates of the column is not less than 3000, calculated with reference to the peak of hydrocortisone sodium succinate. The resolution factor between the peaks of hydrocortisone sodium succinate and the neighbour impurities complies with the related requirements.

Procedure Dissolve a quantity of hydrocortisone sodium succinate in mobile phase to produce a solution of about 40 μg per ml, mix well. Inject 20 μl into the column. Repeat the operation, using hydrocortisone sodium succinate CRS instead of the substance being examined, calculated the content of $C_{25}H_{33}NaO_8$ with respect to the peak area obtained in the chromatogram by the external standard method.

Category Corticosteroid.

Storage Preserve in tightly closed containers and protected from light.

Preparation Hydrocortisone Sodium Succinate for Injection

Hydrocortisone Sodium Succinate for Injection

Hydrocortisone Sodium Succinate for Injection is a sterile lyophilized mixture of hydrocortisone sodium succinate and phosphate buffer. It contains not less than 90.0% and not more than 110.0% of

the labelled amount of hydrocortisone ($C_{21}H_{30}O_5$).

Description A white or almost white lyophilized powder.

Identification (1) To a quantity of 1% solution, add equal volume of alkaline cupric tartrate solution, a red precipitate is produced immediately by heating.

(2) The retention time of principal peak of hydrocortisone sodium succinate in the substance being examined in the chromatogram obtained in the Assay is identical with that of the principal peaks of hydrocortisone sodium succinate CRS in the chromatogram of the reference solution correspondingly.

(3) The aqueous solution yields the reactions characteristic of sodium salts (Appendix III).

Alkalinity A solution of 50 mg per ml in water, pH 7.8-8.0 (Appendix VI H).

Colour of solution Dissolve 0.50 g in 10 ml of water, any colour produced is not more intense than that of reference solution Y₄ (Appendix IX A, method 1).

Free hydrocortisone Calculate the content of free hydrocortisone the amount of free hydrocortisone is not more than 6.7% of labelled amount of hydrocortisone ($C_{21}H_{30}O_5$).

Loss on drying When dried at 105°C for 3 hours, loses not more than 2.0% of its weight (Appendix VIII L).

Pyrogens Complies with the test for pyrogens (Appendix XI D), using 1 ml of a solution of 50 mg of hydrocortisone per 3 ml in Water for Injections per kg of rabbit's weight.

Undue toxicity Complies with the test for undue toxicity (Appendix XI D), using a solution of 10 mg of hydrocortisone per ml in Water for Injections, injected intravenously.

Other requirements Complies with the general requirements for injections (Appendix I B).

Assay Carry out the method for high performance liquid chromatography (Appendix V D), using a column packed with octadecylsilane bonded silica gel and a mixture of methanol-phosphate BS freshly prepared (8 mmol/L potassium dihydrogen phosphate, adjust pH value to 5.0 ± 0.1 with 8 mmol/L dipotassium hydrogen phosphate) (43 : 57) as the mobile phase. Detection wavelength is 242 nm and the number of the theoretical plates of the column is not less than 3000, calculated with reference to the peak of hydrocortisone sodium succinate. The resolution factor between the peaks of hydrocortisone sodium succinate and hydrocortisone complies with the related requirements.

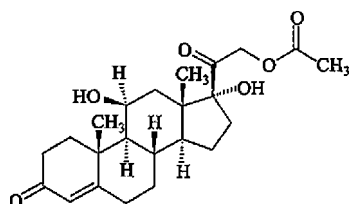
Procedure Dissolve a quantity of mixed powder obtained in the test for weight variation of contents, weighed accurately, in the mobile phase to produce a solution of about 0.04 mg of hydrocortisone sodium succinate per ml, mix well. Inject 20 μl into the column and record the chromatogram. The substances are eluted in the following order: hydrocortisone sodium 17-succinate, hydrocortisone sodium 21-succinate and free hydrocortisone. Dissolve separately a quantity of hydrocortisone sodium succinate CRS and hydrocortisone CRS, weighed accurately, in the mobile phase to produce two solutions of 0.4 mg per ml and 0.1 mg per ml correspondingly. Measured accurately 5 ml each of above two solutions into the same 50 ml volumetric flask, dilute with the mobile phase to the volume, mix well. Measure in the same manner, calculated the content of hydrocortisone ($C_{21}H_{30}O_5$) with respect to the summary areas of the peaks of hydrocortisone 17-succinate and hydrocortisone 21-succinate obtained in the chromatogram by being multiplied by 0.748.

Category As described under Hydrocortisone Sodium.

Strength Calculated as $C_{21}H_{30}O_5$
(1) 0.05 g (2) 0.1 g

Storage Preserve in tightly closed containers and protected from light.

Hydrocortisone Acetate



$C_{23}H_{32}O_6$ 404.50

[50-03-3]

Hydrocortisone Acetate is 11β , 17α , 21-trihydroxypregn-4-ene-3, 20-dione-21-acetate. It contains not less than 97.0% and not more than 102.0% of $C_{23}H_{32}O_6$, calculated on the dried basis.

Description A white or almost white crystalline powder; odourless. Slightly soluble in ethanol or chloroform; insoluble in water.

Melting range 216-224°C, with decomposition (Appendix VI C).

Specific optical rotation $+158^\circ$ to $+165^\circ$, in a solution of 10 mg per ml in dioxane (Appendix VI E).

Specific absorbance Measure the absorbance of a solution of 10 μ g per ml in dehydrated ethanol at 241 nm (Appendix IV A), the value of A (1%, 1 cm) is 383-407.

Identification (1) Dissolve about 0.1 mg in 1 ml of ethanol, add 8 ml of freshly prepared phenylhydrazine sulfate TS, heat at 70°C for 15 minutes; a yellow colour is produced.

(2) Dissolve about 2 mg in 2 ml of sulfuric acid, a yellow or brownish-yellow colour is produced with green fluorescence.

(3) The retention time of principal peak of the substance being examined is identical with that of principal peak of the reference solution in the chromatogram obtained in Assay.

(4) The infrared absorption spectrum (Appendix IV C) is concordant with the reference spectrum of hydrocortisone acetate (Appendix XVI).

Related substances Carry out the method as described under Assay. Dissolve about 17 mg of the substance being examined, weighed accurately, in 20 ml of acetonitrile in a 50 ml volumetric flask and sonicate to make hydrocortisone acetate dissolved, dilute with water to volume and mix well as solution (1). Measure accurately 1 ml of solution (1) into a 100 ml volumetric flask, dilute with mobile phase to volume, mix well as solution (2). Inject 20 μ l of solution (2) into the column, adjust the attenuation so that the peak height of hydrocortisone acetate in the chromatogram is about 40% of full scale of the chart. Inject separately accurately 20 μ l each of the solution (1) and (2) into the column and record the chromatogram for 3 times the retention time of the principal peak. The area of any peak other than the principal peak is not greater than the area of the principal peak in the chromatogram obtained with solution (2) and not more than one such peak has an area greater than half the area of the principal peak in the chromatogram obtained with solution (2). The sum of the areas of all the peaks other than the principal peak is not greater than twice the area of principal peak

in the chromatogram obtained with solution (2).

Loss on drying When dried to constant weight at 105°C, loses not more than 0.5% of its weight (Appendix VII L).

Assay Carry out the method for high performance liquid chromatography (Appendix V D), using a column packed with octadecylsilane bonded silica gel and mixture of acetonitrile-water (38 : 62) as the mobile phase. Detection Wavelength is 254 nm. Dissolve proper quantities of hydrocortisone acetate CRS and cortisone acetate CRS, weighed accurately, in mobile phase to produce solution of each 3.5 μ g per ml. The number of the theoretical plates of the column is generally 6000, calculated with reference to the peak of hydrocortisone acetate. The resolution factor between the peaks of hydrocortisone acetate and cortisone acetate is at least 5.5.

Procedure Dissolve a quantity of the substance being examined, weighed accurately, in methanol to produce a solution of 0.22 mg per ml. Measure accurately 2 ml of the solution into a 25 ml volumetric flask, dilute with mobile phase to volume, mix well as the test solution. Inject 20 μ l of the test solution into the column and record the chromatogram. Dissolve about 11 mg of hydrocortisone acetate CRS, weighed accurately, in proper quantities of methanol in a 50 ml volumetric flask with the aid of ultrasonic bath, then cool to room temperature, dilute with methanol to volume, mix well. Measure accurately 2 ml of the solution into a 25 ml volumetric flask and dilute with mobile phase to volume, mix well, and repeat the operation using the resulting solution, calculate the content of $C_{23}H_{32}O_6$ with respect to the peak area obtained in the chromatogram by the external standard method.

Category Corticosteroid.

Storage Preserve in tightly closed containers, protected from light.

Preparation (1) Hydrocortisone Acetate Cream
(2) Hydrocortisone Acetate Eye Drops
(3) Hydrocortisone Acetate Eye Ointment
(4) Hydrocortisone Acetate Injection
(5) Hydrocortisone Acetate Tablets

Hydrocortisone Acetate Cream

Hydrocortisone Acetate Cream contains not less than 0.90% and not more than 1.10% of hydrocortisone acetate ($C_{23}H_{32}O_6$).

Description Creamy white cream.

Identification To about 6 g of the cream in a beaker add 30 ml of dehydrated ethanol and melt by heating on a water bath, cool in an ice bath, filter and evaporate the filtrate to dryness. The residue complies with tests (1), (2) and (3) for Identification described under Hydrocortisone Acetate.

Other requirements Complies with the general requirements for cream (Appendix I F).

Assay To a quantity of the substance being examined, equivalent to about 5 mg of hydrocortisone acetate, weighed accurately, add accurately 50 ml of methanol, stir for 60 \pm 10 seconds at 9500 rpm by homogenizer, filter with two pieces of paper, discard 5 ml of initial filtrate and measure accurately 5 ml of the successive filtrate into a 25 ml volumetric flask, dilute with methanol to volume, mix well as the test solution (1). Carry out the Assay described under Hydrocortisone Acetate, beginning at the words "Inject 20 μ l of the test solution into the column and record

the chromatogram", calculate the content of $C_{23}H_{32}O_6$ with respect to the peak area obtained in the chromatogram by the external standard method.

Category As described under Hydrocortisone Acetate.

Strength 10 g : 10 mg

Storage Preserve in tightly closed containers, stored in a cool and dark place.

Hydrocortisone Acetate Eye Drops

Hydrocortisone Acetate Eye Drops contain not less than 90.0% and not more than 110.0% of the labelled amount of hydrocortisone acetate ($C_{23}H_{32}O_6$).

Description A suspension of minute granules which deposit on standing, a homogeneous creamy white suspension is obtained on shaking.

Identification Comply with tests (1), (2) and (3) for Identification described under Hydrocortisone Acetate using 12 ml of the substance being examined.

pH value 4.5-7.0 (Appendix VI H).

Other requirements Comply with the general requirements for eye preparations (Appendix I G).

Assay Take several pieces of the substance being examined, and take a sufficient shake, then collect in a stoppered tube, shake again. Measure accurately 2 ml with inner capacity pipet into a 50 ml volumetric flask and add a quantity of methanol, shake to make hydrocortisone acetate dissolved, then dilute with methanol to volume and mix well. Measure accurately 2 ml of the solution into a 25 ml volumetric flask and dilute with mobile phase to volume, mix well as the test solution. Carry out the Assay described under Hydrocortisone Acetate, beginning at the words "Inject 20 μ l of the test solution into the column and record the chromatogram", calculate the content of $C_{23}H_{32}O_6$ with respect to the peak area obtained in the chromatogram by the external standard method.

Category As described under Hydrocortisone Acetate.

Strength (1) 3 ml : 15 mg (2) 5 ml : 25 mg

Storage Preserve in tightly closed containers, protected from light.

Hydrocortisone Acetate Eye Ointment

Hydrocortisone Acetate Eye Ointment contains not less than 90.0% and not more than 110.0% of the labelled amount of hydrocortisone acetate ($C_{23}H_{32}O_6$).

Description A yellow ointment.

Identification Place about 12 g of the ointment in a stoppered conical flask, add 20 ml of petroleum ether, shake thoroughly until the ointment base is dissolved. Filter, wash the residue with several portions of petroleum ether, then add 10 ml of dehydrated ethanol, heat on a water bath to dissolve the hydrocortisone acetate by stirring. Cool in an ice bath and filter again, evaporate the filtrate on a water bath to dryness. The residue complies with tests (1) and (2) for Identification described under Hydrocortisone Acetate.

Other requirements Complies with the general requirements for eye preparations (Appendix I G).

Assay Reference preparation Dissolve 20 mg of hydrocortisone acetate CRS, accurately weighed, in a 100 ml volumetric flask in dehydrated ethanol with shaking, dilute to volume and mix well.

Test preparation To a quantity of the ointment equivalent to 20 mg of hydrocortisone acetate, accurately weighed, in a beaker add 30 ml of dehydrated ethanol. Heat on a water bath to dissolve hydrocortisone acetate, cool in an ice water and filter into a 100 ml volumetric flask. Repeat the extraction for 3 times, combine all the filtrates in the same volumetric flask, dilute with dehydrated ethanol to volume and mix well.

Procedure Transfer 1 ml each of the two preparations, accurately measured, into separate stoppered test tubes, to each tube add exactly 9 ml of dehydrated ethanol and 1 ml of triphenyltetrazolium chloride TS, mix well, add exactly 1 ml of tetramethylammonium hydroxide TS and mix well. Allow to stand in the dark at 25°C for 40-45 minutes and measure the absorbances of the resulting solutions at 485 nm (Appendix IV A). Calculate the content of $C_{23}H_{32}O_6$.

Category As described under Hydrocortisone Acetate.

Strength 0.5%

Storage Preserve in tightly closed containers, stored in a cool place.

Hydrocortisone Acetate Injection

Hydrocortisone Acetate Injection is a sterile suspension of Hydrocortisone Acetate. It contains not less than 90.0% and not more than 110.0% of the labelled amount of hydrocortisone acetate ($C_{23}H_{32}O_6$).

Description A suspension of minute granules which deposit on standing, a homogeneous creamy white suspension is obtained on shaking.

Identification Shake 3 ml of the injection with two 10 ml portions of chloroform, and filter, evaporate the combined filtrate to dryness on a water bath. The residue complies with tests (1), (2) and (3) for Identification described under Hydrocortisone Acetate.

pH value 5.0-7.0 (Appendix VI H).

Other requirements Complies with the general requirements for injections (Appendix I B).

Assay Take several pieces of the substance being examined, and take a sufficient shake, then collect in a cube with plug, shake again. Measure accurately 2 ml with inner capacity pipet into a 200 ml volumetric flask and add proper quantities of methanol, shake to make hydrocortisone acetate dissolved, then dilute with methanol to volume and mix well. Measure accurately 2 ml of the solution into a 25 ml volumetric flask and dilute with mobile phase to volume, mix well as the test solution. Carry out the Assay described under Hydrocortisone Acetate, beginning at the words "Inject 20 μ l of the test solution into the column and record the chromatogram", calculate the content of $C_{23}H_{32}O_6$ with respect to the peak area obtained in the chromatogram by the external standard method.

Category As described under Hydrocortisone Acetate.

Strength (1) 1 ml : 25 mg (2) 5 ml : 125 mg

Storage Preserve in tightly closed containers, protected from light.

Hydrocortisone Acetate Tablets

Hydrocortisone Acetate Tablets contain not less than 90.0% and not more than 110.0% of the labelled amount of hydrocortisone acetate ($C_{23}H_{32}O_6$).

Description White tablets.

Identification Powder a quantity of tablets equivalent to 0.06 g of hydrocortisone acetate, extract with two portions of 10 ml each of chloroform, combine the chloroform solutions, filter and evaporate to dryness on a water bath. The residue complies with the tests (1) and (2) for Identification described under Hydrocortisone Acetate.

Content uniformity Comply with the requirement (Appendix X E). Triturate 1 tablet with absolute ethanol and transfer completely into a 200 ml volumetric flask, dilute with absolute ethanol to volume, shake thoroughly and filter, and use successive filtrate as the test solution. Dissolve 20 mg of hydrocortisone acetate CRS in a 200 ml volumetric flask in absolute ethanol, dilute with absolute ethanol to volume, shake thoroughly, used as the reference solution. Carry out the method described in Assay, beginning at the word "To 1 ml each of two preparations...", calculate the content of $C_{23}H_{32}O_6$.

Other requirements Comply with the general requirements for tablets (Appendix I A).

Assay Weigh accurately and powder 20 tablets. To an accurately weighed quantity, equivalent to about 20 mg of hydrocortisone acetate in a 200 ml volumetric flask add absolute ethanol and shake thoroughly, dilute with absolute ethanol to volume, and filter, using the successive filtrate as the test solution. Dissolve 20 mg of hydrocortisone acetate CRS, accurately weighed, in absolute ethanol into a 200 ml volumetric flask, dilute to volume and shake well, as the reference solution.

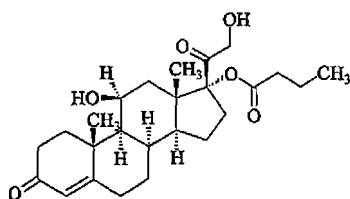
Procedure To 1 ml each of two solutions, accurately measured, in separate stoppered test tubes add accurately 9 ml of absolute ethanol and 1 ml of triphenyltetrazolium chloride TS and mix well; then add accurately 1 ml of tetramethylammonium hydroxide TS and mix well. Allow to stand in the dark at 25°C for 40-45 minutes and measure the absorbance at 485 nm (Appendix IV A). Calculate the content of $C_{23}H_{32}O_6$.

Category As described under Hydrocortisone Acetate.

Strength 20 mg

Storage Preserve in tightly closed containers; protected from light.

Hydrocortisone Butyrate



$C_{25}H_{36}O_6$ 432.56

Hydrocortisone Butyrate is 11 β , 21-dihydroxy-17-

(1-oxotutoxy)-pregn-4-ene-3,20-dione. It contains not less than 97.0% and not more than 102.0% of $C_{25}H_{36}O_6$, calculated on the dried basis.

Description A white or almost white crystalline powder; odourless.

Very soluble in chloroform; soluble in methanol; slightly soluble in absolute ethanol; very slightly soluble in ether; practically insoluble in water.

Melting range 197-208°C, with decomposition (Appendix VI C).

Specific optical rotation +47° to +54°, in a solution of about 10 mg per ml in chloroform (Appendix VI E).

Identification (1) Dissolve 4 mg in 2 ml of sulfuric acid, a yellow to brownish-yellow colour with green fluorescence is produced.

(2) Dissolve 10 mg in 1 ml of methanol, add 1 ml of an alkaline cupric tartrate TS and heat, a red precipitate of cuprous oxide is produced.

(3) The infrared absorption spectrum (Appendix IV C) is concordant with the reference spectrum of Hydrocortisone Butyrate (Appendix XVI).

Related substances Weigh accurately 15 mg of the substance being examined to 50 ml volumetric flask, add 20 ml of acetonitrile to dissolve, dilute with water to volume as test solution. Measure accurately 1 ml, dilute with mobile phase to a 50 ml volumetric flask as the reference solution. Carry out the method as described under Assay. Inject 20 μ l of the reference solution into the column, adjust the attenuation so that the principal peak height in the chromatogram is 20% of full scale of the chart. Inject separately 20 μ l each of solutions into the column, and record the chromatogram for twice the retention time of the principal peak. The sum of the areas of all peaks other than the principal peak in the chromatogram obtained with the test solution is not greater than the area of the principal peak in the chromatogram obtained with reference solution, each peak area other than the principal peak are not greater than 1/2 area of the principal peak in the chromatogram obtained with reference solution.

Loss on drying When dried to constant weight at 75°C in vacuum, loses not more than 0.5% of its weight (Appendix VIII L).

Residue on ignition Not more than 0.1% (Appendix VIII N), using 1.0 g.

Heavy metals Carry out the limit test for heavy metals (Appendix VIII H, method 2), using the residue obtained in the test for Residue on ignition; not more than 0.002%.

Assay Carry out the method for high performance liquid chromatography (Appendix V D), using a column packed with octadecylsilane bonded silica gel and a mixture of water-acetonitrile-glacial acetic acid (55 : 45 : 0.5) as the mobile phase. Detection wavelength is 240 nm and the number of the theoretical plates of the column is not less than 1500, calculated with reference to the peak of hydrocortisone butyrate. The resolution factor between the peaks of hydrocortisone butyrate and internal standard complies with the related requirements.

Internal standard solution Dissolve a quantity of methyltestosterone, accurately weighed, in methanol to produce a solution of 0.18 mg per ml.

Procedure Dissolve a quantity of hydrocortisone butyrate CRS, accurately weighed, in methanol to produce a solution of 0.26 mg per ml as the reference solution. Transfer 5 ml each of the reference solution and the internal standard solution, both measured accurately, in a 50 ml volumetric

flask, dilute with methanol to volume, mix well. Inject 20 μ l of the resulting solution into the column. Repeat the operation, using the substance being examined instead of hydrocortisone butyrate CRS, calculate the content of $C_{25}H_{36}O_6$.

Category Corticosteroid

Storage Preserve in tightly closed containers, protected from light.

Preparation Hydrocortisone Butyrate Cream

Hydrocortisone Butyrate Cream

Hydrocortisone Butyrate Cream contains not less than 90.0% and not more than 110.0% of the labelled amount of Hydrocortisone Butyrate ($C_{25}H_{36}O_6$).

Description A white cream.

Identification The retention time of the principal peak of the substance being examined in the chromatogram obtained in the Assay is identical with that of principal peak of hydrocortisone butyrate CRS.

Other requirements Complies with the general requirements for cream (Appendix I F).

Assay Carry out the method for high performance liquid chromatography (Appendix V D), using a column packed with octadecylsilane bonded silica gel and a mixture of water-acetonitrile-glacial acetic acid (55 : 45 : 0.5) as the mobile phase. Detection wavelength is 240 nm and the number of the theoretical plates of the column is not less than 1500, calculated with reference to the peak of hydrocortisone butyrate. The resolution factor between the peaks of hydrocortisone butyrate and internal standard complies with the related requirements.

Internal standard solution Dissolve a quantity of methyltestosterone, accurately weighed, in methanol to produce a solution of 0.18 mg per ml.

Procedure Dissolve a quantity of hydrocortisone butyrate CRS, accurately weighed, in methanol to produce a solution of 0.26 mg per ml as reference solution. Transfer 5 ml each of the reference solution and the internal standard solution, measured accurately, in a 50 ml volumetric flask, dilute with methanol to volume, mix well. Inject 20 μ l of the resulting solution into the column. Transfer an accurately weighed quantity of the ointment equivalent to about 1.3 mg of hydrocortisone butyrate to a 50 ml beaker, add 15 ml of methanol, stir to dissolve hydrocortisone butyrate on a water bath at 50°C, allow to cool to room temperature. Transfer to a 50 ml volumetric flask, add 5 ml of internal standard solution, dilute with methanol to volume, shake well, allow to cool in ice bath for 2 hours and filter. Inject 20 μ l of the filtrate into the column, calculate the content of $C_{25}H_{36}O_6$.

Category As described under Hydrocortisone Butyrate.

Strength 10 g : 10 mg

Storage Preserve in tightly closed containers, stored in a cool place and protected from light.

Strong Hydrogen Peroxide Solution

H_2O_2 34.01

Strong Hydrogen Peroxide Solution contains 26.0%-28.0% (g/g) of hydrogen peroxide (H_2O_2).

Description A clear, colourless liquid; odourless or with an odour characteristic of ozone; decomposes rapidly in contact with oxidizing or reducing agent with effervescence; deteriorates on exposure to light.

Identification (1) To 0.1 ml add 10 ml of water, 1 drop of dilute sulfuric acid, 2 ml of ether and a few drops of potassium dichromate TS, a blue colour is produced in ether layer on shaking.

(2) Make alkaline a quantity with sodium hydroxide TS and heat, it decomposes with effervescence and liberates oxygen.

Acidity Dilute 5 ml with water to 50 ml, add a few drops of phenolphthalein IS and 0.5 ml of sodium hydroxide (0.1 mol/L) VS, a pale red colour is produced.

Barium To 10 ml add 2 drops of dilute sulfuric acid, no opalescence is produced within 10 minutes.

Nonvolatile matter Evaporate 10 ml to dryness on a water bath and dry to constant weight at 105°C, the residue is not more than 15 mg.

Assay Measure accurately 2 ml to a 200 ml volumetric flask, dilute with water to volume and shake well. To 10 ml, accurately measured, in a flask add 20 ml of dilute sulfuric acid and titrate with potassium permanganate (0.02 mol/L) VS. Each ml of potassium permanganate (0.02 mol/L) VS is equivalent to 1.701 mg of H_2O_2 .

Category Antiseptic and disinfectant

Storage Preserve in tightly closed containers, protected from light, stored in a cool place.

Preparation Hydrogen Peroxide Solution

Hydrogen Peroxide Solution

Hydrogen Peroxide Solution contains not less than 2.5% and not more than 3.5% of H_2O_2 .

Description A clear, colourless liquid; odourless or with an odour characteristic of ozone; rapidly decomposes with effervescence when in contact with oxidizing or reducing substances; deteriorates on exposure to light.

Relative density 1.01, at 25°C (Appendix VI A).

Identification (1) To 1 ml add 10 ml of water, 1 drop of dilute sulfuric acid, 2 ml of ether, and a few drops of potassium dichromate TS and shake; a blue colour is produced in the ether layer.

(2) Decomposes with effervescence, when made alkaline with sodium hydroxide TS and heated, oxygen is evolved.

Acidity To 5 ml add a few drops of phenolphthalein IS and 0.5 ml of sodium hydroxide (0.1 mol/L) VS, a pale red colour is produced.

Barium To 10 ml add 2 drops of dilute sulfuric acid, no opalescence is produced within 10 minutes.

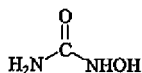
Nonvolatile matter Evaporate 10 ml to dryness on a water bath, dry at 105°C to constant weight, the residue is not more than 15 mg.

Assay Measure accurately 5 ml into a 50 ml volumetric flask, dilute to volume with water, mix well. Measure accurately 10 ml to a conical flask, add 20 ml of dilute sulfuric acid, titrate with potassium permanganate (0.02 mol/L) VS. Each ml of potassium permanganate (0.02 mol/L) VS is equivalent to 1.701 mg of H_2O_2 .

Category As described under Strong Hydrogen peroxide solution.

Storage Preserve in well closed containers, stored in cool place and protected from light.

Hydroxycarbamide



$\text{CH}_4\text{N}_2\text{O}_2$ 76.06

[127-07-1]

Hydroxycarbamide contains not less than 98.5% of $\text{CH}_4\text{N}_2\text{O}_2$, calculated on the dried basis.

Description A white crystalline powder; odourless; taste, slightly astringent.

Freely soluble in water; slightly soluble in ethanol; insoluble in ether.

Melting range 138-145°C, with decomposition (Appendix VI C).

Identification (1) Heat gently about 0.5 g with 3 ml of sulfuric acid, it effervesces with the evolution of carbon dioxide.

(2) Boil about 0.5 g with 5 ml of sodium hydroxide TS, the characteristic odour of ammonia is perceived.

(3) Dissolve about 0.5 g in 5 ml of water, add 1 ml of alkaline cupric tartrate TS, boil for 1-2 minutes, a red precipitate of cuprous oxide is produced.

(4) Dissolve about 0.1 g in 5 ml of water, add 1 drop of ferric chloride TS, a bluish violet colour is produced.

(5) The infrared absorption spectrum (Appendix IV C) is concordant with the reference spectrum of hydroxycarbamide (Appendix XVI).

Clarity of solution A solution of 0.50 g in 10 ml of water is clear.

Chloride Dissolve 0.20 g in 20 ml of water. Carry out the limit test for chloride (Appendix VIII A), using 10 ml of the solution. Any opalescence produced is not more pronounced than that of a reference solution using 5 ml of sodium chloride standard solution (0.05%).

Urea and related substances Dissolve 0.10 g in water in a 10 ml volumetric flask, dilute to volume and mix well as the test solution. Dissolve 0.01 g of urea in water in a 100 ml volumetric flask, dilute to volume and mix well as the reference solution. Treat a chromatographic filter paper strip by immersing it in phosphate BS (pH 6.5) (mix 700 ml of 0.02 mol/L disodium hydrogen phosphate solution and 300 ml of 0.1 mol/L citric acid solution). After removal of the paper strip, dry in air. Carry out the method for descending paper chromatography (Appendix V A). Apply to the chromatographic paper strip previously treated as described above 10 μl of the test solution and 50 μl of the reference solution. Place the lower layer of a mixture of isobutanol and water (1:1) in the bottom of the developing chamber, and the upper layer is used as mobile phase. Develop for 24 hours. After developing and removal of the strip, dry in air, and develop for another 24 hours. After removal of the strip, dry in air, spray with phosphomolybdic acid solution (shake to dissolve 1.0 g of *p*-dimethylaminobenzaldehyde in a mixture of 50 ml of ethanol and 2 ml of hydrochloric acid in a 100 ml volumetric flask, dilute with ethanol to volume and mix well), heat for 1-2 minutes at 90°C. Any spots, other than the principal spot,

obtained with the test solution is not more intense than the principal spot obtained with the reference solution, and the number of the secondary spot is not more than 2.

Loss on drying When dried in vacuum over phosphorous pentoxide to constant weight, loses not more than 1.0% of its weight (Appendix VIII L).

Residue on ignition Not more than 0.1% (Appendix VIII N).

Heavy metals Dissolve 1.0 g in 23 ml of water, add 2 ml of acetate BS (pH 3.5). Carry out the limit test for heavy metals (Appendix VIII H, method 1); not more than 0.002%.

Assay Dissolve about 0.15 g, accurately weighed, in 50 ml of water, add 10 ml of hydrochloric acid solution (1→3). Carry out the method for dead-stop titration (Appendix VII A), titrate with sodium nitrite (0.1 mol/L) VS. Each ml of sodium nitrite (0.1 mol/L) VS is equivalent to 7.606 mg of $\text{CH}_4\text{N}_2\text{O}_2$.

Category Antineoplastic.

Storage Preserve in tightly closed containers, protected from light.

Preparation Hydroxycarbamide Tablets

Hydroxycarbamide Tablets

Hydroxycarbamide Tablets contain not less than 95.0% and not more than 105.0% of the labelled amount of hydroxycarbamide ($\text{CH}_4\text{N}_2\text{O}_2$).

Description White tablets

Identification Comply with tests (1), (2), (3) and (4) for Identification described under Hydroxycarbamide, using a quantity of the powdered tablets.

Other requirements Comply with the general requirements for tablets (Appendix I A).

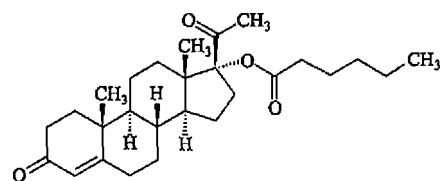
Assay Weigh accurately and powder 20 tablets. To a quantity, accurately weighed, of the powdered tablets equivalent to about 0.15 g of hydroxycarbamide add 50 ml of water, stir well, proceed as described under Hydroxycarbamide beginning at the words "add 10 ml of hydrochloric acid solution (1→3)..." Each ml of sodium nitrite (0.1 mol/L) VS is equivalent to 7.606 mg of $\text{CH}_4\text{N}_2\text{O}_2$.

Category As described under Hydroxycarbamide.

Strength 0.5 g

Storage Preserve in tightly closed containers, protected from light.

Hydroxyprogesterone Caproate



$\text{C}_{27}\text{H}_{46}\text{O}_4$ 428.62

[630-56-8]

Hydroxyprogesterone Caproate is the caproic ester of 17 α -hydroxypregn-4-ene-3,20-dione. It contains

not less than 97.0% and not more than 103.0% of $C_{27}H_{40}O_4$, calculated on the dried basis.

Description A white or almost white crystalline powder; odourless, tasteless.

Freely soluble in ethanol, acetone or ether; sparingly soluble in camellia oil or castor oil; insoluble in water.

Melting range 120-124°C (Appendix VI C).

Specific optical rotation +58° to +64°, in a solution of about 10 mg per ml in chloroform (Appendix VI E).

Identification (1) To about 1 mg add 1 ml of sulfuric acid, allow to stand for 2 minutes, a slightly yellow colour is produced; add 0.5 ml of water, the colour changes from green to red and finally to reddish-violet with blue fluorescence.

(2) The retention time of principal peak of the substance being examined in the chromatogram obtained in the Assay is identical with that of principal peak of hydroxyprogesterone caproate CRS.

(3) The infrared absorption spectrum (Appendix VI C) is concordant with the reference spectrum of hydroxyprogesterone caproate (Appendix XVI).

Acidity Dissolve 0.20 g in 25 ml of dehydrated ethanol neutral to bromothymol blue, promptly add several drops of bromothymol blue IS and titrate with sodium hydroxide (0.02 mol/L) VS to a slight blue colour; not more than 0.50 ml of sodium hydroxide VS is required.

Related substances Carry out the method described under Assay. Dissolve a quantity of the substance being examined, with methanol to produce a solution of about 1 mg per ml as solution (1). Measure accurately proper quantities of solution (1) and dilute with methanol to produce a solution of 16 µg per ml as solution (2). Inject 5 µl of solution (2) into the column, adjust the attenuation so that the principal peak height in the chromatogram is about full scale of the chart. Inject separately accurately 5 µl each of the solution (1) and (2) into the column and record the chromatogram for twice the retention time of the principal peak. No more than four secondary peaks in the chromatogram obtained with solution (1), each secondary peak and the sum of the areas of all secondary peaks are not greater than 1/2 and 3/4 of the area of the principal peak of solution (2) respectively.

Loss on drying When dried to constant weight at 105°C, loses not more than 0.5% of its weight (Appendix VIII L).

Assay Carry out the method for high performance liquid chromatography (Appendix V D), using a column packed with octadecylsilane bonded silica gel and a mixture of methanol-water (85 : 15) as the mobile phase. Detection wavelength is 254 nm and the number of theoretical plates of the column is not less than 2000, calculated with reference to the peak area of hydroxyprogesterone caproate. The resolution factor between the peaks of hydroxyprogesterone caproate and internal standard complies with the related requirements.

Internal standard solution Dissolve a quantity of norethisterone, accurately weighed, in methanol to produce a solution of 1 mg per ml.

Procedure Dissolve a quantity of hydroxyprogesterone caproate CRS, accurately weighed, in methanol to produce a solution of 1 mg per ml as the reference solution. Transfer 2 ml each of the reference solution and the internal standard solution, both measured accurately, into a 10 ml volumetric flask, dilute with methanol to volume, mix well, inject 5 µl of the resulting solution into the column. Repeat the operation, using a quantity of the substance being examined instead of hydroxyprogesterone caproate CRS, calculate the content of $C_{27}H_{40}O_4$.

Category Progestoid.

Storage Preserve in tightly closed containers, protected from light.

Preparation (1) Hydroxyprogesterone Caproate Injection
(2) Compound Hydroxyprogesterone Caproate Injection

Hydroxyprogesterone Caproate Injection

Hydroxyprogesterone Caproate Injection is a sterile solution of Hydroxyprogesterone Caproate in oil. It contains not less than 90.0% and not more than 110.0% of the labelled amount of Hydroxyprogesterone Caproate ($C_{27}H_{40}O_4$).

Description A slight yellow to yellow clear oily liquid.

Identification Dilute a quantity of the injection with chloroform to produce a solution containing 1.0 mg per ml of hydroxyprogesterone caproate (solution 1), dissolve a quantity of hydroxyprogesterone caproate CRS in chloroform to produce a solution of 1.0 mg per ml (solution 2). Carry out the method for thin-layer chromatography (Appendix V B), using silica gel HF₂₅₄ as the coating substance and a mixture of cyclohexane-ethyl acetate (1 : 1) as the mobile phase. Apply separately to the plate 10 µl each of the two solutions. After developing and removal of the plate, dry in air and examine under an ultraviolet light (254 nm). The principal spots in the chromatogram obtained with the two solutions are identical in position.

Other requirements Complies with the general requirements for injections (Appendix I B).

Assay Carry out the method for high performance liquid chromatography (Appendix V D), using a column packed with octadecylsilane bonded silica gel and a mixture of methanol-water (85 : 15) as the mobile phase. Detection wavelength is 254 nm. Dissolve proper quantities of hydroxyprogesterone caproate and estradiol valerate CRS, weighed accurately, in methanol to produce a solution of each 20 µg per ml. The resolution factor between the peaks of hydroxyprogesterone caproate and estradiol valerate should comply with the related requirements.

Procedure Measure accurately a quantity of the substance being examined by inner capacity pipet, in methanol to produce a solution of 20 µg per ml as solution (1). Inject 10 µl of solution (1) into the column and record the chromatogram. Dissolve a quantity of hydroxyprogesterone caproate CRS, weighed accurately, with methanol to produce a solution of about 20 µg per ml, repeat the operation, calculate the content of $C_{27}H_{40}O_4$ with respect to the peak area obtained in the chromatogram by the external standard method.

Category As described under Hydroxyprogesterone Caproate.

Strength (1) 1 ml : 0.125 g (2) 2 ml : 0.25 g
(3) 1 ml : 0.25 g

Storage Preserve in well closed containers, protected from light.

Compound Hydroxyprogesterone Caproate Injection

Compound Hydroxyprogesterone Caproate Injection is a sterile solution of hydroxyprogesterone caproate and estradiol valerate in oil. It contains not less

than 90.0% and not more than 110.0% of the labelled amount of hydroxyprogesterone caproate ($C_{27}H_{40}O_4$).

Description Pale yellow or yellow clear oily liquid.

Identification Dilute a quantity with absolute ethanol to produce a solution containing 0.1 mg of estradiol valerate and 5 mg of hydroxyprogesterone caproate per ml as the test solution. Prepare the reference solution of 0.1 mg per ml of estradiol valerate CRS and 5 mg per ml of hydroxyprogesterone caproate CRS. Carry out the method for thin-layer chromatography (Appendix V B), using silica gel G as the coating substance and a mixture of cyclohexane-ethyl acetate-triethanolamine (50 : 50 : 0.5) as the mobile phase. Apply separately to the same plate 20 μ l each of above solutions, after developing and removal of the plate, dry it in air, spray with sulfuric acid-ethanol (1 : 1), heat at 110°C for 5-10 minutes. The colour and position of the two principal spots in the chromatogram obtained with the test solution correspond to the principal spots obtained with the reference solutions.

Other requirements Complies with the general requirements for injections (Appendix I B).

Assay Carry out the method for high performance liquid chromatography (Appendix V D), using a column packed with octadecylsilane bonded silica gel and a mixture of methanol-water (85 : 15) as the mobile phase with flow rate of 0.7 ml per minute and detection wavelength is 225 nm. The resolution factor between the peaks of hydroxyprogesterone caproate and estradiol valerate should comply with the related requirements.

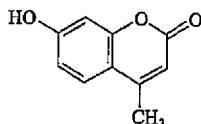
Procedure Measure accurately 1 ml of the injection into a 25 ml volumetric flask with an inner capacity pipet. Dissolve in methanol and dilute to volume, mix well; measure accurately 1 ml to a 10 ml volumetric flask, and dilute with methanol to volume, as the test solution of estradiol valerate; measure accurately 1 ml into a 50 ml volumetric flask, dilute with methanol to volume, mix well as the test solution of hydroxyprogesterone caproate. Inject separately 10 μ l each of the two test solutions, accurately measured, into the column, record the chromatogram and measure the peak areas. Dissolve separately a quantity of estradiol valerate CRS and hydroxyprogesterone caproate CRS in methanol to produce two solutions each of 0.02 mg per ml, as reference solutions, repeat the operation, inject separately 10 μ l each of the two reference solutions accurately measured, calculate the contents of $C_{27}H_{40}O_4$ and $C_{23}H_{32}O_3$ respectively with respect to the peak area obtained in chromatogram by the external standard method.

Category Contraceptive.

Strength 1 ml : 250 mg of hydroxyprogesterone caproate and 5 mg of estradiol valerate

Storage Preserve in well closed containers, protected from light.

Hymecromone



$C_{10}H_8O_3$ 176.17

[90-33-5]

Hymecromone is 7-hydroxy-4-methyl-2H-1-benzopyran-2-one. It contains not less than 98.0% and not more than 102.0% of $C_{10}H_8O_3$, calculated on the dried basis.

Description A white or almost white crystalline powder; odourless; tasteless.

Sparingly soluble in methanol, ethanol or acetone; insoluble in water; freely soluble in sodium hydroxide solution.

Melting range 188-192°C (Appendix VI C).

Identification (1) Dissolve a quantity in 2 ml of ethanol, examine under diffused sun light, a pale violet fluorescence is produced; add 2 drops of sodium hydroxide TS, a blue fluorescence is produced; the fluorescence disappears on adding 2-3 drops of dilute hydrochloric acid. An intense yellowish-green fluorescence is produced under ultraviolet light.

(2) The light absorption of a solution of 5 μ g per ml in ethanol exhibits a maximum at 323 nm (Appendix IV A).

(3) The infrared absorption spectrum (Appendix IV C) is concordant with the reference spectrum of hymecromone (Appendix XVI).

Acidity Shake 1.0 g with 50 ml of water for 10 minutes and filter, the pH value of the filtrate is 6.0-7.0 (Appendix VI H).

Sulfate Shake 1.0 g with 40 ml of water for 5 minutes and filter. Carry out the limit test for sulfate (Appendix VIII B), using 20 ml of the filtrate. Any opalescence produced is not more pronounced than that of a reference solution using 2.0 ml of potassium sulfate standard solution (0.040%).

Loss on drying When dried to constant weight at 105°C, loses not more than 0.5% of its weight (Appendix VIII L).

Residue on ignition Not more than 0.1% (Appendix VIII N), using 1.0 g.

Heavy metals Carry out the limit test for heavy metals (Appendix VIII H, method 2), using the residue obtained in the test for Residue on ignition; not more than 0.001%.

Assay Protect from light throughout the procedure. Shake thoroughly about 0.1 g, accurately weighed, in a 100 ml amber coloured volumetric flask, with 10 ml of 0.1 mol/L sodium hydroxide solution, accurately measured, dilute with water to volume and mix well. Transfer 5 ml of the solution, accurately measured, to a 50 ml amber coloured volumetric flask, dilute with 0.002 mol/L sodium hydroxide solution to volume and mix well. Transfer 5 ml of this solution, accurately measured, to a 100 ml amber coloured volumetric flask, dilute with 0.002 mol/L sodium hydroxide solution to volume and mix well. Measure the absorbance of the resulting solution at 360 nm (Appendix IV A). Repeat the operation, using about 0.1 g of hymecromone CRS instead of the substance being examined. Calculate the content of $C_{10}H_8O_3$.

Category Cholagogic.

Storage Preserve in tightly closed containers, stored in a cool and dry place, protected from light.

Preparation (1) Hymecromone Capsules
(2) Hymecromone Tablets

Hymecromone Capsules

Hymecromone capsules contain not less than 90.0% and not more than 110.0% of the labelled amount of hymecromone ($C_{10}H_8O_3$).

Description Hard capsules containing white or almost white powders.

Identification The contents comply with test (1) for Identification described under Hymecromone.

Other requirements Comply with the general requirements for capsules (Appendix I E).

Assay Protect from light throughout the procedure. Weigh accurately a quantity of the mixed contents obtained in the test for weight variation of contents, equivalent to about 0.1 g of hymecromone. Carry out the Assay described under Hymecromone Tablets, beginning at the words "in a 100 ml amber coloured volumetric flask with 10 ml of 0.1 mol/L sodium hydroxide solution, accurately measured...", calculate the content of $C_{10}H_8O_3$.

Category As described under Hymecromone.

Strength (1) 0.2 g (2) 0.4 g

Storage Preserve in tightly closed containers, stored in a cool place, protected from light.

Hymecromone Tablets

Hymecromone Tablets contain not less than 93.0% and not more than 107.0% of the labelled amount of hymecromone ($C_{10}H_8O_3$).

Description White or almost white tablets.

Identification To a quantity of powdered tablets equivalent to about 30 mg of hymecromone add 10 ml of ethanol, shake to dissolve hymecromone, filter, the filtrate complies with test (1) for Identification described under Hymecromone.

Other requirements Comply with the general requirements for tablets (Appendix I A).

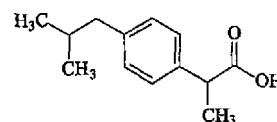
Assay Protect from light throughout the procedure. Weigh accurately and powder 10 tablets. Shake an accurately weighed quantity of the powder equivalent to about 0.1 g of hymecromone in a 100 ml amber coloured volumetric flask with 10 ml of 0.1 mol/L sodium hydroxide solution, dilute with water to volume, mix well and filter. Measure accurately 5 ml of the successive filtrate to a 50 ml amber coloured volumetric flask, dilute with 0.002 mol/L sodium hydroxide solution to volume, mix well. Transfer 5 ml of this solution, accurately measured, to a 100 ml amber coloured volumetric flask, dilute with 0.002 mol/L sodium hydroxide solution to volume and mix well. Measure the absorbance of the resulting solution at 360 nm (Appendix IV A), calculate the content of $C_{10}H_8O_3$, taking 1085 as the value of A (1%, 1 cm).

Category As described under Hymecromone.

Strength 0.2 g

Storage Preserve in tightly closed containers, stored in a cool place and protected from light.

Ibuprofen



$C_{13}H_{18}O_2$ 206.28

[15687-27-1]

Ibuprofen is α -methyl-4-(2-methylpropyl) benzeneacetic acid. It contains not less than 98.5% of $C_{13}H_{18}O_2$, calculated on the dried basis.

Description A white crystalline powder; odour, slightly characteristic; almost tasteless.

Freely soluble in ethanol, acetone, chloroform or ether; practically insoluble in water; freely soluble in sodium hydroxide TS or sodium carbonate TS.

Melting point 74.5-77.5°C (Appendix VI C).

Identification (1) The light absorption of a solution of 0.25 mg per ml in 0.4% sodium hydroxide solution exhibits maxima at 265 nm and 273 nm; minima at 245 nm and 271 nm, and a shoulder at 259 nm (Appendix IV A).

(2) The infrared absorption spectrum (Appendix VI C) is concordant with the reference spectrum of ibuprofen (Appendix XVI).

Chloride To 1.0 g add 50 ml of water, shake for 5 minutes and filter. Carry out the limit test for chlorides (Appendix VIII A), using 25 ml of the successive titrate. Any opalescence produced is not more pronounced than that of a reference using 5.0 ml of sodium chloride standard solution (0.010%).

Related substances Carry out the method for thin layer chromatography (Appendix V B), using silica gel G as the coating substance and *n*-hexane-ethyl acetate-glacial acetic acid (15 : 5 : 1) as the mobile phase. Apply separately to the plate 5 μ l each of two solutions in chloroform containing (1) 100 mg per ml, (2) 1.0 mg per ml of the substance being examined. After developing and removal of the plate, dry it in air and spray with 1% potassium permanganate solution in dilute sulfuric acid, heat at 120°C for 20 minutes and examine under ultraviolet light (365 nm). No spot other than the principal spot in the chromatogram, obtained with solution (1) is more intense than the principal spot obtained with solution (2).

Loss on drying When dried in vacuum over phosphorus pentoxide to constant weight, loses not more than 0.5% of its weight (Appendix VIII L).

Residue on ignition Not more than 0.1% (Appendix VIII N).

Heavy metals Dissolve 1.0 g in 22 ml of ethanol, add 2 ml of acetate BS (pH 3.5) and a quantity of water to produce 25 ml. Carry out the limit test for heavy metals (Appendix VIII H, method 1); not more than 0.001%.

Assay Dissolve about 0.5 g, accurately weighed, in 50 ml of neutral ethanol (neutral to phenolphthalein IS), add 3 drops of phenolphthalein IS, titrate with sodium hydroxide (0.1 mol/L) VS. Each ml of sodium hydroxide (0.1 mol/L) VS is equivalent to 20.63 mg of $C_{13}H_{18}O_2$.

Category Antipyretic and analgesic, non-steroids anti-inflammatory.

Storage Preserve in tightly closed containers.

- Preparation** (1) Ibuprofen Capsules
 (2) Ibuprofen Drops
 (3) Ibuprofen Oral Solution
 (4) Ibuprofen Sustained-release Capsules
 (5) Ibuprofen Syrup
 (6) Ibuprofen Tablets

Ibuprofen Capsules

Ibuprofen Capsules contain not less than 93.0% and not more than 107.0% of the labelled amount of Ibuprofen ($C_{13}H_{18}O_2$).

Description Capsules containing white crystalline powder or powder.

Identification Dissolve a quantity of the contents in 0.4% sodium hydroxide solution to produce a solution of about 0.25 mg per ml and filter, the successive filtrate complies with the test (1) for Identification described under Ibuprofen.

Dissolution Carry out the dissolution test (Appendix X C, Method 1), using 900 ml of phosphate BS (pH 7.2) as the dissolution medium, adjust the rotational speed of the basket to 120 rpm. Withdraw 5 ml of the solution after exactly 30 minutes and filter, accurately transfer 1 ml of the successive filtrate in a 25 ml volumetric flask, dilute with dissolution medium to volume, mix well and measure the absorbance at 222 nm (Appendix IV A). Calculate the dissolution of $C_{13}H_{18}O_2$ from each capsule, taking 449 as the value of A (1%, 1 cm), not less than 70% of the labelled amount is dissolved.

Other requirements Comply with the general requirements for capsules (Appendix I E).

Assay Weigh accurately a quantity of the mixed contents obtained in the test for weight variation of contents, equivalent to about 0.5 g of ibuprofen, add 20 ml of neutral ethanol (neutral to phenolphthalein IS), shake to dissolve ibuprofen, add 5 drops of phenolphthalein IS, titrate with sodium hydroxide (0.1 mol/L) VS. Each ml of sodium hydroxide (0.1 mol/L) VS is equivalent to 20.63 mg of $C_{13}H_{18}O_2$.

Category As described under Ibuprofen.

Strength 0.2 g

Storage Preserve in tightly closed containers.

Ibuprofen Drops

Ibuprofen Drops contain not less than 90.0% and not more than 110.0% of the labelled amount of Ibuprofen ($C_{13}H_{18}O_2$).

Description A pink suspension; taste, sweet.

Identification (1) Dissolve a quantity in 0.4% sodium hydroxide solution to produce a solution of about 0.25 mg per ml (Filter if necessary). The light absorption of the solution exhibits maxima at 265 nm and 273 nm (Appendix IV A). (2) The retention time of the principal peak of the substance being examined in the chromatogram obtained in the Assay is identical with that of the principal peak of ibuprofen CRS.

pH value 3.5-4.5 (Appendix VI H).

Relative density 1.10-1.15 (Appendix VI A).

Other requirements Comply with the general requirements

for Oral Suspensions (Appendix I O).

Assay Carry out the method for high performance liquid chromatography (Appendix V D), using a column packed with octadecylsilane bonded silica gel and a mixture of sodium acetate BS (dissolve 6.13 g of sodium acetate in 750 ml of water, by shaking, adjust to pH 2.5 with glacial acetic acid)-acetonitrile (40 : 60) as the mobile phase. Detection wavelength is 263 nm and the number of theoretical plates of the column is not less than 1000, calculated with reference to the peak of ibuprofen.

Procedure Transfer accurately 2 ml with a "to contain" pipette in a 100 ml volumetric flask, wash the interior of the pipette with 80 ml of a mixture of methanol-water (50 : 50), transfer the washings to the same volumetric flask, shake for 30 minutes, dilute with a mixture of methanol-water (50 : 50) to volume, mix well. Filter and accurately inject 20 μ l of the successive filtrate into the column, record the chromatogram. Repeat the operation, using ibuprofen CRS instead of the substance being examined. Calculate the content of $C_{13}H_{18}O_2$.

Category As described under Ibuprofen.

Strength 20 ml : 0.8 g

Storage Preserve in tightly closed containers, stored in a cool place.

Ibuprofen Oral Solution

Ibuprofen Oral Solution contains not less than 93.0% and not more than 107.0% of the labelled amount of ibuprofen ($C_{13}H_{18}O_2$).

Description A pale yellow to yellow solution.

Identification (1) Adjust about 20 ml to pH 2.0 with 1 mol/L hydrochloride acid solution, filter, wash the residue with a little water and dry. Dissolve a quantity of the residue in 0.4% sodium hydroxide solution to produce a solution of about 0.25 mg per ml. The light absorption of the solution exhibits maxima at 265 nm and 273 nm, minima at 245 nm and 271 nm, and a shoulder at 259 nm (Appendix IV A). (2) The retention time of the principal peak of the substance being examined in the chromatogram obtained in the Assay is identical with that the principal peak of ibuprofen CRS.

pH value 7.0-9.0 (Appendix VI H).

Other requirements Comply with the general requirements for Oral Solution (Appendix I O).

Assay Carry out the method for high performance liquid chromatography (Appendix V D), using a column packed with octadecylsilane bonded silica gel and a mixture of sodium acetate BS (dissolve 6.13 g of sodium acetate in 750 ml of water, by shaking, adjust to pH 2.5 with glacial acetic acid)-acetonitrile (40 : 60) as the mobile phase. Detection wavelength is 263 nm and the number of theoretical plates of the column is not less than 2500, calculated with reference to the peak of ibuprofen.

Procedure Transfer accurately a quantity with a "to contain" pipette, dilute with methanol to produce a solution of 0.5 mg per ml. Accurately inject 20 μ l into the column, record the chromatogram. Repeat the operation, using ibuprofen CRS instead of the substance being examined. Calculate the content of $C_{13}H_{18}O_2$ with respect to the peak area obtained in chromatogram by the external standard method.

Category As described under Ibuprofen.

Strength (1) 10 ml : 0.1 g

Storage Preserve in tightly closed containers, stored in a cool place.

Ibuprofen Sustained-release Capsules

Ibuprofen Sustained-release Capsules contains not less than 93.0% and not more than 107.0% of the labelled amount of ibuprofen ($C_{13}H_{18}O_2$).

Description The contents of white spherical small pills.

Identification The retention time of the principal peak of the substance being examined in the chromatogram obtained in the Assay is identical with that of ibuprofen CRS.

Drug Release Carry out the drug release test (Appendix X D, method 1), with the apparatus of dissolution test method 1, using 900 ml of phosphate BS (to 68.05 g of potassium dihydrogen phosphate add 56 ml of 1 mol/L sodium hydroxide solution, dilute with water to 10000 ml, mix well, pH 6.0 ± 0.05) as the release medium, adjust the rotational speed of the basket to 30 rpm. Withdraw 5 ml of the solution at 1, 2, 4 and 7 hours respectively, and add immediately 5 ml of the same release medium to the vessel to compensate the volume. Filter, inject 20 μ l of the successive filtrate into the column, as described in the Assay. Dissolve a quantity of ibuprofen CRS, accurately weighed, in phosphate BS to produce a solution of 300 μ g per ml, repeat the operation. Calculate the amount of ibuprofen dissolved at different time for each capsule. The amount of ibuprofen dissolved in 1, 2, 4 and 7 hours is 10%-35%, 25%-55%, 50%-80% and not less than 75% of the labelled amount, respectively.

Other requirements Comply with the general requirements for capsules (Appendix I E).

Assay Carry out the method for high performance liquid chromatography (Appendix V D), using a column packed with octadecylsilane bonded silica gel. The mobile phase is a mixture of sodium acetate BS (dissolve 6.13 g of sodium acetate in 750 ml of water, by shaking, adjust with glacial acetic acid to pH 2.5)-acetonitrile (40 : 60). The wavelength of the detector is 263 nm. The number of theoretical plates of the column is not less than 1100, calculated with reference to the peak area of ibuprofen.

Procedure Weigh accurately a quantity of the mixed contents obtained in the weight variation of contents of the capsules, equivalent to about 0.1 g of ibuprofen, in a 200 ml volumetric flask, add 100 ml of methanol, shake for 30 minutes, dilute with water to volume, mix well and filter. Inject 20 μ l of the successive filtrate into the column, record the chromatogram. Repeat the operation, using ibuprofen CRS instead of the substance being examined. Calculate the content of $C_{13}H_{18}O_2$ with respect to the peak area obtained in chromatogram by the external standard method.

Category As described under Ibuprofen.

Strength 0.3 g

Storage Preserve in tightly closed containers.

Ibuprofen Syrup

Ibuprofen Syrup contains not less than 93.0% and not more than 107.0% of the labelled amount of ibuprofen ($C_{13}H_{18}O_2$).

Description A clear, pale yellow-brown viscous liquid; odour, fragrant.

Identification (1) Adjust about 20 ml to pH 2.0 with 1 mol/L hydrochloric acid solution, filter, wash the residue with a little water and dry. Dissolve a quantity of the residue in 0.4% sodium hydroxide solution to produce a solution of about 0.25 mg per ml. The light absorption of the solution exhibits maxima at 265 nm and 273 nm, minima at 245 nm and 271 nm, and a shoulder at 259 nm (Appendix IV A). (2) The retention time of the principal peak of the substance being examined in the chromatogram obtained in the Assay is identical with that of the principal peak of ibuprofen CRS.

Relative density not less than 1.200 (Appendix VI A).

pH value 7.0-8.5 (Appendix VI H).

Other requirements Complies with the general requirements for syrups (Appendix I K).

Assay Carry out the method for high performance liquid chromatography (Appendix V D), using a column packed with octadecylsilane bonded silica gel and a mixture of acetate BS (dissolve 6.13 g of sodium acetate in 750 ml of water, by shaking, adjust to pH 2.5 with glacial acetic acid)-acetonitrile (40 : 60) as the mobile phase. Detection wavelength is 263 nm and the number of theoretical plates of the column is not less than 2500, calculated with reference to the peak of ibuprofen.

Procedure Transfer accurately a quantity with a "to contain" pipette, dilute with methanol to produce a solution of 0.5 mg per ml. Accurately inject 20 μ l into the column, record the chromatogram. Repeat the operation, using ibuprofen CRS instead of the substance being examined. Calculate the content of $C_{13}H_{18}O_2$ with respect to the peak area obtained in chromatogram by the external standard method.

Category As described under Ibuprofen.

Strength (1) 10 ml : 0.2 g (2) 90 ml : 1.8 g

Storage Preserve in tightly closed containers, protected from light.

Ibuprofen Tablets

Ibuprofen Tablets contain not less than 95.0% and not more than 105.0% of the labelled amount of ibuprofen ($C_{13}H_{18}O_2$).

Description Sugar coated or film coated tablets with white core.

Identification (1) The light absorption of a solution of 0.25 mg per ml in 0.4% sodium hydroxide solution exhibits maxima at 265 nm and 273 nm, minima at 245 nm and 271 nm, and a shoulder at 259 nm (Appendix IV A).

(2) Dissolve 5 powdered tablets of ibuprofen in 20 ml of acetone, filter. After evaporating the filtrate in air, dry it in vacuum. The infrared absorption spectrum (Appendix VI C) is concordant with the reference spectrum of ibuprofen (Appendix XVI).

Dissolution Carry out the dissolution test (Appendix X C, method 1), using 900 ml of phosphate BS (pH 7.2) as the dissolution medium, adjust the rotational speed of the basket to 120 rpm. Withdraw 5 ml of the solution after exactly 30 minutes and filter, measure accurately 2 ml of the successive filtrate, dilute to 25 ml with the dissolution medium, mix well and measure the absorbance at 222 nm (Appendix IV A). Calculate the dissolution of $C_{13}H_{18}O_2$ from each tablet,

taking 449 as the value of A (1%, 1 cm). Not less than 70% of the labelled amount is dissolved.

Other requirements Comply with the general requirements for tablets (Appendix I A).

Assay Weigh accurately and powder 20 tablets with the coating removed. To an accurately weighed quantity, equivalent to about 0.5 g of ibuprofen add 20 ml of neutral ethanol (neutral to phenolphthalein IS) and shake to dissolve ibuprofen. Filter through a sintered glass filter, wash the container and filter with four portions of 10 ml each of neutral ethanol, combine the washings and filtrate, add 5 drops of phenolphthalein IS, and titrate with sodium hydroxide (0.1 mol/L) VS. Each ml of sodium hydroxide (0.1 mol/L) VS is equivalent to 20.63 mg of $C_{13}H_{18}O_2$.

Category As described under Ibuprofen.

Strength (1) 0.1 g (2) 0.2 g

storage Preserve in tightly closed containers.

Ibuprofen and Pseudoephedrine Hydrochloride Tablets

Ibuprofen and Pseudoephedrine hydrochloride Tablets contain not less than 93.0% and not more than 107.0% of the labelled amount of ibuprofen ($C_{13}H_{18}O_2$), and not less than 90.0% and not more than 110.0% of the labelled amount of pseudoephedrine hydrochloride ($C_{10}H_{15}NO \cdot HCl$).

Formula	Ibuprofen	200 g
	Pseudoephedrine hydrochloride	30 g
	pharmaceutical aid	sufficient quantity
	To make	1000 tablets

Description White tablets or film coated tablets with white or almost white core.

Identification (1) The retention time of the two principle peaks of the substance being examined in the chromatogram obtained in the Assay are identical with that of the principle peaks of ibuprofen CRS and pseudoephedrine hydrochloride CRS.

(2) Shake a quantity of powdered tablets with water, filter. The filtrate yields the reactions characteristic of chlorides (Appendix III).

Dissolution Carry out the dissolution test (Appendix X C, Method 1), using 900 ml of phosphate BS (pH 7.2) as the dissolution medium, adjust the rotational speed of the basket to 120 rpm. Withdraw 10 ml of the solution after exactly 30 minutes and filter, use the successive filtrate as the test solution. Carry out the procedure as described under the Assay, calculate the dissolution of $C_{13}H_{18}O_2$ and $C_{10}H_{15}NO \cdot HCl$ from each tablet respectively, not less than 80% of the labelled amount is dissolved respectively.

Other requirements Comply with the general requirements for tablets (Appendix I A).

Assay Carry out the method for high performance liquid chromatography (Appendix V D), using a column packed with octadecylsilane bonded silica gel and a mixture of phosphate BS (dissolve 0.68 g of sodium dodecyl sulfonate in a mixture of 250 ml of acetonitrile and 250 ml of 0.02 mol/L potassium dihydrogen phosphate, adjust to pH 3.5 with phosphoric acid)-methanol (1:1) as the mobile phase. Detection wavelength is 215 nm and the number of theoretical

plates of the column is not less than 3000, calculated with reference to the peak of ibuprofen. The resolution factor between the peaks of ibuprofen and pseudoephedrine hydrochloride complies with the related requirements.

Procedure Weigh accurately and powder 20 tablets. Dissolve an accurately weighed quantity of the powder equivalent to 100 mg of ibuprofen and 15 mg of pseudoephedrine hydrochloride respectively, in a 50 ml volumetric flask with methanol and dilute to volume, mix well. Filter and accurately transfer 5 ml of the successive filtrate in a 50 ml volumetric flask, dilute with methanol to volume, mix well. Accurately inject 20 μ l into the column, record the chromatogram. Repeat the operation, using ibuprofen CRS and pseudoephedrine hydrochloride CRS instead of the substance being examined. Calculate the content of $C_{13}H_{18}O_2$ and $C_{10}H_{15}NO \cdot HCl$ respectively with respect to the peak area obtained in chromatogram by the external standard method.

Category Anti-inflammatory and analgesic, vasoconstrictor.

Storage Preserve in tightly closed containers.

Ichthammol

Ichthammol contains not less than 10.5% of organically combined sulfur (s), and the content of inorganic sulfur (s) is not more than 25.0% of the total sulfur, calculated on the dried basis.

Description A brownish-black, viscous liquid; odour, characteristic.
Soluble in water.

Identification (1) Heat with an equal volume of sodium hydroxide TS, an ammonia odour is received.

(2) Dissolve about 1 g in 50 ml of water, add a small quantity of hydrochloric acid, a brown precipitate is produced; a blackish-brown resinous precipitate is deposited on the inner wall and bottom of the container on standing.

Solubility in water Stir to dissolve 0.50 g in 50 ml of water in a 100 ml beaker. Transfer to a 50 ml Nessler cylinder, examine at a distance of 10-20 cm under 25 W incandescent light. It is a brown homogeneous solution without any granules or liquid drops.

Solubility in glycerol 1.0 g dissolve completely in 9 ml of glycerol.

Loss on drying Weigh accurately about 1 g, add 5 ml of anhydrous ethanol and macerate for 15 minutes. When dried to constant weight at 105°C, it loses not more than 50.0% of its weight (Appendix VIII L).

Residue on ignition Not more than 0.25% (Appendix VIII N).

Assay Total sulfur Mix 0.5 g, accurately weighed, with 4 g of anhydrous sodium carbonate and 3 ml of chloroform in a crucible, heat gently with stirring to evaporate chloroform, crush the residue. Add 10 g of coarsely powdered copper nitrate, mix thoroughly and heat the mixture with a small flame. When the oxidative reaction has subsided, raise the temperature slightly until most of the material has been charred, cool, add 20 ml of hydrochloric acid. When the reaction has ceased, transfer the molten mass to a beaker with 100 ml of water in portions and boil until all the copper oxides are dissolved. Filter and wash the residue with water in portions, combine the washings with the filtrate, add water to about 200 ml, boiling and add 40 ml of barium chloride TS. Heat for 30 minutes on a water bath, allow it

to cool, filter through an ashless filter paper. Wash the precipitate with warm water in portions until the washing is free from chloride, dry and ignite to constant weight. Perform a blank determination and make any necessary correction. Each g of residue is equivalent to 0.1374 g of total sulfur.

Inorganic sulfur Dissolve 2 g, accurately weighed, in 100 ml of water in a 250 ml beaker (heat if necessary), add 20 ml of 10% copper chloride solution, mix well and boil. Allow the solution to cool, add 5 ml of ammonia TS, mix well and filter. Transfer the filtrate to a 200 ml volumetric flask, wash the precipitate with water in portions, combine the washings with the filtrate, add water to volume, mix well. Measure accurately 100 ml, boil and neutralize with hydrochloric acid, add 1 ml of hydrochloric acid and 10 ml of barium chloride TS slowly, heat for 30 minutes on a water bath, allow to cool to room temperature. Filter through an ashless filter paper, wash the precipitate with warm water in portions until the washing is free from chloride, dry and ignite to constant weight. Perform a blank determination and make any necessary correction. Each g of residue is equivalent to 0.1374 g of inorganic sulfur.

Organic sulfur Calculated by subtracting the percentage content of inorganic sulfur from the percentage content of total sulfur.

Category Antiseptic disinfectant

Storage Preserve in tightly closed containers and stored in a cool place.

Preparation Ichthammol Ointment

Ichthammol Ointment

Description Brownish-black ointment; odour, characteristic.

Identification (1) Heat about 0.5 g with 1 ml of sodium hydroxide TS in a test tube, an ammonia odour is evolved, and the vapour turns moistened red litmus paper to blue.

(2) Heat about 5 g with 25 ml of water, stir to dissolve ichthammol, allow to cool and filter. To the filtrate add a small quantity of hydrochloric acid, a brown precipitate is produced; a blackish-brown resinous precipitate is deposited on the inner wall and bottom of the container on standing.

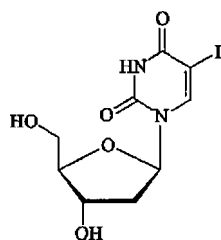
Other requirements Comply with the general requirements for ointments (Appendix I F).

Category As described under Ichthammol.

Strength 10%

Storage Preserve in well closed containers.

Idoxuridine



$C_9H_{11}IN_2O_5$ 354.10

[54-42-2]

Idoxuridine is 2'-deoxy-5-iodo-uridine. It contains not less than 97.0% and not more than 103.0% of

$C_9H_{11}IN_2O_5$, calculated on the dried basis.

Description A white crystalline powder.

Slightly soluble in water, methanol, ethanol or acetone; practically insoluble in chloroform or ether; freely soluble in sodium hydroxide TS; slightly soluble in dilute hydrochloric acid.

Melting range 176-184°C with decomposition (Appendix VI C).

Specific optical rotation +25° to +30° in a solution of 10 mg per ml in sodium hydroxide TS measured at 25°C (Appendix VI E).

Identification (1) Heat 2 mg to melt, violet vapour is evolved.

(2) To 2 mg add 0.2 ml of water and 2 drops of 5% cysteine hydrochloride solution then add 2 ml of sulfuric acid solution (7→10) slowly. A pink colour is produced, which changes to brownish-red gradually.

(3) The light absorption of the solution obtained in Assay exhibits a maximum at 279 nm and a minimum at 253 nm (Appendix IV A).

(4) The infrared absorption spectrum (Appendix IV C) is concordant with the reference spectrum of idoxuridine (Appendix XVI).

5-Iodo-uridine Measure the light absorbance of the solution obtained in Assay, the ratio of the absorbance at 303 nm to that at 279 nm is not more than 0.40 (Appendix IV A).

Loss on drying When dried in vacuum to constant weight at 60°C, loses not more than 1.0% of its weight (Appendix VIII L).

Assay Dissolve an accurately weighed quantity in 0.01 mol/L sodium hydroxide solution to produce a solution of 30 µg per ml, measure the absorbance at 279 nm (Appendix IV A). Calculate the content of $C_9H_{11}IN_2O_5$, taking 158 as the value of A (1%, 1 cm).

Category Antiviral.

Storage Preserve in tightly closed containers, protected from light.

Preparation Idoxuridine Eye Drops

Idoxuridine Eye Drops

Idoxuridine Eye Drops contain not less than 90.0% and not more than 110.0% of the labelled amount of idoxuridine ($C_9H_{11}IN_2O_5$). A suitable quantity of preservative may be added.

Description A clear, colourless liquid.

Identification (1) Heat 2 ml with 2 ml of 5% sulfuric acid solution and 0.2 g of zinc powder in a water bath for 10 minutes, cool to room temperature and filter. To the filtrate add a drop of potassium dichromate TS and 1 ml of starch IS; a blue colour is produced.

(2) To 3 ml add 2 drops of 5% cysteine hydrochloride solution, and mix. Add 3 ml of sulfuric acid with caution to produce two layers; a brown colour is produced at the interface.

pH value 4.0-7.0 (Appendix VI H).

5-Iodo-uridine Measure the light absorbance of the solution obtained in Assay, the ratio of the absorbance at 303 nm to that at 279 nm is not more than 0.41 (Appendix IV A).

Other requirements Comply with the general requirements for eye preparations (Appendix I G).

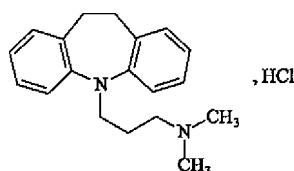
Assay Transfer 5 ml, accurately measured, to a 200 ml volumetric flask, dilute with 0.01 mol/L sodium hydroxide solution to volume and mix well. Measure the absorbance at 279 nm (Appendix IV A). Calculate the content of $C_{19}H_{24}N_2 \cdot HCl$, taking 158 as the value of A (1%, 1 cm).

Category As described under Idoxuridine.

Strength (1) 8 ml : 8 mg (2) 10 ml : 10 mg

Storage Preserve in tightly closed containers, stored in a cool place and protected from light.

Imipramine Hydrochloride



$C_{19}H_{24}N_2 \cdot HCl$ 316.88

[113-52-0]

Imipramine Hydrochloride is *N*, *N*-dimethyl-10, 11-dihydro-5*H*-dibenz (*b*, *f*) azepine-5-propan-amine hydrochloride. It contains not less than 98.0% of $C_{19}H_{24}N_2 \cdot HCl$, calculated on the dried basis.

Description A white or almost white crystalline powder; odourless or almost odourless; discoloured on exposure to light.

Freely soluble in water, ethanol or chloroform; practically insoluble in ether.

Melting range 170–175°C (Appendix VI C).

Identification (1) Dissolve about 5 mg in 2 ml of nitric acid, a deep blue colour is produced immediately.

(2) The light absorption of a 20 µg per ml solution in hydrochloric acid solution (9→1000) exhibits a maximum at 251 nm; the absorbance is about 0.53 (Appendix IV A).

(3) The infrared absorption spectrum (Appendix IV C) is concordant with the reference spectrum of imipramine hydrochloride (Appendix XVI).

(4) Dissolve about 50 mg in water, make alkaline with ammonia TS and filter. The filtrate, acidified with nitric acid, yields the reactions characteristic of chlorides (Appendix III).

Clarity and colour of solution Dissolve 1.0 g in 10 ml of water, the solution is clear and colourless. Any opalescence produced is not more pronounced than that of reference suspension I (Appendix IX B); any colour produced is not more intense than that of reference solution Y_3 (Appendix IX A, method 1).

Acidity Dissolve 1.0 g in 10 ml of water, pH 4.2–5.2 (Appendix VI H).

Iminodibenzyl To 50 mg in a 20 ml volumetric flask add 10 ml of hydrochloric acid-ethanol (1 : 1). Add 5 ml of a 0.4% solution of furfural in ethanol and 5 ml of hydrochloric acid under cooling, mix well. Allow to stand in a dark place at 25°C for 3 hours. Dilute with hydrochloric acid-ethanol (1 : 1) to volume. Measure the absorbance at 565 nm, not greater than 0.25 (Appendix IV A).

Related substances Carry out the method for thin-layer chromatography (Appendix V B), using silica gel G as the coating substance and a mixture of ethyl acetate-glacial acetic acid-hydrochloric acid-water (55 : 35 : 5 : 5) as the mobile

phase. Apply separately to the plate 10 µl each of two solutions in ethanol containing (1) 10 mg per ml and (2) 0.10 mg per ml of the substance being examined. After developing and removal of the plate, dry it in air, spray with a 0.5% solution of potassium dichromate in a mixture of sulfuric acid-water (1 : 4) and examine immediately. No spot other than the principal spot in the chromatogram obtained with solution (1) is more intense than the principal spot obtained with solution (2).

Loss on drying When dried to constant weight at 105°C, loses not more than 0.5% of its weight (Appendix VII L).

Residue on ignition Not more than 0.1% (Appendix VII N).

Assay Dissolve about 0.2 g, accurately weighed, in 20 ml of glacial acetic acid, add 10 ml of mercuric acetate TS. Carry out the method for potentiometric titration (Appendix VII A), titrate with perchloric acid (0.1 mol/L) VS. Perform a blank determination and make any necessary correction. Each ml of perchloric acid (0.1 mol/L) VS is equivalent to 31.69 mg of $C_{19}H_{24}N_2 \cdot HCl$.

Category Antidepressant

Storage Preserve in tightly closed containers, protected from light.

Preparation Imipramine Hydrochloride Tablets

Imipramine Hydrochloride Tablets

Imipramine Hydrochloride Tablets contain not less than 93.0% and not more than 107.0% of the labelled amount of imipramine hydrochloride ($C_{19}H_{24}N_2 \cdot HCl$).

Description Sugar-coated or film-coated tablets with white core.

Identification (1) Weigh a quantity of the powdered tablets with coating removed equivalent to 0.1 g of imipramine hydrochloride, triturate with 10 ml of chloroform and filter. Evaporate the filtrate to dryness. The residue complies with tests (1) and (4) for Identification described under Imipramine Hydrochloride.

(2) The light absorption of a solution obtained in Assay exhibits a maximum at 251 nm (Appendix IV A).

Related substances Weigh accurately a quantity of the powdered tablets equivalent to 0.2 g of imipramine hydrochloride. Extract with three 10 ml portions of chloroform, filter, evaporate the combined extracts to dryness. Dissolve the residue in 10 ml of ethanol (solution 1). Dilute an accurately measured quantity of solution (1) with ethanol to produce a solution of 0.2 mg per ml (solution 2). Carry out the test for Related substances described under Imipramine Hydrochloride.

Dissolution Carry out the dissolution test (Appendix X C, method 1), using 900 ml of hydrochloric acid solution (9→1000) as the dissolution medium, adjust the rotational speed of the basket to 100 rpm. Withdraw 10 ml of the solution after exactly 45 minutes and filter. Measure the absorbance of the successive filtrate at 251 nm (Appendix IV A). Calculate the dissolution of $C_{19}H_{24}N_2 \cdot HCl$ from each tablet, taking 264 as the value of A (1%, 1cm), not less than 75% of the labelled amount is dissolved.

Other requirements Comply with the general requirements for tablets (Appendix I A).

Assay Weigh accurately and powder 20 tablets with coating

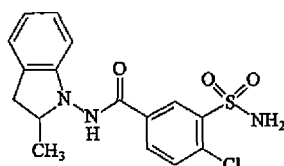
removed. Transfer an accurately weighed quantity of the powdered tablets, equivalent to 75 mg of imipramine hydrochloride, to a 250 ml volumetric flask, add about 80 ml of hydrochloric acid solution (9→1000) and shake to dissolve imipramine hydrochloride. Dilute to volume with the same solvent, shake thoroughly, filter. Dilute 5 ml of the successive filtrate accurately measured, in a 100 ml volumetric flask with hydrochloric acid solution (9→1000) to volume, mix well. Measure the absorbance of the resulting solution at 251 nm (Appendix IV A). Calculate the content of $C_{19}H_{24}N_2 \cdot HCl$, taking 264 as the value of A (1%, 1 cm).

Category As described under Imipramine Hydrochloride.

Strength (1) 12.5 mg (2) 25 mg

Storage Preserve in tightly closed containers, protected from light.

Indapamide



$C_{16}H_{16}ClN_3O_3S$ 365.83

[26807-65-8]

Indapamide is 4-chloro-*N*-(2-methyl-1-indolyl)-3-sulfamoylbenzamide. It contains not less than 98.5% of $C_{16}H_{16}ClN_3O_3S$, calculated on the dried basis.

Description Almost white needle crystals or a crystalline powder; odourless; tasteless.

Freely soluble in acetone or glacial acetic acid; soluble in ethanol or ethyl acetate; slightly soluble in chloroform or ether; practically insoluble in water or dilute hydrochloric acid.

Melting range 162-167°C, the substance forms a curve surface of crescent moon that temperature is regarded as the end of melting (Appendix VI C).

Identification (1) Dissolve about 50 mg in 3 ml of water, shake, add 0.5 ml of hydrogen peroxide TS, shake well, heat gently to nearly boil, cool to room temperature and filter. Add 3 drops of ferric chloride TS to the filtrate, shake and add 1-2 drops of sodium hydroxide TS; a brownish red precipitate is produced.

(2) To about 50 mg add 1-2 ml of sodium hydroxide solution (0.4→100) dropwise to produce a saturated solution, filter. Add 1 drop of cupric sulfate TS to the filtrate, a yellowish brown or brown precipitate is produced.

(3) The infrared absorption spectrum (Appendix IV C) is concordant with the reference spectrum of indapamide (Appendix XVI).

(4) To about 50 mg in a porcelain crucible add 0.2 g of anhydrous sodium carbonate, mix, ignite until the incineration is complete. Cool, add 5 ml of water, heat to boil, cool to room temperature and filter. The filtrate yields the reactions characteristic of chlorides (Appendix III).

Related substances Dissolve a quantity of the substance being examined in the mobile phase by shaking in a hot water bath, dilute with the mobile phase to produce a solution of about 0.5 mg per ml as the test solution. Dilute a quantity of above solution, accurately measured, with the mobile phase

to produce a solution of about 5 µg per ml as the reference solution. Carry out the method described under Assay. Inject 20 µl of the reference solution into the column, adjust the attenuation so that the principal peak height in the chromatogram is 20% of the full scale of the chart. Inject separately 20 µl each of the test solution and the reference solution into the column and record the chromatogram for three times the retention time of the principal peak. The sum of the secondary peak areas is not greater than the area of the principal peak in the chromatogram obtained with the reference solution.

Loss on drying When dried to constant weight at 105°C, loses not more than 2.4% of its weight (Appendix VIII L).

Residue on ignition Not more than 0.1% (Appendix VIII N), using 1.0 g.

Heavy metals Carry out the test for heavy metals (Appendix VIII H, method 2), using the residue obtained in the test for Residue on ignition; not more than 0.001%.

Assay Carry out the method for high performance liquid chromatography (Appendix V D), using a column packed with octadecylsilane bonded silica gel and a mixture of methanol-water-glacial acetic acid (45 : 55 : 0.1) as the mobile phase. Detection wavelength is 240 nm and the number of theoretical plates of the column is not less than 2500, calculated with reference to the peak of indapamide. The retention time of the peak of indapamide and internal standard complies with the related requirements.

Internal standard solution Dissolve 20 mg of acetanilide in 5 ml of methanol and dilute to 100 ml with the mobile phase.

Procedure Dissolve about 20 mg of indapamide CRS, accurately weighed, in 5 ml of methanol in a 100 ml volumetric flask and dilute to volume with the mobile phase, mix well. Transfer 10 ml of the resulting solution and 5 ml of the internal standard solution, both accurately measured, into a 50 ml volumetric flask, dilute to volume with the mobile phase, mix well. Inject 20 µl of the resulting solution and record the chromatogram. Repeat the operation using a quantity of the substance being examined instead of indapamide CRS. Calculate the content of $C_{16}H_{16}ClN_3O_3S$.

Category Hypotensive.

Storage Preserve in tightly closed containers, protected from light.

Preparation Indapamide Tablets

Indapamide Tablets

Indapamide Tablets contain not less than 90.0% and not more than 110.0% of the labelled amount of indapamide ($C_{16}H_{16}ClN_3O_3S$).

Description Sugar coated tablets with white core.

Identification (1) Triturate a quantity of powder equivalent to about 50 mg of indapamide with 20 ml of acetone, filter, evaporate the filtrate on water bath to dryness. The residue complies with tests (1) and (2) for Identification described under Indapamide.

(2) A quantity of powder equivalent to about 25 mg of indapamide complies with test (4) for Identification described under Indapamide.

Related substances To a quantity of the powder add a quantity of the mobile phase, shake for 5 minutes in a hot water bath to dissolve indapamide. Dilute with the mobile phase to produce a solution of 0.5 mg per ml, filter, taking

the successive filtrate as the test solution. Carry out the test for Related substances described under Indapamide, beginning at the words "dilute a quantity of above solution".

Content uniformity Comply with the requirement (Appendix X E). Triturate 1 tablet with a quantity of ethanol in a mortar, transfer to a 100 ml volumetric flask with ethanol in portions, shake thoroughly, dilute to volume and mix well, filter. Measure accurately 10 ml of the successive filtrate to a 50 ml volumetric flask, dilute to volume and mix well. Measure the absorbances of this solution and the reference solution under the Assay at 242 nm (Appendix IV A), calculate the content of $C_{16}H_{16}ClN_3O_3S$.

Dissolution Carry out dissolution test (Appendix X C, method 2), using 900 ml of ethanol-water (5 : 895) as the dissolution medium, adjust the rotational speed of the paddle to 75 rpm. Withdraw the solution after exactly 45 minutes and filter. Measure the absorbance of the successive filtrate at 242 nm (Appendix IV A). Dissolve 25 mg of indapamide CRS, accurately weighed, in a 50 ml volumetric flask in ethanol and dilute to volume, mix well. Measure accurately 10 ml of this solution in a 100 ml volumetric flask, dilute to volume with water and mix well. Measure accurately 5 ml of this solution in 100 ml volumetric flask, dilute to volume with water and mix well. Repeat the operation, calculate the dissolution of $C_{16}H_{16}ClN_3O_3S$ from each tablet. Not less than 65% of the labelled amount is dissolved.

Other requirements Comply with the general requirements for tablets (Appendix I A).

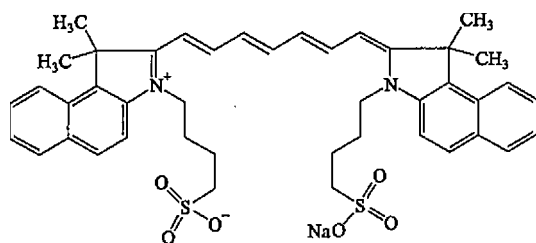
Assay Weigh accurately and powder 20 tablets. Shake well and accurately weighed quantity of the powder equivalent to 5.0 mg of indapamide with a quantity of ethanol in a 100 ml volumetric flask, dilute to volume and mix well, filter. Measure accurately 5 ml of the successive filtrate in a 50 ml volumetric flask, dilute to volume and mix well. Weigh accurately a quantity of indapamide CRS, add ethanol to produce a solution of 5.0 μg per ml. Measure the absorbances of the solutions at 242 nm (Appendix IV A). Calculate the content of $C_{16}H_{16}ClN_3O_3S$.

Category As described under Indapamide.

Strength 2.5 mg

Storage Preserve in tightly closed containers, protected from light.

Indocyanine Green



$C_{43}H_{47}N_2NaO_6S_2$ 774.96

[3599-32-4]

Indocyanine Green is 2-[7-[1, 1-Dimethyl-3-(4-sulfobutyl) benz[e]indolin-2-ylidene]-1, 3, 5-heptatrienyl]-1, 1-dimethyl-3-(4-sulfobutyl)-1H-benz[e]indolium hydroxide, inner salt, sodium salt. It contains not less than 94.0% and not more than 105.0% of $C_{43}H_{47}N_2NaO_6S_2$, calculated on the dried basis.

Description A dark olive-green, or dark brown red powder; odourless; deteriorated easily on exposure to light and heat. Soluble in water or methanol; practically insoluble in acetone.

Identification (1) Dissolve 10 mg in 5 ml of water, add 10 drops of sodium hydroxide TS, and heat to about 60°C. Add 10 drops of 3% hydrogen peroxide solution: a dark red brown colour is produced, which changes to orange-yellow on standing.

(2) The light absorption of a solution obtained in Assay exhibits three maxima at 216 nm, 263 nm and 784 nm (Appendix IV A).

(3) The infrared absorption spectrum (Appendix IV C) is concordant with the reference spectrum of Indocyanine Green (Appendix XVI).

(4) Ignite a portion of it; the residue yields the reactions characteristic of sodium and sulfate (Appendix III).

Loss on drying When dried in vacuum at 50°C for 3 hours, loses not more than 6.0% of its weight (Appendix VIII L).

Heavy metals Place 1.0 g in a crucible, heat gently until the substance is charred, and cool to room temperature. Add 2 ml of nitric acid and 5 drops of sulfuric acid, heat until white fumes are no longer evolved. Ignite at 500-600°C unless the substance is thoroughly incinerated, and cool to room temperature. Add 2 ml of hydrochloric acid, evaporate to dryness on a water bath. Moisten the residue with 3 drops of hydrochloric acid, add 7 ml of hot water, heat for 2 minutes, and add 1 drop of phenolphthalein IS, add ammonia TS until a pale red is produced. Add 0.4 ml of dilute acetic acid, filter if necessary, transfer to a Nessler cylinder, wash the crucible with 2 ml of water, dilute with water to 10 ml, as the test solution. Evaporate 2 ml of nitric acid, 5 drops of sulfuric acid and 2 ml of hydrochloric acid to dryness on a water bath. Moisten the residue with 3 drops of hydrochloric acid, add 7 ml of hot water, heat for 2 minutes, and add 1 drop of phenolphthalein IS, add ammonia TS until a pale red is produced. Add 0.4 ml of dilute acetic acid, transfer to another Nessler cylinder, add 1.0 ml of standard lead solution, dilute with water to 10 ml, as the reference solution. To each of the tubes containing the reference solution and the test solution, add 1 drop of sodium sulfide TS (Dissolve 5 g of sodium sulfide in 10 ml of water, add 30 ml of glycerin, mix well. Store in a refrigerator and use within 3 months), mix well and allow to stand for 5 minutes. Carry out the limit test for heavy metals (Appendix VIII H); not more than 0.001%.

Arsenic Mix about 0.25 g with 0.5 g of sodium hydroxide, add a quantity of water and stir well. After it is evaporated to dryness, heat gently first until the substance is charred, and then ignite at 600-700°C unless the substance is thoroughly incinerated, and cool to room temperature. Dissolve in 5 ml of hydrochloric acid and 23 ml of water. Carry out the limit test for arsenic (Appendix VIII J); not more than 0.0008%.

Sodium iodide Dissolve about 0.2 g, accurately weighed, in 100 ml of water, add 1 ml of nitric acid, mix well. Carry out the method for potentiometric titration (Appendix VII A), titrate with silver nitrate (0.01 mol/L) VS, using silver and glass electrodes. Each ml of silver nitrate (0.01 mol/L) VS is equivalent to 1.499 mg of NaI. Not more than 5.0% of sodium iodide, calculated on the dried basis.

Assay Dissolve a quantity, accurately weighed, in methanol and dilute to produce a solution of about 2 μg per ml. Measure the absorbance of the resulting solution at 784 nm (Appendix IV A), calculate the content of $C_{43}H_{47}N_2NaO_6S_2$ taking 3120 as the value of A (1%, 1 cm).

Category Diagnostic.

Storage Preserve in tightly closed containers, stored in a cool and dry place and protected from light.

Preparation Indocyanine Green for Injection

Indocyanine Green for Injection

Indocyanine Green for Injection is a sterile lyophilized preparation of indocyanine green. It contains not less than 90.0% and not more than 110.0% of the labelled amount of indocyanine green ($C_{43}H_{47}N_2NaO_6S_2$).

Description A dark olive-green lyophilized mass; deteriorated easily on exposure to light and heat.

Identification (1) Dissolve 10 mg in 5 ml of water, add 10 drops of sodium hydroxide TS, and heat to about 60°C. Add 10 drops of 3% hydrogen peroxide solution; a dark red colour is produced, which changes to orange-yellow on standing.

(2) Ignite a portion of it; the residue yields the reactions characteristic of sodium and sulfate (Appendix III).

Acidity Dissolve 50 mg in 10 ml of water, pH 5.0-7.0 (Appendix VI H).

Content uniformity Carry out the method described under Assay, using 5 vials. Calculate the content of $C_{43}H_{47}N_2NaO_6S_2$ in each vial and the average content of 5 vials. Not more than 1 vial of the individual content deviates from the average content by more than 15%, and none of the individual content deviates by more than 20%.

Sterility Complies with the test for sterility (Appendix XI H).

Other requirements Complies with the general requirements for injections (Appendix I B).

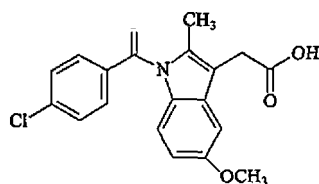
Assay Dissolve the contents of five containers separately in a quantity of methanol, transfer to 10 ml volumetric flasks, and wash the containers with methanol in portions. Combine the washings to the same volumetric flask and dilute to volume with methanol. Dilute a quantity, accurately measured, with methanol to produce a solution of 2.5 µg per ml. Measure the absorbance of the solution at 784 nm (Appendix IV A), calculate the content of $C_{43}H_{47}N_2NaO_6S_2$ in each container, taking 3120 as the value of A (1%, 1 cm), and calculate the average content of the five containers.

Category As described under Indocyanine Green.

Strength (1) 10 mg (2) 25 mg

Storage Preserve in well closed containers, stored in a cold place and protected from light.

Indometacin



$C_{19}H_{16}ClNO_4$ 357.79

[53-86-1]

Indometacin is 1-(4-chlorobenzoyl)-5-methoxy-2-methyl-1H-

indole-3-acetic acid. It contains not less than 99.0% of $C_{19}H_{16}ClNO_4$, calculated on the dried basis.

Description An almost white to pale yellow crystalline powder; almost odourless; tasteless.

Soluble in acetone; sparingly soluble in methanol, ethanol, chloroform or ether; slightly soluble in benzene; very slightly soluble in toluene; practically insoluble in water.

Melting range 158-162°C (Appendix VI C).

Specific absorbance Dissolve 50 mg, accurately weighed, in 50 ml of methanol in a 100 ml volumetric flask and shake, add phosphate BS (pH 7.2) to volume and mix well. Measure accurately 5 ml of the solution to 100 ml volumetric flask, dilute with a mixture of methanol-phosphate BS (pH 7.2) (1 : 1) to volume and mix well. Measure the absorbance of the resulting solution at 320 nm (Appendix IV A), the value of A (1%, 1 cm) is 185-200.

Identification (1) Dissolve about 10 mg in a mixture of 10 ml of water and 2 drops of 20% sodium hydroxide solution. To 1 ml of the solution add 0.3 ml of 0.03% potassium dichromate solution, heat to boiling and allow to cool to room temperature. Add 2-3 drops of sulfuric acid, then heat gently on a water bath; a violet colour is produced. Heat another 1 ml of the solution to boiling with 0.3 ml of 0.1% sodium nitrite solution and allow to cool to room temperature. Add 0.5 ml of hydrochloric acid; a green colour is produced, turning to yellow on standing.

(2) The infrared absorption spectrum (Appendix IV C) is concordant with the reference spectrum of indometacin (Appendix XVI).

Chloride Shake thoroughly 0.30 g with 25 ml of water for 3 minutes and filter. Carry out the limit test for chlorides (Appendix VIII A), using the filtrate. Any opalescence produced is not more pronounced than that of a reference using 6.0 ml of sodium chloride standard solution (0.02%).

Related substances Carry out the method for high performance liquid chromatography (Appendix V D), using a column packed with octadecylsilane bonded silica gel and a mixture of acetonitrile-0.1 mol/L glacial acetic acid solution (50 : 50) as the mobile phase. Detection wavelength is at 228 nm, and the number of theoretical plates of the column is not less than 2000, calculated with reference to the peak of indometacin, the resolution factor between the peaks of indometacin and the adjacent impurity complies with the related requirements. To a quantity equivalent to about 50 mg of indometacin to 100 ml volumetric flask add a quantity of ethanol, shake to dissolve indometacin and dilute with ethanol to the volume, mix well. Measure 5 ml in 25 ml volumetric flask and dilute with 50% ethanol solution to the volume, use as the test solution. Measure accurately 1 ml of the test solution to 200 ml volumetric flask and dilute with 50% ethanol solution to the volume to produce the reference solution. Inject 50 µl of the reference solution into the column, adjust the attenuation so that the principal peak height in the chromatogram is 20% of the full scale of the chart. Inject separately 50 µl each of the test and reference solution, into the column and record the chromatogram for three times the retention time of the principal peak. The sum of the areas of all peaks other than the principal peak in the chromatogram obtained with the test solution is not greater than the principal peak area of the reference solution.

Loss on drying When dried at 105°C to constant weight, loses not more than 0.5% of its weight (Appendix VIII L).

Residue on ignition Not more than 0.1% (Appendix VIII N), using 1.0 g.

Heavy metals Not more than 0.001%, using the residue obtained in the test for Residue on ignition (Appendix VIII H,

method 2).

Assay Dissolve about 0.5 g, accurately weighed, in 30 ml of ethanol with gentle heating and allow to cool. Add 20 ml of water and 7-8 drops of phenolphthalein IS, titrate immediately with sodium hydroxide (0.1 mol/L) VS. Perform a blank determination and make any necessary correction. Each ml of sodium hydroxide (0.1 mol/L) VS is equivalent to 35.78 mg of $C_{19}H_{16}ClNO_4$.

Category Analgesic and antipyretic, non-steroids anti-inflammatory.

Storage Preserve in tightly closed containers, protected from light.

Preparation

- (1) Indometacin Capsules
- (2) Indometacin Cream
- (3) Indometacin Enteric-Coated Tablets
- (4) Indometacin Liniment
- (5) Indometacin Patches
- (6) Indometacin Suppositories

Indometacin Capsules

Indometacin Capsules contain not less than 90.0% and not more than 110.0% of the labelled amount of indometacin ($C_{19}H_{16}ClNO_4$).

Identification Shake thoroughly a quantity of the contents of the capsules equivalent to about 10 mg of indometacin with 10 ml of water, add 3 drops of 20% sodium hydroxide solution and shake to dissolve indometacin, filter. The filtrate complies with test (1) for Identification described under Indometacin.

Related Substances Use the test solution obtained in Assay as the test solution. Measure 1 ml of the test solution in 100 ml volumetric flask and dilute with 50% ethanol solution to the volume, use as the reference solution. Proceed as described under Assay, inject 50 μ l of the reference solution into the column, adjust the attenuation so that the principal peak height in the chromatogram is 20% of the full scale of the chart. Inject separately 50 μ l each of the test and reference solution, into the column and record the chromatogram for 3 times the retention time of the principal peak. The sum of the areas of all peaks other than principal peak in the chromatogram obtained with the test solution is not greater than twice of the principal peak area of the reference solution (2.0%).

Content uniformity Comply with the requirements (Appendix X E). Transfer the content of 1 capsule to a 50 ml volumetric flask, wash the shell with 35 ml of methanol in portions, transfer the washings into the same volumetric flask. Warm and shake thoroughly to dissolve indometacin, cool to room temperature, add methanol to volume, mix well and allow to stand. Measure accurately 5 ml of the supernatant liquid to a 100 ml volumetric flask, add a mixture of methanol-phosphate BS (pH 7.2) (1 : 1) to volume and mix well. Measure the absorbance of the solution at 320 nm (Appendix IV A). Calculate the content of $C_{19}H_{16}ClNO_4$, taking 193 as the value of A (1%, 1 cm).

Dissolution Carry out the dissolution test (Appendix X C, method 2), using 900 ml of phosphate BS (pH 7.2)-water (1 : 4) as the dissolution medium, adjust the rotational speed of the paddle to 100 rpm. Withdraw the solution after exactly 45 minutes and filter. Measure the absorbance of the successive filtrate at 320 nm (Appendix IV A) and calculate the dissolution of $C_{19}H_{16}ClNO_4$ from each capsule, taking

193 as the value of A (1%, 1cm), not less than 70% of the labelled amount is dissolved.

Other requirements Comply with the general requirements for capsules (Appendix I E).

Assay Carry out the method for high performance liquid chromatography (Appendix V D), using a column packed with octadecylsilane bonded silica gel and a mixture of acetonitrile-0.1 mol/L glacial acetic acid solution (50 : 50) as the mobile phase. Detection wavelength is at 228 nm, and the number of theoretical plates of the column is not less than 2000, calculated with reference to the peak of indometacin, the resolution factor between the peaks of indometacin and the adjacent impurity complies with the related requirements. Weigh accurately 20 capsules, remove the content. To a quantity equivalent to about 50 mg of indometacin, accurately weighed, add a quantity of ethanol to 100 ml volumetric flask, shake to dissolve indometacin and dilute with ethanol to the volume, mix well and filter. Measure 5 ml of the successive filtrate in 25 ml volumetric flask and dilute with 50% ethanol solution to the volume, mix well, use as the test solution. Inject 20 μ l of the test solution into the column and record the chromatogram. Weigh accurately 25 mg of indometacin CRS to 50 ml volumetric flask and add a quantity of ethanol, shake to dissolve indometacin and dilute with ethanol to the volume, mix well. Measure accurately a quantity and dilute with 50% ethanol solution to produce the reference solution of 0.1 mg per ml. Repeat the operation, calculate the content of $C_{19}H_{16}ClNO_4$ with respect to the peak area obtained in the chromatogram by the external standard method.

Category As described under Indometacin.

Strength 25 mg

Storage Preserve in tightly closed containers, protected from light.

Indometacin Cream

Indometacin Cream contains not less than 90.0% and not more than 110.0% of the labelled amount of Indometacin $C_{19}H_{16}ClNO_4$.

Description A pale yellow cream.

Identification To about 2.5 g add 50 ml of cyclohexane and 25 ml of methanol, shake to extract. Allow to stand and separate, using the lower layer of methanol, carry out the test for Identification as follows.

(1) To 1 ml of the methanol solution add 3-4 drops of 0.1 mol/L sodium hydroxide solution and 0.5 ml of 0.03% potassium dichromate solution, heat to boiling and cool. Add 4-5 drops of sulfuric acid, heat gently on a water bath; a violet colour is produced.

(2) To 1 ml of methanol solution add 3-4 drops of 0.1 mol/L sodium hydroxide solution and 0.5 ml of 0.1% sodium nitrite solution, heat to boiling and cool. Add 0.5 ml of hydrochloric acid; a green colour is produced, turning to yellow on standing.

Other requirements Complies with the general requirements for creams (Appendix I F).

Assay **Reference solution** Dissolve 50 mg of indometacin CRS, accurately weighed, in a 100 ml volumetric flask with methanol and dilute to volume, mix well. Measure accurately 5 ml to a 100 ml volumetric flask, dilute with a mixture of phosphate BS (pH 7.0)-methanol (1 : 1) to volume, mix well.

Test solution Dissolve a quantity accurately weighed, equivalent about 50 mg of indometacin in a separator, with 50 ml of cyclohexane and 25 ml of methanol by shaking, allow to stand, separate the lower layer of solution to another separator containing 100 ml of 2% sodium chloride solution. Extract the supernatant solution with 15 ml and 10 ml of methanolic sodium chloride solution (To 20 ml of 10% sodium chloride solution dilute with methanol to 100 ml, mix well) separately, combine the lower layer of extracts to the above separator and extract with 25 ml, 20 ml and 10 ml of chloroform separately, filter all the chloroform extracts through a same filter containing 10 g dehydrated sodium sulfate to a beaker. Evaporate the extracts in a water bath of 70°C to dryness. Add 20 ml of methanol to the residue, warm to dissolve, cool and filter, transfer the filtrate to a 100 ml volumetric flask, wash the filter with methanol, combine the washing and the filtrate, dilute with methanol to volume, mix well. Measure accurately 5 ml to a 100 ml volumetric flask, dilute with a mixture of phosphate BS (pH 7.0)-methanol (1 : 1) to volume, mix well, filter, collect the successive filtrate as the test solution.

Procedure Measure the absorbances of the two solutions at 320 nm (Appendix IV A), calculate the content of $C_{19}H_{16}ClNO_4$.

Category As described under Indometacin.

Strength 10 g : 100 mg

Storage Preserve in tightly closed containers, stored in cool place, protected from light.

Indometacin Enteric-coated Tablets

Indometacin Enteric-coated Tablets contain not less than 90.0% and not more than 110.0% of the labelled amount of indometacin ($C_{19}H_{16}ClNO_4$).

Description Enteric-coated tablets with white core.

Identification Powder finely some tablets with enteric-coating removed. Shake thoroughly a quantity of the powdered tablets equivalent to about 10 mg of indometacin with 10 ml of water, add 2 drops of 20% sodium hydroxide solution and shake to dissolve indometacin, filter. The filtrate complies with test (1) for Identification described under Indometacin.

Drug release Carry out the drug release test (Appendix X D, method 2 (2)), with the apparatus of dissolution test method 1 and using 1000 ml of 0.1 mol/L hydrochloric acid solution as the release medium, adjust the rotational speed of the basket to 100 rpm. Stop rotating after exactly 2 hours, elevate the basket from the liquid, no tablet shows signs of cracks or disintegration. Replace the basket into 1000 ml of phosphate BS (pH 6.8), keep the same rotational speed as above. Withdraw a quantity of the solution after exactly 45 minutes and filter. Measure the absorbance of the filtrate at 320 nm (Appendix IV A). Calculate the dissolution of $C_{19}H_{16}ClNO_4$ from each tablet, taking 196 as the value of A (1%, 1cm). Not less than 70% of the labelled amount is dissolved.

Other requirements Comply with the general requirements for tablets (Appendix I A).

Assay Weigh accurately and powder finely 10 tablets with enteric-coating removed. Weigh accurately a quantity of the powdered tablets equivalent to about 25 mg of indometacin and dissolve in 35 ml of methanol in a 50 ml volumetric flask with warming. Allow to cool to room temperature, add methanol to volume, shake thoroughly and filter. Measure

accurately 5 ml of the successive filtrate to a 100 ml volumetric flask, add methanol-phosphate BS (pH 7.2) (1 : 1) to volume and mix well. Measure the absorbance of the resulting solution at 320 nm (Appendix IV A), calculate the content of $C_{19}H_{16}ClNO_4$, taking 193 as the value of A (1%, 1 cm).

Category As described under Indometacin.

Strength 25 mg

Storage Preserve in tightly closed containers, protected from light.

Indometacin Liniment

Indometacin liniment contains not less than 90.0% and not more than 110.0% of the labelled amount of indometacin ($C_{19}H_{16}ClNO_4$).

Description A clear, slightly viscous yellow liquid.

Identification Dilute 2 ml equivalent to about 20 mg of indometacin to 10 ml with water, add 2-3 drops of 20% sodium hydroxide solution, and mix well. The resulting solution complies with the following tests.

(1) To 1 ml add 0.3 ml of 0.03% potassium dichromate solution, heat to boiling and cool to room temperature, add 2-3 drops of sulfuric acid, warm gently on a water bath; a red-violet colour is produced.

(2) To 1 ml add 0.3 ml of 0.1% sodium nitrite solution, heat to boiling and cool to room temperature, add 0.5 ml of hydrochloric acid; a green colour is produced, which turns to yellow gradually on standing.

pH value 6.0-7.0 (Appendix VI H).

Ethanol content 52.0%-62.0% (Appendix VII E).

Other requirements Complies with the general requirements for liniments (Appendix I T).

Assay Measure accurately a quantity equivalent to about 50 mg of indometacin into a 100 ml volumetric flask, dilute to volume with methanol, and mix well. Measure accurately 5 ml into another 100 ml volumetric flask, dilute to volume with methanol-phosphate BS (pH 7.2) (1 : 1), and mix well. Measure the absorbance of the resulting solution at 320 nm (Appendix IV A), calculate the content of $C_{19}H_{16}ClNO_4$, taking 193 as the value of A (1%, 1 cm).

Category As described under Indometacin.

Strength (1) 20 ml : 200 mg (2) 50 ml : 500 mg

Storage Preserve in tightly closed containers, stored in a cool place and protected from light.

Indometacin Suppositories

Indometacin Suppositories contain not less than 90.0% and not more than 110.0% of the labelled amount of indometacin ($C_{19}H_{16}ClNO_4$).

Description White to pale yellow suppositories made by incorporating indometacin in fatty bases.

Identification To a quantity equivalent to about 50 mg of indometacin add a mixture of 50 ml of water and 0.5 ml of 20% sodium hydroxide solution, heat and stir to dissolve indometacin. Allow to cool until the mass just solidifies and filter. The filtrate complies with test (1) for Identification described under Indometacin.

Related Substances Use the test solution obtained in Assay as the test solution. Measure accurately 1 ml of the test solution in 100 ml volumetric flask and dilute with 50% ethanol solution to the volume, use as the reference solution. Proceed as described under Assay, inject 50 μ l of the reference solution into the column, adjust the attenuation so that the principal peak height in the chromatogram is 20% of the full scale of the chart. Inject separately 50 μ l each of the test and reference solution, into the column and record the chromatogram for 3 times the retention time of the principal peak. The sum of the areas of all peaks other than principle peak in the chromatogram obtained with the test solution is not greater than twice of the principal peak area of the reference solution.

Other requirements Comply with the general requirements for suppositories (Appendix I D).

Assay Carry out the method for high performance liquid chromatography (Appendix V D), using a column packed with octadecylsilane bonded silica gel and a mixture of acetonitrile -0.1 mol/L glacial acetic acid solution (50 : 50) as the mobile phase. Detection wavelength is at 228 nm, and the number of theoretical plates of the column is not less than 2000, calculated with reference to the peak of indometacin, the resolution factor between the peaks of indometacin and the adjacent impurity complies with the related requirements. Weigh accurately 10 suppositories, cut carefully and mix well. To a quantity equivalent to about 25 mg of indometacin, accurately weighed, add a quantity of ethanol to 50 ml volumetric flask, heat on water bath to dissolve indometacin, cool to room temperature and dilute with ethanol to the volume, mix well and filter. Measure accurately 5 ml of the successive filtrate in 25 ml volumetric flask and dilute with 50% ethanol solution to the volume, mix well, use as the test solution. Inject 20 μ l of the test solution into the column and record the chromatogram. Weigh accurately 25 mg of indometacin CRS to 50 ml volumetric flask and add a quantity of ethanol, shake to dissolve indometacin and dilute with ethanol to the volume, mix well. Measure accurately a quantity and dilute with 50% ethanol solution to produce the reference solution of 0.1 mg per ml. Repeat the operation, calculate the content of $C_{19}H_{16}ClNO_4$ with respect to the peak area obtained in the chromatogram by the external standard method.

Category As described under Indometacin.

Strength (1) 25 mg (2) 50 mg (3) 100 mg

Storage Preserve in tightly closed containers, protected from light and stored at a temperature below 25°C.

Indometacin Patches

Indometacin patches contain not less than 80.0% and not more than 120.0% of the labelled amount of indometacin ($C_{19}H_{16}ClNO_4$).

Description Colourless, transparent, polyacrylate patches.

Identification Measure 40 ml of the methanol solution obtained in the Assay, equivalent to about 10 mg of indometacin, evaporate to dryness on a water bath. Add 10 ml of water and 2 drops of 20% sodium hydroxide solution to the residue, stir to dissolve indometacin and filter. The filtrate complies with the following tests.

(1) To 1 ml add 0.3 ml of 0.03% potassium dichromate solution, heat to boiling and cool to room temperature, add 2-3 drops of sulfuric acid, warm gently on a water bath; a violet colour is produced.

(2) To 1 ml add 0.3 ml of 0.1% sodium nitrite solution,

heat to boiling and cool, add 0.5 ml of hydrochloric acid; a green colour is produced, which turns to yellow gradually on standing.

Content uniformity Comply with the requirements for Content uniformity (Appendix X E). Cut a patch in chips and remove the protective layer. Transfer into a dried conical flask with stopper, add 50 ml, accurately measured, of methanol, carry out the method described under the Assay, beginning at the words "allow to stand in the place of protecting from light...". Calculate the content of $C_{19}H_{16}ClNO_4$. The limit of Content uniformity is $\pm 20\%$.

Other requirements Comply with the general requirements for patches (Appendix I V), with the exception of both content uniformity and drug release.

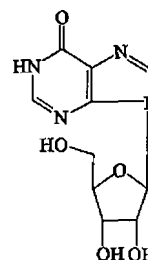
Assay Transfer 5 patches, cut in chips and remove the protective layer, into a dried conical flask with stopper, add 250 ml, accurately measured, of methanol, allow to stand in the place of protecting from light for 2 hours, mix well. Measure accurately 5 ml into a 50 ml volumetric flask, dilute to volume with methanol and mix well. Measure the absorbance of the resulting solution at 320 nm (Appendix IV A), calculate the content of $C_{19}H_{16}ClNO_4$, taking 179 as the value of A (1%, 1cm).

Category As described under Indometacin.

Strength 7.2 cm \times 7.2 cm, 12.5 mg (indometacin)

Storage Preserve in tightly closed containers, stored in a dry place.

Inosine



$C_{10}H_{12}N_4O_5$ 268.23

[58-63-9]

Inosine is 9 β -D-ribofuranosylhypoxanthine. It contains not less than 98.0% and not more than 102.0% of $C_{10}H_{12}N_4O_5$, calculated on the dried basis.

Description A white crystalline powder; odourless; taste, slightly bitter.

Sparingly soluble in water; insoluble in chloroform or ethanol; freely soluble in dilute hydrochloric acid and sodium hydroxide TS.

Identification (1) To a quantity of a solution containing 0.01% of the substance being examined add the same volume of 3, 5-dihydroxytoluene solution (dissolve 0.1 g of 3, 5-dihydroxytoluene and 0.1 g of ferric chloride in 100 ml of hydrochloric acid), mix well, heat in a water bath for 10 minutes; a green colour is produced.

(2) To a quantity of a solution containing 1% of the substance being examined, add several drops of ammoniated silver nitrate TS, a white colloidal precipitate is produced.

(3) The retention time of principal peak of the substance being examined in the chromatogram obtained in the Assay is identical with that of the principal peak of inosine CRS.

(4) The infrared absorption spectrum (Appendix IV C) is concordant with the reference spectrum of Inosine (Appendix

XVI).

Transmittance of solution Dissolve 0.5 g in 50 ml of water, the transmittance at 430 nm is not less than 98.0% (Appendix IV A) (for Injections).

Loss on drying When dried to constant weight at 105°C, loses not more than 1.0% of its weight (Appendix VII L).

Residue on ignition Not more than 0.1% (for Injections); or not more than 0.2% (for preparations of oral administration) (Appendix VII N).

Heavy metals Carry out the limit test for heavy metals (Appendix VII H, method 3), using 1.0 g; not more than 0.001%.

Related substances Dissolve a quantity of the substance being examined in water to produce a solution of 0.5 mg per ml as the test solution. Transfer 1 ml of the test solution, accurately measured, into a 100 ml volumetric flask, dilute with water to volume, mix well, and use this solution as the reference solution. Carry out the method described under the Assay. Inject 20 μ l of the reference solution into the column. Adjust the attenuation so that the principal peak height in the chromatogram is 20% of the scale of the chart. Inject separately 20 μ l each of the test solution and the reference solution into the column, and record the chromatogram for twice the retention time of the principal peak. The sum of the areas of all peaks other than the principal peak in the chromatogram obtained with the test solution are not greater than the area of the principal peak in the chromatogram obtained with the reference solution.

Assay Carry out the method for high performance liquid chromatography (Appendix V D), using a column packed with octadecylsilane bonded silica gel and a mixture of methanol-water (10 : 90) as the mobile phase. The detection wavelength is 248 nm and the number of the theoretical plates of the column is not less than 2000, calculated with reference to the peak of inosine. Dissolve a quantity of the substance being examined, accurately weighed, in water to produce a solution of about 20 μ g per ml, mix well. Inject 20 μ l into the column, record the chromatogram. Repeat the operation, using inosine CRS instead of the substance being examined, calculate the content of $C_{10}H_{12}N_4O_5$ with respect to the peak area obtained in the chromatogram by the external standard method.

Category Medicines for improving cell metabolism.

Storage Preserve in well closed containers, protected from light.

Preparation (1) Inosine Capsules (2) Inosine Injection
(3) Inosine Oral Solution (4) Inosine Tablets

Inosine Capsules

Inosine capsules contain not less than 90.0% and not more than 110.0% of the labelled amount of Inosine ($C_{10}H_{12}N_4O_5$).

Description Capsules containing white powder.

Identification (1) Dissolve a quantity of the contents of the capsules equivalent to about 0.2 g of inosine in 10 ml of water by shaking, filter and the successive filtrate complies with test (1) and (2) for identification described under Inosine.

(2) The retention time of principal peak of the substance being examined in the chromatogram obtained in the Assay is identical with that of the principal peak of inosine CRS.

Other requirements Comply with the general requirements

for capsules (Appendix I E).

Assay Transfer an accurately weighed quantity of the triturated contents obtained in the test for weight variation of contents equivalent to about 0.1 g of inosine into a 100 ml volumetric flask, add about 70 ml of water, shake thoroughly to dissolve the inosine, dilute with water to volume and mix well. Filter and transfer 2 ml of the successive filtrate, measured accurately, into a 100 ml volumetric flask, dilute with water to volume, mix well. Carry out the method as described under Inosine, and calculate the content of $C_{10}H_{12}N_4O_5$.

Category As described under Inosine.

Strength 0.2 g

Storage Preserve in tightly closed containers, protected from light.

Inosine Injection

Inosine injection is a sterile solution of Inosine in Water for Injection. It contains not less than 90.0% and not more than 110.0% of the labelled amount of Inosine ($C_{10}H_{12}N_4O_5$).

Description A clear, colourless or almost colourless liquid.

Identification Complies with tests (1), (2) and (3) for Identification described under Inosine.

pH value 8.5-9.5 (Appendix VI H)

Related substances Dilute a quantity of the substance being examined with water to produce a solution of 0.5 mg per ml as the test solution. Transfer 1 ml of the test solution, measured accurately, into a 50 ml volumetric flask, dilute with water to volume, mix well, and use this solution as the reference solution. Carry out the method described under Inosine. The sum of the areas of all peaks other than the principal peak in the chromatogram obtained with the test solution is not greater than the area of the principal peak in the chromatogram obtained with the reference solution.

Bacterial endotoxin Carry out the test for bacterial endotoxin (Appendix XI E): less than 0.25 EU per mg.

Other requirements Complies with the general requirements for injections (Appendix I B)

Assay Dilute a quantity of the substance being examined, measured accurately, with water to produce a solution of about 20 μ g per ml. Carry out the Assay described under Inosine, and calculate the content of $C_{10}H_{12}N_4O_5$.

Category As described under Inosine.

Strength (1) 2 ml : 50 mg (2) 2 ml : 100 mg
(3) 5 ml : 100 mg (4) 5 ml : 200 mg

Storage Preserve in well closed containers, protected from light.

Inosine Oral Solution

Inosine oral solution is a solution of Inosine in water with stevioside or sucrose. It contains not less than 90.0% and not more than 110.0% of the labelled amount of Inosine ($C_{10}H_{12}N_4O_5$).

Description A colourless to slightly yellow liquid.

Identification Complies with tests (2) and (3) for Identification described under Inosine.

pH value 7.5-8.5 (Appendix V H)

Other requirements Comply with the general requirements for oral solutions (Appendix I O).

Assay Dilute a quantity of the oral solution being examined, accurately measured, with water to produce a solution of about 20 µg per ml. Carry out the Assay described under Inosine, and calculate the content of $C_{10}H_{12}N_4O_5$.

Category As described under Inosine.

Strength (1) 10 ml : 0.1 g (2) 10 ml : 0.2 g
(3) 20 ml : 0.2 g (4) 20 ml : 0.4 g

Storage Preserve in tightly closed containers, protected from light.

Inosine Tablets

Inosine tablets contain not less than 93.0% and not more than 107.0% of the labelled amount of Inosine ($C_{10}H_{12}N_4O_5$).

Description White or sugar coated or film coated tablets with white core.

Identification (1) Powder 2 tablets, add 10 ml of water to dissolve inosine, filter and the successive filtrate complies with tests (1) and (2) for Identification described under Inosine.

(2) The retention time of principal peak of the substance being examined in the chromatogram obtained in the Assay is identical with that of the principal peak of inosine CRS.

Other requirements Comply with the general requirements for tablets (Appendix I A)

Assay Weigh accurately and powder finely 10 tablets (for sugar coated tablets remove the coating). Transfer an accurately weighed quantity of the powdered tablets equivalent to about 0.1 g of inosine into a 100 ml volumetric flask, add 70 ml of water, shake thoroughly to dissolve inosine, dilute with water to volume and mix well. Filter and transfer 2 ml of the successive filtrate, measured accurately, into a 100 ml volumetric flask, dilute with water to volume, mix well. Carry out the Assay described under Inosine, and calculate the content of $C_{10}H_{12}N_4O_5$.

Category As described under Inosine.

Strength 0.2 g

Storage Preserve in tightly closed containers, protected from light.

Insulin

Insulin is a hypoglycemic principle obtained from the pancreas of pigs or cattle. It has a potency of not less than 26 Units per mg, calculated on the dried basis.

Description A white or almost white crystalline powder. Practically insoluble in water, ethanol, chloroform or ether; freely soluble in solutions of mineral acids or sodium hydroxide.

Identification (1) 10 mg is completely soluble in 6 ml of water with pH of 2.5-3.0. Adjust with alkali to pH 5.1-5.3, a precipitate is produced, which is redissolved on acidifying to pH 2.5-3.5. Adjust with alkali to pH 8.0-8.5, only a slight turbidity is formed.

(2) Carry out the method for high performance liquid

chromatography (Appendix V D), using a column packed with octadecylsilane bonded silica gel (5 µm) and maintain the column temperature at 40°C. a mixture of 0.1 mol/L sodium dihydrogen phosphate solution (adjust to pH 3.0 with phosphoric acid) -acetonitrile (73 : 27) or a mixture of suitable proportion (contain 0.1 mol/L sodium sulfate) as the mobile phase with a flow rate of 1 ml per minute. Detection wavelength is 214 nm. Dissolve separately the substance being examined and Insulin (pigs or cattle) RS in 0.01 mol/L hydrochloric acid solution to produce the solutions of 40 Units per ml. Inject 5 µl of the resulting solutions into the column respectively. The retention time of the two principal peaks is concordant with each other.

(3) Dissolve an accurately weighed quantity in water (adjust with acid to pH 2.5-3.0) to produce a solution of 5 Units per ml. At 20-30°C, inject subcutaneously into five mice, weighing 20-24 g each, using 0.25 ml per 20 g of mouse's weight. The solution causes convulsions of not less than four mice in 2 hours. Immediately after convulsions occur in a mouse, inject intraperitoneally into that mouse 1 ml of 10% Dextrose Injection, the convulsions should be relieved.

Light absorption The light absorption of a solution of 0.5 mg per ml in 0.01 mol/L hydrochloric acid solution exhibits a maximum at 276 nm; the absorbance is 0.48-0.55 (Appendix IV A).

Related proteins Dissolve an accurately weighed quantity of Insulin RS in urea solution (to 96 g of urea, 1.5 g of trometamol and 12 ml of 1 mol/L hydrochloric acid solution add water to 200 ml) to produce five solutions containing (1) 0.5 µg per 100 µl, (2) 1.0 µg per 100 µl, (3) 3.0 µg per 100 µl, (4) 5.0 µg per 100 µl and (5) 100 µg per 100 µl. Dissolve an accurately weighed quantity of the substance being examined in above urea solution to produce two solutions containing (6) 100 µg per 100 µl and (7) 500 µg per 100 µl. Carry out the method for polyacrylamide gel electrophoresis (Appendix V F).

The test is not valid unless a band can be detected in the gel prepared with solution (1) and a gradation is observed in the intensity of staining of the gels prepared with solutions (1) to (4).

The principal band in the gel obtained with solution (6) and solution (7) corresponds in position to the principal band in the gel obtained with solutions (5).

In the gel prepared with solution (6) any band corresponding in position to a faster band behind the principal band in the gel prepared with solution (5) is not more intense than the principal band in the gel prepared with solution (3). In the gel prepared with solution (7) any band corresponding in position to a slower band behind the principal band in the gel prepared with solution (5) is not more intense than the principal band in the gel prepared with solution (1).

Proteins of higher molecular weight Dissolve about 100 mg of the substance being examined, accurately weighed, in 1 mol/L acetic acid solution to produce a solution of 50 mg per ml. Carry out the method for column chromatography (Appendix V C), using a column (80 cm × 2 cm) packed with about 50 g of glucosan gel G-50 (type of Ultra-fine) and 1 mol/L acetic acid solution as the eluent with a flow rate 22-25 ml per hour. Detection wavelength is 280 nm. Inject 0.6 ml of the resulting solution into the column. The sum of the areas of all the peaks eluting before the principal peak is not more than 1% of the total area of the peaks.

Nitrogen Carry out the method for determination of nitrogen (Appendix VII D, method 2): not less than 14.5% and not more than 16.0% of N, calculated on the dried basis.

Loss on drying When dried to constant weight at 105°C, loses not more than 10.0% of its weight (Appendix VIII L), using 0.2 g.

Zinc Transfer, separately, an accurately weighed quantity equivalent to about 40 Units and 1.6 ml of zinc standard solution (dissolve 44 mg of zinc sulfate, accurately weighed, in water in a 100 ml volumetric flask, dilute with water to volume and mix well. Transfer accurately 10 ml to another 100 ml volumetric flask, add water to volume and mix well, each ml of this solution is equivalent to 10 μ g of Zn) to two 10 ml volumetric flasks. To each flask add 2 ml of boric acid potassium chloride BS (pH 9.0) and 1 ml of freshly-prepared zincon test solution (dissolve 0.13 g of zincon in 2 ml of sodium hydroxide TS, add water to 100 ml), dilute with water to volume and mix well. Allow to stand for 30 minutes and measure the absorbances of the two solutions at 620 nm (Appendix IV A). Calculate the content of zinc: not more than 0.4 mg per 1000 Units.

Assay Carry out the biological assay of insulin (Appendix III G), the estimated potency is not less than 91% and not more than 110% of the labelled potency.

Category Hypoglycemic.

Storage Preserve in tightly closed containers, Stored at a temperature not higher than -15°C .

Preparation (1) Neutral Insulin Injection
(2) Protamine Zinc Insulin Injection

Neutral Insulin Injection

Neutral Insulin Injection is a sterile solution of Insulin (pigs or cattle) in Water for Injection. It has a potency of not less than 91% and not more than 116% of the labelled potency. It may contain 1, 4-1.6 g of glycine and 0.22 g of m-cresol per 100 ml.

Description A clear, colourless or almost colourless liquid.

Identification (1) Adjust the pH value of the injection with acid to about 5.5, a precipitate is produced, which is redissolved on acidifying to pH 2.5-3.5.

(2) Comply with test (2) for Identification described under Insulin. In the chromatogram, the first appearance is the peak of preservative, then appears the peak of Insulin, the retention time of the peak of insulin is identical with the principal peak of the same strain of insulin RS.

(3) Comply with test (3) for Identification described under Insulin.

pH value 6.6-8.0 (Appendix VI H).

Related proteins Transfer 10 ml, accurately measured, into a evaporating dish, after dried in vacuum, add the urea solution to produce solutions containing 2.6. Units per 100 μ l and 13 Units per 100 μ l (equivalent to about 100 μ g and 500 μ g respectively). Comply with the requirement described under Insulin, using the resulting solutions.

Zinc Comply with the requirement described under Insulin, using a quantity equivalent to about 40 Units.

Bacterial endotoxin Carry out the test for bacterial endotoxin (Appendix XI E): less than 0.8 EU per Unit.

Other requirements Complies with the general requirements for injections (Appendix I B).

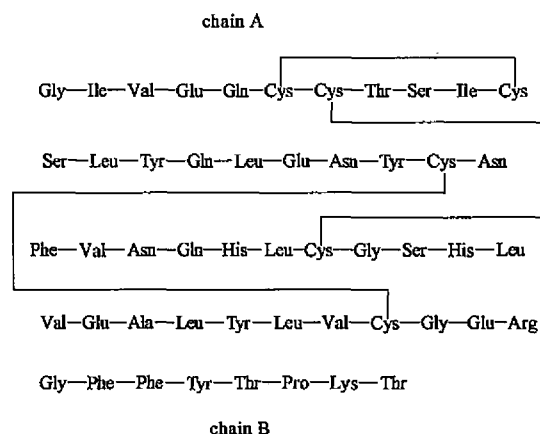
Assay Carry out the biological assay of insulin (Appendix III G), it complies with the related requirements for potency.

Category As described under Insulin.

Strength (1) 10 ml : 400 Units (2) 10 ml : 800 Units

Storage Preserve in well closed containers, stored in a cold place, avoid freezing.

Recombinant Human Insulin



$\text{C}_{257}\text{H}_{383}\text{N}_{65}\text{O}_{77}\text{S}_6$ 5807.69

Recombinant Human Insulin is a protein having 51 amino acid residues and produced by a method based on recombinant DNA technology. The content of human insulin $\text{C}_{257}\text{H}_{383}\text{N}_{65}\text{O}_{77}\text{S}_6$ plus A_{21} desamido human insulin is not less than 95.0% and not more than 105.0%, calculated on the dried basis. By convention, for the purpose of labelling insulin preparations, 0.0347 mg of human insulin is equivalent to 1 IU of insulin.

Host-cell and vector-derived DNA and host-cell derived proteins are potential specific impurities related to the manufacturing process and must be controlled strictly during the manufacturing process, the host cell derived proteins content of human insulin derived from a recombinant DNA process, determined by an appropriate and validated method, is not more than 10 ppm, the host cell or vector derived DNA content and limit of human insulin derived from a recombinant DNA process that utilizes prokaryotic or eukaryotic host cells are determined by a validated method.

Description A white or almost white crystalline powder. Practicably insoluble in water, ethanol or ether; freely soluble in dilute hydrochloric acid solution or dilute sodium hydroxide solution.

Identification (1) The retention time of principal peak of the substance being examined in the chromatogram obtained in the Assay is identical with that of the principal peak of recombinant human insulin RS.

(2) Dissolve a quantity substance being examined in 0.1% trifluoroacetic acid solution to produce a solution of 10 mg per ml, measure 20 μ l of above solution, add 20 μ l of 0.2 mol/L trimetamol-hydrochloric acid BS (pH 7.3), 20 μ l of 0.1% V8 enzyme solution and 140 μ l of water, mix well, warm in a water bath at 37°C for 2 hours, then add 3 μ l of phosphoric acid, as test solution. Repeat the operation, using a quantity of recombinant human insulin CRS instead of the substance being examined, as reference solution. Carry out the method for Assay, using a mixture of 0.2 mol/L sulfate BS (pH 2.3) -acetonitrile (90 : 10) as mobile phase A, and a mixture of acetonitrile-water (50 : 50) as mobile

Description It contains a pale yellow to yellow clear oily liquid; odour, slightly alliaceous.

Identification Transfer a few drops of the content of the capsules to a dry test tube, heat gently. It becomes red to brown with the evolution of purplish iodine vapour which turns moistened starch-iodide TP to blue.

Acidity Dissolve 1.0 g in 5 ml of chloroform, add 2 drops of phenolphthalein IS and 0.25 ml of sodium hydroxide (0.1 mol/L) VS, mix well, a pink colour is produced.

Free iodine To 1.0 g of the content add 5 ml of chloroform, mix well, add 10 ml of water and 0.5 g of potassium iodide, shake thoroughly, add 1 ml of starch IS, mix well. If a bluish-violet colour is produced in the aqueous layer, add 0.25 ml of sodium thiosulfate (0.02 mol/L) VS, the colour disappears.

Other requirements Comply with the general requirements for capsules (Appendix I E).

Assay Weigh accurately a quantity of the mixed contents obtained in the test for weight variation, equivalent to about 100 mg of iodine, to a conical flask, add 20 ml of ethanolic potassium hydroxide solution (2→10). Reflux at 90°C on a water bath for 1 hour, transfer while hot to a suitable vessel, rinse the condenser and conical flask with a small quantity of hot water, and combine the washings to the same vessel. Cool to the room temperature, add 5 ml of glacial acetic acid, carry out the method for potentiometric titration (Appendix VII A), titrate with silver nitrate (0.1 mol/L) VS. Each ml of silver nitrate (0.1 mol/L) VS is equivalent to 12.69 mg of I.

Category Iodine replenisher

Strength (1) 10 mg (I) (2) 20 mg (I) (3) 50 mg (I)
(4) 0.1 g (I) (5) 0.2 g (I)

Storage Preserve in tightly closed containers, protected from light, stored in a dry, cool and dark place.

Iodine

I 126.90 [7553-56-2]

Iodine contains not less than 99.5% of I.

Description Grayish-black or bluish-black crystals in plate form or lump with a metallic luster; heavy, brittle; odour, characteristic. Volatilizes room temperature.

Freely soluble in ethanol, ether or carbon disulfide; soluble in chloroform; sparingly soluble in carbon tetrachloride; practically insoluble in water; soluble in aqueous solution of potassium iodide or sodium iodide.

Identification (1) Its ethanolic solution or aqueous solution containing potassium iodide or sodium iodide exhibits a reddish-brown colour. It exhibits a purple colour in chloroform. (2) A saturated aqueous solution yields a blue colour in the presence of starch solution. The colour disappears when the solution is boiled and reappears on cooling but does not reappear when boiled for a longer time.

Chlorides and bromides Triturate 1.0 g with 40 ml of water, added in several portions, filter. Add a small quantity of zinc powder to decolourise the solution. To 10 ml of the solution add gradually 5 ml of ammonia TS and 5 ml of silver nitrate TS. Allow to stand for 5 minutes, filter into a 50 ml Nessler cylinder, add water to produce 40 ml. Add dropwise nitric acid until the solution is neutral to litmus TP, add 1 ml of nitric acid and sufficient water to produce 50 ml. Any opalescence produced is not more pronounced than that of a reference solution, prepared by diluting 3.5 ml of

standard sodium chloride solution with water to produce 40 ml, add 1 ml of nitric acid, 1 ml of silver nitrate TS and sufficient water to produce 50 ml (0.014%).

Sulfates Volatilize 1.0 g by heating on a water bath. Wash the residue with 40 ml of water in several portions. Transfer the washings to a 50 ml Nessler cylinder, filter, if necessary. Carry out the limit test for sulfates (Appendix VII B). Any opalescence produced is not more pronounced than that of a reference using 3.0 ml of potassium sulfate standard solution (0.03%).

Non-volatile matter Heat the substance being examined in an evaporating dish, previously dried to constant weight at 105°C, on a water bath until the iodine is completely volatilized dry to constant weight at 105°C. The residue is not more than 0.05%.

Assay Place 5 ml of 20% potassium iodide solution in a weighing bottle and weigh accurately. Add about 0.4 g of the substance being examined, finely powdered, weigh again accurately and swirl to effect dissolution. Transfer the solution to a conical flask with stopper, add water to produce 50 ml. Add 1 ml of dilute hydrochloric acid and titrate with sodium thiosulfate (0.1 mol/L) VS. Add 2 ml of starch IS when the end point is nearly approached, continue the titration until the blue colour disappears. Each ml of sodium thiosulfate (0.1 mol/L) VS is equivalent to 12.69 mg of I.

Category Antiseptics

Storage Preserve in tightly closed containers, protected from light and stored in a cool place.

Preparation (1) Iodine Glycerol (2) Iodine Tincture

Iodine Glycerol

Iodine Glycerol contains not less than 0.90% (g/ml) and not more than 1.10% (g/ml) of iodine (I).

Formula	Iodine	10 g
	Potassium iodide	10 g
	Water	10 ml
	Glycerol	a sufficient quantity
	To make	1000 ml

Processing Dissolve potassium iodide in water, add iodine with stirring to effect dissolution. Add glycerol to produce 1000 ml and mix well.

Description A reddish-brown viscous liquid with the characteristic odour of iodine.

Identification (1) Dilute 1 ml with water and add sodium thiosulfate TS, the brown colour is discharged. (2) To the solution obtained in the above test add sodium cobaltinitrite TS, a yellow precipitate is produced.

Assay *Iodine* Transfer 20 ml, accurately measured, to a conical flask with stopper, add 100 ml of water and 1 drop of acetic acid. Titrate with sodium thiosulfate (0.1 mol/L) VS until the solution is colourless. Each ml of sodium thiosulfate (0.1 mol/L) VS is equivalent to 12.69 mg of I.

Category As described under Iodine.

Storage Preserve in tightly closed containers, protected from light.

Iodine Tincture

Iodine Tincture contains not less than 1.80% (g/ml) and not more than 2.20% (g/ml) of iodine (I); not less than 1.35% (g/ml) and not more than 1.65% (g/ml) of potassium iodide (KI).

Formula	Iodine	20 g
	Potassium iodide	15 g
	Ethanol	500 ml
	Water	a sufficient quantity
	To make	1000 ml

Processing Dissolve potassium iodide in 20 ml of water, add iodine and ethanol with stirring to effect dissolution. Add sufficient water to produce 1000 ml.

Description A reddish-brown clear liquid with the characteristic odour of iodine and ethanol.

Identification (1) Add 1 drop to a mixture of 1 ml of starch IS and 10 ml of water. A deep blue colour is produced. (2) Evaporate 5 ml on a water bath to dryness, ignite gently to expel all free iodine, dissolve the residue in water. The solution yields the reactions characteristic of potassium salts and iodides (Appendix III).

y I
with stopper, add 1 drop of acetic acid and titrate with sodium thiosulfate (0.1 mol/L) VS until the solution is colourless. Each ml of sodium thiosulfate (0.1 mol/L) VS is equivalent to 12.69 mg of I.

Potassium iodide To the above titrated solution add 2 ml of acetic acid and 0.1 ml of eosin sodium IS, titrate with silver nitrate (0.1 mol/L) VS until the precipitate changes from yellow to rose-red. Subtract the volume (ml) of sodium thiosulfate (0.1 mol/L) VS consumed from the volume (ml) of silver nitrate (0.1 mol/L) VS consumed. Each ml of silver nitrate (0.1 mol/L) VS is equivalent to 16.60 mg of KI.

Category As described under Iodine.

Storage Preserve in tightly closed containers, protected from light and stored in cool place.

Compound Iodine Oral Solution

Compound Iodine Oral Solution contains not less than 4.5% and not more than 5.5% of iodine (I), not less than 9.5% and not more than 10.5% of potassium iodide (KI).

Formula	Iodine	50 g
	Potassium iodide	100 g
	Water	a sufficient quantity
	To make	1000 ml

Processing Dissolve iodine and potassium iodide in 100 ml of water, add a quantity of water to produce 1000 ml.

Description A clear, dark brown liquid with an odour characteristic of iodine.

Identification (1) Add 1 drop to a mixture of 1 ml of starch IS and 10 ml of water, a deep blue colour is produced. (2) Evaporate 5 ml to dryness on a water bath, ignite gently until free iodine is expelled completely. Dissolve the residue

in water, the resulting solution yields the reactions characteristic of potassium salts and iodides (Appendix III).

other requirements Complies with the general requirements for oral solutions (Appendix I O).

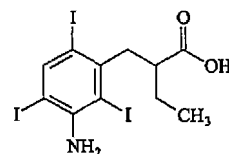
Assay Iodine Measure accurately 15 ml to a 50 ml volumetric flask, dilute to volume with water, mix well. Measure accurately 10 ml of the resulting solution to a conical flask with stopper, add 1 drop of acetic acid, titrate with sodium thiosulfate (0.1 mol/L) VS until the solution becomes colourless. Each ml of sodium thiosulfate (0.1 mol/L) VS is equivalent to 12.69 mg of I.

Potassium iodide To the above titrated solution add 2 ml of acetic acid and 0.5 ml of eosin sodium IS. Titrate with silver nitrate (0.1 mol/L) VS until the precipitate changes from yellow to rose-red. Subtract the volume (ml) of sodium thiosulfate (0.1 mol/L) VS consumed from the volume (ml) of silver nitrate (0.1 mol/L) VS consumed. Each ml of silver nitrate (0.1 mol/L) is equivalent to 16.60 mg of KI.

Category Iodine preparations

Storage Preserve in tightly closed containers, protected from light.

Iopanoic Acid



$C_{11}H_{12}I_3NO_2$ 570.93

[96-83-3]

Iopanoic Acid is α -ethyl- β -(3-amino-2, 4, 6-triiodophenyl) propanoic acid. It contains not less than 98.5% of $C_{11}H_{12}I_3NO_2$, calculated on the dried basis.

Description An almost white to slightly red powder; odourless; tasteless.

Soluble in ethanol or acetone; sparingly soluble in chloroform; practically insoluble in water; freely soluble in sodium hydroxide solution.

Melting range 152-158°C, with decomposition (Appendix VI C).

Identification (1) Heat 10 mg in a crucible gently; violet vapours of iodine are evolved.

(2) To about 20 mg add 0.2 ml of hydrochloric acid and heat gently until one drop is left. Cool to room temperature, add 0.2 ml of 0.1 mol/L sodium nitrite solution and allow to stand for several minutes. Add 2 ml of sodium carbonate TS and 20 mg of resorcinol; an orange red colour is produced.

(3) The light absorption of a solution of 10 μ g per ml in 0.04% sodium hydroxide solution exhibits a maximum at 230 nm; the absorbance is about 0.70 (Appendix IV A).

(4) The infrared absorption spectrum (Appendix IV C) is concordant with the reference spectrum of iopanoic acid (Appendix XVI).

Halides Dissolve 1.0 g in 3 ml of sodium hydroxide TS, add 10 ml of water, add 3 ml of nitric acid solution (1→2) dropwise, shake, filter and wash the residue with a quantity of water. Combine the filtrate and washings in a 50 ml Nessler cylinder, add water to produce 40 ml. Carry out the limit test for chlorides (Appendix VIII A). Any opalescence

produced is not more pronounced than that of a reference using 7.0 ml of sodium chloride standard solution (0.007%).

Loss on drying When dried to constant weight at 105°C, loses not more than 0.5% of its weight (Appendix VII L).

Residue on ignition Not more than 0.1% (Appendix VII N).

Assay Reflux about 0.3 g, accurately weighed, with 30 ml of sodium hydroxide TS and 1 g of zinc powder for 30 minutes. Cool, rinse the condenser with a small quantity of water, filter, wash the flask and filter with three quantities of water, each of 15 ml. To the combined filtrate and washings, add 5 ml of glacial acetic acid and 1 ml of eosin sodium IS, titrate with silver nitrate (0.1 mol/L) VS. Each ml of silver nitrate (0.1 mol/L) VS is equivalent to 19.03 mg of $C_{11}H_{12}I_3NO_2$.

Category Diagnostic agent

Storage Preserve in tightly closed containers, protected from light.

Preparation Iopanoic Acid Tablets

Iopanoic Acid Tablets

Iopanoic Acid Tablets contain not less than 95.0% and not more than 105.0% of the labelled amount of iopanoic acid ($C_{11}H_{12}I_3NO_2$).

Description Almost white to slightly red tablets.

Identification Stir a quantity of finely powdered tablets equivalent to about 0.1 g of iopanoic acid with 4 ml of chloroform to dissolve iopanoic acid, filter and evaporate to dryness; the residue complies with tests (1) and (2) for Identification described under Iopanoic Acid.

Other requirements Comply with the general requirements for tablets (Appendix I A).

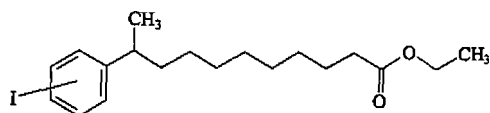
Assay Weigh accurately and powder 10 tablets. Carry out the Assay described under Iopanoic Acid using an accurately weighed quantity of powdered tablets, equivalent to about 0.25 g of iopanoic acid. Each ml of silver nitrate (0.1 mol/L) VS is equivalent to 19.03 mg of $C_{11}H_{12}I_3NO_2$.

Category As described under Iopanoic Acid.

Strength 0.5 g

Storage Preserve in tightly closed containers, protected from light.

Iophendylate



$C_{19}H_{29}IO_2$ 416.34

[1320-11-2]

Iophendylate is a mixture of isomers of ethyl iodophenylundecanoate, consisting mainly of ethyl 10-(4-iodophenyl) undecanoate. It contains not less than 97.0% of $C_{19}H_{29}IO_2$.

Description A colourless to pale yellow, viscous oily liquid; odour, faintly estereal.

Very soluble in ethanol, chloroform or ether; insoluble in

water.

Relative density 1.248-1.260 (Appendix VI A).

Refractive index 1.525-1.527 (Appendix VI F).

Saponification value 132-142 (Appendix VII H).

Identification To 1 ml add 15 ml of water and 7 g of potassium dichromate, then add cautiously and slowly 10 ml of sulfuric acid while cooling in a water bath. When the reaction has subsided, reflux the mixture on a water bath for 2 hours. Pour the cooled contents into 25 ml of water, filter and wash the precipitate with water and dry. Sublime the dried precipitate; white needle crystals are produced.

Acidity Dissolve 1.0 ml in 10 ml of neutralized ethanol (neutral to phenolphthalein IS), add 3 drops of phenolphthalein IS; the solution turns to red on addition of not more than 0.25 ml of sodium hydroxide (0.1 mol/L) VS.

Free iodine Shake 1.0 ml with 5 ml of chloroform, 10 ml of potassium iodide TS and 1 ml of starch IS; no blue or violet colour is produced in aqueous layer.

Iodine attached to the straight chain Reflux 0.50 g with 10 ml of ethanolic potassium hydroxide (1 mol/L) VS on a water bath for 1 hour. Add 40 ml of water and 5 ml of sulfuric acid (1→2), cool to room temperature and filter. Wash the precipitate with 10 ml of water, combine the filtrate and washing. Add 1-2 drops of potassium permanganate solution (1→10000) and 1 ml of starch IS. If a blue colour is produced, titrate with silver nitrate (0.1 mol/L) VS until the blue colour disappears; not more than 0.20 ml of silver nitrate (0.1 mol/L) VS is consumed.

Assay Carry out the method for oxygen flask combustion (Appendix VII C), using about 20 mg, accurately weighed, use a mixture of 2 ml of sodium hydroxide TS and 10 ml of water as the absorbing liquid. After the completion of combustion, add 10 ml of bromine-acetic acid solution (dissolve 10 g of potassium acetate in a quantity of glacial acetic acid, add 0.4 ml of bromine and sufficient glacial acetic acid to produce 100 ml). Stopper the flask, shake and allow to stand for several minutes. Add about 1 ml of formic acid and rinse the mouth of the flask with water. Sweep off any bromine vapour with a current of air. Add 2 g of potassium iodide, stopper the flask and mix well, then titrate with sodium thiosulfate (0.02 mol/L) VS. Add starch IS when the end point is nearly approached, continue the titration until the blue colour disappears. Perform a blank determination and make any necessary correction. Each ml of sodium thiosulfate (0.02 mol/L) VS is equivalent to 1.388 mg of $C_{19}H_{29}IO_2$.

Category Diagnostic agent

Storage Preserve in tightly closed containers, protected from light.

Preparation Iophendylate Injection

Iophendylate Injection

Iophendylate Injection is a sterile preparation of iophendylate. It contains not less than 97.0% of iophendylate ($C_{19}H_{29}IO_2$).

Description A colourless to pale yellow, viscous oily liquid.

Identification Complies with the test for Identification described under Iophendylate.

Acidity and Free iodine Complies with the tests described under Iophendylate.

Other requirements Complies with the general requirements for injections (Appendix I B).

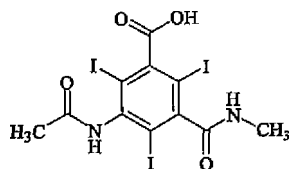
Assay As described under Iophendylate.

Category As described under Iophendylate.

Strength (1) 2 ml (2) 3 ml (3) 5 ml

Storage Preserve in well closed containers, protected from light.

Iotalamic Acid



$C_{11}H_9I_3N_2O_4$ 613.92

[2276-90-6]

Iotalamic Acid is 3-(acetamino)-5-[(methylamino) carbonyl]-2, 4, 6-triiodobenzoic acid. It contains not less than 98.5% of $C_{11}H_9I_3N_2O_4$, calculated on the dried basis.

Description A white, crystalline powder; odourless; tasteless. Slightly soluble in water or ethanol; insoluble in chloroform; easily soluble in alkaline hydroxide solutions.

Identification (1) Heat gently about 10 mg in a crucible, violet iodine vapour is produced with decomposition. (2) The infrared absorption spectrum (spectrum IV C) is concordant with the reference spectrum of iotalamic acid (Appendix XVI).

Chlorides Dissolve 0.5 g in 20 ml of water and a few drops of ammonia TS, add in dropwise of 1.5 ml of nitric acid with stirring to precipitate iotalamic acid. Filter, wash the precipitate with a small quantity of water. Combine the filtrate and washings in a Nessler cylinder, add water to a volume of 40 ml. Carry out the limit test for chlorides (Appendix VII A), any opalescence produced is not more pronounced than that of a reference using 2.5 ml of sodium chloride standard solution (0.005%).

Free iodine Dissolve 0.20 g in 2.0 ml of sodium hydroxide TS, add 2.5 ml of dilute sulfuric acid to precipitate iotalamic acid. Allow it to stand for 10 minutes, shake on adding 5 ml of chloroform, no colour is produced in chloroform layer.

Amino compound Dissolve 1.25 g in a mixture of 5 ml of water and 5 ml of sodium hydroxide TS, dilute with water to 100 ml and shake well. To 10 ml of the solution add 5 ml of 0.1 mol/L sodium nitrite and 10 ml of hydrochloric acid solution (9 → 100), shake well, allow to stand for 10 minutes, add 5 ml of 2.5% ammonium sulfamate solution shake well and allow the reaction mixture to stand for 5 minutes. Add 2 ml of alkaline β -naphthol TS, 15 ml of sodium hydroxide TS and water to a volume of 50 ml and shake well. Measure the absorbance of the resulting solution at 485 nm (Appendix IV A); not more than 0.25.

Loss on drying When dried to constant weight at 105°C, loses not more than 1.0% of its weight (Appendix VIII L).

Residue on ignition Not more than 0.1% (Appendix VIII N), using 1.0 g.

Heavy metals Carry out the limit test for heavy metals (Appendix VIII H, method 2), using the residue obtained in

Residue on ignition; not more than 0.001%.

Assay Heat under reflux about 0.4 g, accurately weighed, with 30 ml of sodium hydroxide TS and 1.0 g of zinc powder for 30 minutes. Cool, wash the condenser with a small amount of water. Filter, wash the flask and the filter with water for 3 times, each of 15 ml. Combine the filtrate and washings, add 5 ml of glacial acetic acid and 5 drops of eosin sodium IS, titrate with silver nitrate (0.1 mol/L) VS. Each ml of silver nitrate (0.1 mol/L) VS is equivalent to 20.46 mg of $C_{11}H_9I_3N_2O_4$.

Category Diagnostic agent.

Storage Preserve in tightly closed containers, protected from light.

Preparation Meglumine Iotalamate Injection

Meglumine Iotalamate Injection

Meglumine Iotalamate Injection is a sterile solution of equivalent molecular amount of iotalamic acid and meglumine in Water for Injection. It contains not less than 95.0% and not more than 105.0% of the labelled amount of meglumine iotalamate ($C_{11}H_9I_3N_2O_4 \cdot C_7H_{17}NO_5$).

Description A clear, colourless to pale yellow, liquid.

Identification (1) Evaporate about 1 ml to dryness, heat the residue gently, a violet vapour of iodine is produced. (2) To about 0.1 ml add 1 ml of ferric chloride TS and 2 ml of 20% sodium hydroxide solution in dropwise, a brownish-red precipitate is produced which is dissolved to produce a brownish-red solution. (3) Stir well 4 ml with 40 ml of water and 5 ml of dilute hydrochloric acid, a white precipitate is produced. Filter, wash the residue with 2 quantities of 10 ml of water and dry it at 105°C for 4 hours. Its infrared absorption spectrum (Appendix IV C) is concordant with the reference spectrum of iotalamic acid (Appendix XVI).

pH value 6.0-8.0 (Appendix VI H).

Colour Not more intense than that of reference solution Y₆ (Appendix IX A, method 1).

Iodide Carry out the test for Iodide described under Sodium Diatrizoate Injection, using a quantity equivalent to about 1.0 g of meglumine iotalamate. It complies with the requirements.

Pyrogens Complies with the test for pyrogens (Appendix XI D), using 3 ml per kg of the rabbit's weight.

Other requirements Complies with the general requirement for injections (Appendix I B).

Assay Dilute a quantity equivalent to about 6 g of meglumine iotalamate to volume with water in 100 ml volumetric flask, and shake well. Carry out the Assay described under diatrizoic acid, beginning at the words "add 30 ml of sodium hydroxide TS and 1.0 g of powdered zinc", using 10 ml accurately measured, of injection. Each ml of silver nitrate (0.1 mol/L) VS is equivalent to 26.97 mg of $C_{11}H_9I_3N_2O_4 \cdot C_7H_{17}NO_5$.

Category Diagnostic agent.

Strength (1) 1 ml : 0.125 g (2) 10 ml : 6 g
(3) 20 ml : 12 g (4) 50 ml : 30 g
(5) 100 ml : 60 g

Storage Preserve in well closed containers, protected from

light.

Iron Dextran

Iron Dextran is a complex compound of ferric hydroxide with dextran of weight average molecular mass between 5000 and 7500. It contains not less than 25.0% of iron, calculated on the dried basis.

Description A dark brown to brown black crystalline powder, odourless.

Sparingly soluble in hot water; insoluble in ethanol.

Identification (1) Dissolve about 40 mg in 5 ml of water by heating, cool to room temperature, add ammonia TS, no precipitate is produced. To about 80 mg add 20 ml of water and 5 ml of hydrochloric acid, heat to boiling for 5 minutes, cool to room temperature, add excessive ammonia TS, a red brown precipitate is produced, filter, wash the precipitate with water, add a quantity of hydrochloric acid to dissolve, add water to 20 ml, the solution yields the reactions characteristic of iron (Appendix III).

(2) Dissolve about 40 mg in 500 ml of water by heating, transfer 1 ml to a tube, add 2 ml of anthrone solution (dissolve 0.4 g of anthrone in a mixture of 10 ml of water and 190 ml of sulfuric acid) along the wall of the tube in an ice bath, mix well and heat, the colour changes from green to blue green.

Free iron Weigh about 0.10 g substance being examined in a 50 ml of Nessler cylinder, in 10 ml of water, shake to dissolve, add 1.0 ml of iron standard stock solution and 15 ml of potassium thiocyanate solution (dissolve 15 g of potassium thiocyanate in 50 ml of water in a 100 ml volumetric flask, add 50 ml of water and 15 ml of acetone, dilute with water to volume and mix well) and 24 ml of acetone mix well, allow to stand and examine the colour of the supernatant. Any colour produced is not more intense than that of a reference solution using 3.0 ml of iron standard stock solution (0.2%).

Chlorides To 0.25 g add 2 ml of water and 1 ml of sulfuric acid, heat until the solution turns to pale yellow, cool to room temperature, dilute with water to 200 ml. Carry out the limit test for chlorides (Appendix VIII A), using 2 ml. Any opalescence produced is not more pronounced than that of a reference solution using 5.0 ml of sodium chloride standard solution (2.0%).

Molecular weight and molecular weight distribution Weigh a quantity of substance being examined, equivalent to 40 mg iron dextran, in a test tube, add 2 ml of water, heat to dissolve, cool to room temperature, add 1 ml of 4 mol/L sodium dihydrogen phosphate, mix well, standing over night, add mobile phase to 10 ml, filter, using the successive filtrate as the test solution. Repeat the preparation, using 4 to 5 of dextran CRS with known molecular mass, as the reference solutions. Carry out the method for size exclusion chromatography (Appendix H), using a specific gel column for polysaccharides, and 0.71% sodium sulfate solution containing 0.02% sodium azide as the mobile phase and a differential refractometer as detector. The column temperature is at 35°C and flow rate is 0.5 ml per minute. Dissolve separately a quantity of glucose and blue dextran 2000 in mobile phase to produce a solution containing about 10 mg per ml. Inject 20 µl into the column, record the retention time t_r and t_0 . The retention times obtained from chromatogram of the test solution and the reference solution are all between t_r and t_0 . The number of the theoretical plates of the column is not less than 5000, calculated with reference the peak of glucose. Inject 20 µl of the reference

solutions and 50 µl of the test solution separately into the column, record the chromatogram. The data is processed by special software for GPC. Distribution coefficient D (M_w/M_n) is not more than 2.0.

Loss on drying When dried to constant weight at 105°C, loses not more than 5.0% of its weight (Appendix VIII L).

Heavy metals To 1.0 g add 6 ml of water and 4 ml of nitric acid, heat in a water bath until the volume is about 2-3 ml, cool, add 2 ml of sulfuric acid, heat in a water bath until the solution changes to white powder entirely, if not, add 1-2 ml of nitric acid again, heat in a water bath, cool, add 15 ml of hydrochloric acid, heat to dissolve, extract with four 8 ml portions of isobutyl acetate, discard organic layers, evaporate the combined aqueous layers on a water bath to 8 ml, cool, add 1 drop of phenolphthalein IS, neutralize with ammonia TS, add 2 ml of acetate BS (pH 3.5), add water to 25 ml. Carry out the limit test for heavy metals (Appendix VIII H, method 1); not more than 0.002%.

Arsenic To 0.4 g add 0.5 g of calcium hydroxide, mix well, ignite slowly until thoroughly charred, ignite again at 500-600°C until the incineration is complete, cool to room temperature, add 14 ml of hydrochloric acid and 7 ml of water to dissolve, transfer to a distillator, add 0.5 ml of acidic stannous chloride TS, distill to about 5 ml, introduce the distillate to a bottle for Arsenic containing 10 ml of water, carry out the limit test for arsenic (Appendix VIII J, method 1); not more than 0.0005%.

Assay Measure accurately about 0.3 g to a conical flask with stopper, add 34 ml of water and 2 ml of sulfuric acid, heat until the solution turns to orange yellow, cool to room temperature, add potassium permanganate TS dropwise just until a pink colour is produced and persist for 5 seconds, add 30 ml of hydrochloric acid and 30 ml of potassium iodide TS, stopper tightly, allow to stand for 3 minutes, add 50 ml of water, titrate with sodium thiosulfate (0.1 mol/L) VS, add 2 ml of starch IS towards the end of titration, continue the titration until the blue colour disappears. Each ml of sodium thiofulfate (0.1 mol/L) VS is equivalent to 5.585 mg of iron (Fe).

Category Antiexsanguine

Storage Preserve in tightly closed containers, protected from light.

Preparation (1) Iron Dextran Injection
(2) Iron Dextran Tablets

Iron Dextran Injection

Iron Dextran Injection is a sterile colloidal solution of iron dextran. It contains not less than 95.0% and not more than 105.0% of the labelled amount of iron (Fe).

Description A dark brown colloidal solution.

Identification (1) Dilute 0.5 ml with 5 ml of water, the solution complies with test (1) for Identification described under Iron Dextran.

(2) Dilute 1 ml to 1000 ml with water, the solution complies with test (2) for Identification described under Iron Dextran.

pH value 5.2~6.5 (Appendix VI H).

Chlorides Carry out the test for Chlorides described under Iron Dextran, using 1 ml. Any opalescence produced is not more pronounced than that of a reference solution using 5.0 ml of sodium chloride standard solution (0.5%).

Molecular weight and weight distribution Measure a quantity, equivalent to 5.0 mg iron, add 1 ml of 4 mol/L sodium dihydrogen phosphate, mix well, standing over night, add water to 10 ml, filter. Inject 5 μ l of the successive filtrate into the column, carry out the method described under Iron Dextran, the weight average molecular weight (Mw) of dextran is about 5000 to 7500, and the molecular weight distribution coefficient D (Mw/Mn) is not less than 2.0.

Heavy metals Carry out the test for Heavy metals described under Iron Dextran, using 2 ml, not more than 0.0015%.

Arsenic Carry out the test for Arsenic described under Iron Dextran, using 1 ml, not more than 0.0002%.

Iron absorption in the injection site *preparation of test solution and reference solution* Using two healthy rabbits, each weighing between 1.5 kg and 2.5 kg, clip the legs free from hair over the inner sites and swab the area with a bactericidal solution. Use one leg of each rabbit for injecting substance being examined, and the other leg for reference. Inject each site with a dose of 0.4 ml (for the strength of 25 mg of iron per ml) or 0.2 ml (for the strength of 50 mg of iron per ml) per kg of body weight in the following manner. Insert the needle in the distal end of the semitendinosus muscle, passing through the sartorius and entering the vastus medialis. Seven days after the injection, sacrifice the rabbits, carefully dissect the coloured vastus medialis of the site of injection. Homogenize the flesh and transfer the homogenized paste to a 1000 ml beaker, add 75 ml of 2 mol/L sodium hydroxide solution and sufficient water over the flesh, cover the beaker with a lid and boil until no solid matter exists, cool, cautiously add 50 ml of sulfuric acid, heat the mixture till boiling and add about 10 ml of nitric acid dropwise in several portions until no charring occurs, heat until the excess of nitric acid is boiled off, cool, transfer to a 250 ml volumetric flask, add water to volume. Use this solution as the test solution. Repeat the operation, beginning at the word "carefully dissect...", using the same site and equal amount of the vastus medialis from the reference leg as the reference solution.

Calibration curve Transfer separately 0 ml, 0.5 ml, 1.0 ml, 2.0 ml and 3.0 ml of iron standard stock solution (containing 100 μ g of iron per ml), accurately measured, to each 100 ml volumetric flask, add 10 ml of 20% citric acid solution and 1 ml of thioglycollic acid respectively, mix well, add strong ammonia solution dropwise until the purplish-red colour is fully developed, dilute with water to volume. Measure the absorbance at 530 nm (Appendix IV A), using the solution obtained with 0 ml of the iron standard stock solution as a blank solution. A regression equation is obtained with the amount of iron versus the corresponding absorbance.

Procedure To 5.0 ml of the test solution, accurately measured, add 3 ml of sulfuric acid, heat till fuming, add a quantity of nitric acid, continue heating until the solution turns to colourless, cool, add 20 ml of water, boil for 3 minutes, cool, add 10 ml of 20% citric acid solution and 1 ml of thioglycollic acid, add strong ammonia solution dropwise until the purplish-red colour is fully developed. Transfer to a 100 ml volumetric flask, dilute with water to volume. Use this solution as a test solution to be determined. Measure the absorbance (A_T) at 530 nm (Appendix IV A), using the solution obtained with 0 ml of the iron standard stock solution described under calibration curve as a blank solution. Calculate the amount of iron (Fe_T) from the regression equation. Repeat the operation, using the reference solution instead of the test solution, calculate the amount of iron (Fe_R) from the regression equation.

The content of iron in injection site (%)

$$= \frac{Fe_T - Fe_R}{\text{The amount of iron injected}} \times 50 \times 100\%$$

The content of unabsorbed iron: not more than 20%

Iron Dextran Tablets

Iron Dextran Tablets contain not less than 90.0% and not more than 110.0% of the labelled amount of iron dextran, calculated on iron.

Description Sugar coated tablets with dark brown core.

Identification A quantity of the powdered tablets equivalent to about 12.5 mg of iron complies with tests (1) and (2) for Identification described under Iron Dextran.

Free iron Comply with the requirements described under Iron Dextran (0.2%), using 10 tablets.

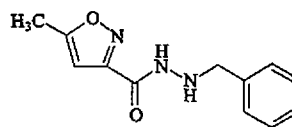
Other requirements Comply with the general requirements for Tablets (Appendix I A).

Assay Weigh accurately and powder 20 tablets with sugar coating removed. Weigh accurately a quantity equivalent to about 100 mg of iron, carry out the Assay described under Iron Dextran.

Category, Storage As described under Iron Dextran.

Strength 25 mg (iron)

Isocarboxazid



$C_{12}H_{13}N_3O_2$ 231.25

[59-63-2]

Isocarboxazid is 5-methyl-3-isoxazolecarboxylic acid 2-benzylhydrazide. It contains not less than 98.5% of $C_{12}H_{13}N_3O_2$, calculated on the dried basis.

Description A white or almost white crystalline powder; odour, slightly characteristic. Very soluble in chloroform; soluble in ethanol; slightly soluble in water.

Melting point 105-108°C (Appendix VI C).

Identification (1) Dissolve about 10 mg in 10 ml of acetone, add 0.2 ml each of water and 1% solution of ammonium molybdate in dilute hydrochloric acid, an orange colour is produced.

(2) Dissolve about 15 mg in ethanol, add 1 ml of 0.1% ethanolic p-dimethylaminobenzaldehyde solution, a yellow colour is produced.

(3) The infrared absorption spectrum (Appendix IV C) is concordant with the spectrum of isocarboxazid CRS.

Chloride To 0.1 g add 3 ml of 30% hydrogen peroxide solution, 5 ml of 2 mol/L sodium hydroxide solution and 7 ml of water, heat to boil for 2 minutes, allow to cool, add water to produce 40 ml, add dropwise dilute nitric acid to neutralize the solution. Carry out the limit test for chlorides (Appendix VIII A), any opalescence produced is not more pronounced than that of a reference solution using 2 ml of sodium chloride standard solution (0.02%).

Related substances Dissolve a quantity in methanol to produce a solution of 50 mg per ml as test solution. Transfer

12.5 mg of methyl 5-methyl-3-isoxazolecarboxylate CRS to 50 ml volumetric flask, add methanol to dissolve and dilute to volume, mix well, use the solution as reference solution (1). Dissolve 12.5 mg of 1-benzyl-3-methyl-5-aminopyrazole CRS in 50 ml of methanol, add 1 g of sodium carbonate, shake thoroughly for 2 minutes and filter, use the filtrate as reference solution (2). Carry out the thin-layer chromatography (Appendix V B), using silica gel GF₂₅₄ as the coating substance and a mixture of ethyl acetate-*n*-heptane (3 : 2) as the mobile phase. Apply separately to the same plate 20 µl each of above three solutions, after developing and removal of the plate, dry it in air and examine under ultraviolet light (254 nm). Any spot in the chromatogram other than the principal spot obtained with the test solution is not more intense than the principal spot obtained with the reference solution (1) (0.5%). Spray with a mixture of ferric chloride-potassium ferricyanide (mix 20 ml of 10% ferric chloride solution and 20 ml of 20% potassium ferricyanide solution, freshly prepared). Any spot in the chromatogram other than the principal spot obtained with the test solution is not more intense than the principal spot obtained with the reference solution (2) (0.5%).

Loss on drying When dried in vacuum at 60°C for 4 hours, loses not more than 0.3 % of its weight (Appendix VII L).

Residue on ignition Not more than 0.1 % (Appendix VIII N).

Assay Dissolve about 0.5 g, accurately weighed, in 20 ml of glacial acetic acid, add 10 ml of hydrochloric acid and 40 ml of water. Carry out the method for dead-stop titration (Appendix VII A), titrate with sodium nitrite (0.1 mol/L) VS. Each ml of sodium nitrite (0.1 mol/L) VS is equivalent to 23.13 mg of C₁₂H₁₃N₃O₂.

Category Antidepressant.

Storage Preserve in tightly closed containers, protected from light.

Preparation Isocarboxazid Tablets

Isocarboxazid Tablets

Isocarboxazid Tablets contain not less than 90.0% and not more than 110.0% of the labelled amount of isocarboxazid (C₁₂H₁₃N₃O₂).

Description White tablets.

Identification (1) To a quantity of the powdered tablets equivalent to about 10 mg of isocarboxazid, add 5 ml of acetone to dissolve isocarboxazid and filter. Add 4 drops of water and 4 drops of a solution of 1% ammonium molybdate in dilute hydrochloric acid to the filtrate, an orange colour is produced.

(2) To a quantity of the powdered tablets equivalent to about 10 mg of isocarboxazid, add 5 ml of ethanol to dissolve isocarboxazid and filter. Add 1 ml of a solution of 1% dimethylaminobenzaldehyde in ethanol (contain 1% hydrochloric acid), a yellow colour is produced.

Content uniformity Comply with the requirements (Appendix X E). Take 1 tablet in a 100 ml volumetric flask with a quantity of phosphate BS (pH 7.6), shake to dissolve isocarboxazid and dilute to volume with the same solvent, mix well and filter, measure accurately 5 ml of the successive filtrate in a 50 ml volumetric flask, dilute with phosphate BS (pH 7.6) to volume, mix well, use as the test solution. Dissolve a quantity of isocarboxazid CRS, accurately weighed, in phosphate BS (pH 7.6) to produce a solution of 10 µg per ml as reference solution. Measure the

absorbance of the resulting solutions at 232 nm (Appendix IV A), calculate the content of C₁₂H₁₃N₃O₂.

Dissolution Comply with the dissolution test (Appendix X C, method 2), using 900 ml of phosphate BS (pH 7.6) as the dissolution medium, adjust the rotational speed of paddle to 100 rpm. Withdraw the solution at 45 exact minutes and filter, use the successive filtrate as the test preparation. Dissolve a quantity of isocarboxazid CRS, in phosphate BS (pH 7.6) to produce a solution of 10 µg per ml as reference preparation. Measure the absorbances of the resulting solutions at 232 nm (Appendix IV A). Calculate the dissolution of C₁₂H₁₃N₃O₂ from each tablet, not less than 75% of the labelled amount is dissolved.

Other requirements Comply with the general requirements for tablets (Appendix I A).

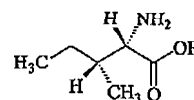
Assay Weigh accurately and powder 80 tablets. Dissolve a quantity of the powdered tablets equivalent to about 0.35 g of isocarboxazid, accurately weighed, in 20 ml of glacial acetic acid, add 10 ml of hydrochloric acid and 40 ml of water. Carry out the method for dead-stop titration (Appendix VII A), titrate with sodium nitrite (0.1 mol/L) VS. Each ml of sodium nitrite (0.1 mol/L) VS is equivalent to 23.13 mg of C₁₂H₁₃N₃O₂.

Category As described under Isocarboxazid.

Strength 10 mg

Storage Preserve in tightly closed containers, protected from light.

Isoleucine



C₆H₁₃NO₂ 131.17

[73-32-5]

Isoleucine is (L)-2-amino-3-methylpentanoic acid. It contains not less than 98.5% of C₆H₁₃NO₂, calculated on the dried basis.

Description White crystals or a white crystalline powder; odourless; taste, slightly bitter. Sparingly soluble in water; practically insoluble in ethanol or ether.

Specific optical rotation +38.9° to +41.8°, in a solution of 40 mg per ml in 6 mol/L hydrochloric acid solution (Appendix VI E).

Identification The infrared absorption spectrum (Appendix IV C) is concordant with the reference spectrum of isoleucine (Appendix XVI).

Acidity Dissolve 0.20 g in 20 ml of water, pH 5.5-6.5 (Appendix VI H).

Transmittance of solution Dissolve 0.5 g in 20 ml of water, the transmittance at 430 nm is not less than 98.0% (Appendix IV A).

Chlorides Carry out the limit test for chlorides (Appendix VII A), using 0.25 g. Any opalescence produced is not more pronounced than that of a reference solution using 5.0 ml of sodium chloride standard solution (0.02%).

Sulfates Carry out the limit test for sulfates (Appendix VII B), using 1.0 g. Any opalescence produced is not more pronounced than that of a reference solution using 2.0 ml of

potassium sulfate standard solution (0.02%).

Ammonium Carry out the limit test for ammonium (Appendix VIII K), using 0.10 g. Any colour produced is not more intense than that of a reference solution using 2.0 ml of ammonium chloride standard solution (0.02%).

Other amino acids Carry out the method for thin-layer chromatography (Appendix V B), using silica gel G as the coating substance and a mixture of *n*-butanol-water-glacial acetic acid (3 : 1 : 1) as the mobile phase. Apply separately to the plate 5 μ l of each of two solutions of the substance being examined in water containing (1) 4 mg per ml, (2) 20 μ g per ml. After developing and removal of the plate, dry in air and spray with ninhydrin solution (dissolve 1 g of ninhydrin in 50 ml of acetone) and heat at 80°C until the colour is produced and examine immediately. Any spot other than the principal spot in the chromatogram, obtained with solution (1) is not more intense than the principal spot obtained with solution (2).

Loss on drying When dried at 105°C for 3 hours, loses not more than 0.2% of its weight (Appendix VIII L).

Residue on ignition Not more than 0.1%, using 1.0 g (Appendix VIII N).

Heavy metals Carry out the limit test for heavy metals (Appendix VIII H, method 2), using the residue obtained in the test for Residue on ignition: not more than 0.001%.

Arsenic Dissolve 2.0 g in 5 ml of water, add 1 ml of sulfuric acid and 10 ml of sulfite acid. evaporate to about 2 ml on a water bath, add 5 ml of water and add dropwise ammonia TS until phenolphthalein IS change the colour. Add 5 ml of hydrochloric acid and sufficient water to produce 28 ml. Carry out the limit test for arsenic (Appendix VIII J, method 1): not more than 0.0001%.

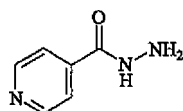
Bacterial endotoxin Carry out the test for bacterial endotoxin (Appendix XI E): less than 20 EU per g of isoleucine (for injection).

Assay Dissolve about 0.10 g, accurately weighed, in 1 ml of dehydrated formic acid. Add 25 ml of glacial acetic acid. Carry out the method for potentiometric titration (Appendix VII A), titrate with perchloric acid (0.1 mol/L) VS. Perform a blank determination and make any necessary correction. Each ml of perchloric acid (0.1 mol/L) VS is equivalent to 13.12 mg of $C_6H_7N_3O$.

Category Amino acid.

Storage Preserve in tightly closed containers, protected from light.

Isoniazid



$C_6H_7N_3O$ 137.14

[54-85-3]

Isoniazid is 4-pyridinecarboxylic acid hydrazide. It contains not less than 99.0% of $C_6H_7N_3O$, calculated on the dried basis.

Description Colourless crystals or a white or almost white crystalline powder; odourless; taste, slightly sweet at first and then bitter; deteriorates gradually on exposure to light. Freely soluble in water; slightly soluble in ethanol; very slightly soluble in ether.

Melting point 170-173°C (Appendix VI C).

Identification (1) Dissolve about 0.1 g in 5 ml of water, add 1 ml of 10% solution of vanillin in ethanol, mix well, heat gently, cool to room temperature, yellow crystals are produced; filter, recrystallize with dilute ethanol. The crystals, after drying at 105°C, melt at 228-231°C, with decomposition (Appendix VI C).

(2) Dissolve about 10 mg in 2 ml of water in a test tube, add 1 ml of ammoniated silver nitrate TS, bubbles and a black turbidity are produced immediately, and a silver mirror is formed on the wall of the tube.

(3) The infrared absorption spectrum (Appendix IV C) is concordant with the reference spectrum of isoniazid (Appendix XVI).

Acidity or alkalinity Dissolve 0.50 g in 10 ml of water, pH 6.0-8.0 (Appendix VI H).

Clarity and colour of solution A solution of 1.0 g in 10 ml of water is clear and colourless. Any opalescence is not more pronounced than that of reference suspension I (Appendix IX B); any colour produced is not more intense than equal volume of reference solution (mix 3.0 ml of standard potassium chromate CS and standard copper sulfate CS, add water to produce 250 ml).

Free hydrazine Prepare a solution of 50 mg per ml in water as the test solution, and a solution of hydrazine sulfate CRS of 0.20 mg (equivalent to 50 μ g of free hydrazine) per ml as the reference solution. Carry out the method for thin-layer chromatography (Appendix V B), using silica gel G as the coating substance, and a mixture of isopropyl alcohol-acetone (3 : 2) as the mobile phase. Apply separately to the plate 10 μ l of the test solution and 2 μ l of the reference solution. After developing and removal of the plate, dry it in air, spray with 4-dimethylamino-benzaldehyde TS and allow to stand for 15 minutes. No yellow spot corresponding to the hydrazine sulfate spot in the chromatogram is obtained with the test solution.

Loss on drying When dried at 105°C to constant weight, loses not more than 0.5% of its weight (Appendix VIII L).

Residue on ignition Not more than 0.1% (Appendix VIII N), using 1.0 g.

Heavy metals Carry out the limit test for heavy metals, using the residue obtained in the test for Residue on ignition (Appendix VIII H, method 2): not more than 0.001%.

Sterility Complies with the test for sterility (Appendix XI H) (for injection).

Assay Dissolve about 0.2 g, accurately weighed, in water in a 100 ml volumetric flask, add water to volume, mix well. Measure accurately 25 ml, add 50 ml of water, 20 ml of hydrochloric acid and 1 drop of ethoxychrysoidine IS. Titrate slowly, at a temperature of 18-25°C, with potassium bismuthate (0.01667 mol/L) VS. Each ml of potassium bromate (0.01667 mol/L) VS is equivalent to 3.429 mg of $C_6H_7N_3O$.

Category Antituberculous.

Storage Preserve in hermetically sealed containers, protected from light.

Preparation (1) Isoniazid for Injection
(2) Isoniazid Tablets

Isoniazid for Injection

Isoniazid for Injection is a sterile powder of isoniazid. It contains not less than 95.0% and not more

than 105.0% of the labelled amount of isoniazid ($C_6H_7N_3O$), calculated on the basis of average content.

Description Colourless crystals a white or almost white crystalline powder.

Identification Complies with tests for Identification described under Isoniazid.

Colour of solution Dissolve the contents of 5 containers in 10 ml of water. Any colour produced is not more intense than equal volume of a reference solution (3.0 ml of standard potassium dichromate CS and 0.10 ml of standard copper sulfate CS, dilute to 250 ml with water).

Acidity or alkalinity, Free hydrazine Complies with the test described under Isoniazid.

Loss on drying When dried at 105°C to constant weight, loses not more than 1.0% of its weight (Appendix VIII L).

Sterility Dissolve the contents of each of containers in sterile water separately to produce solutions of 20 mg per ml, the solutions comply with the test for sterility (Appendix XI H).

Other requirements Complies with the general requirements for injections (Appendix I B).

Assay Carry out the Assay described under Isoniazid, using about 0.2 g, accurately weighed, of the mixed contents obtained in the test for weight variation. Each ml of potassium bromate (0.01667 mol/L) VS is equivalent to 3.429 mg of $C_6H_7N_3O$.

Category As described under Isoniazid.

Strength 0.1 g

Storage Preserve in well closed containers, protected from light.

Isoniazid Tablets

Isoniazid Tablets contain not less than 95.0% and not more than 105.0% of the labelled amount of isoniazid ($C_6H_7N_3O$).

Description White tablets.

Identification Shake a quantity of the powdered tablets equivalent to about 0.1 g of isoniazid with 10 ml of water, filter. The filtrate complies with test (2) for Identification described under Isoniazid.

Dissolution Carry out the method for dissolution test (Appendix X C, method 1), using 1000 ml of water as the dissolution medium, adjust the rotational speed of the basket to 100 rpm. Withdraw 5 ml of the solution at 30 exact minutes and filter. To a quantity of the successive filtrate, measured accurately, add water to produce a solution of 10–20 µg per ml. Measure the absorbance of the solution at 263 nm (Appendix IV A), taking 307 as the value of A (1%, 1 cm). Calculate the dissolution of $C_6H_7N_3O$ from each tablet, not less than 60% of the labelled amount is dissolved.

Other requirements Comply with general requirements for tablets (Appendix I A).

Assay Weigh accurately and powder 20 tablets. Dissolve a quantity of the powdered tablets equivalent to about 0.2 g of isoniazid, accurately weighed, in a quantity of water in a 100 ml volumetric flask with shaking, add water to volume, mix well and filter. Carry out the Assay described under

Isoniazid, using accurately 25 ml of the successive filtrate, beginning at the words "add 50 ml of water, 20 ml of hydrochloric acid...". Each ml of potassium bromate (0.01667 mol/L) VS is equivalent to 3.429 mg of $C_6H_7N_3O$.

Category As described under Isoniazid.

Strength (1) 50 mg (2) 100 mg (3) 300 mg

Storage Preserve in tightly closed containers, protected from light and stored in a dry place.

Isophane Protamine Recombinant Human Insulin Injection

Isophane Protamine Recombinant Human Insulin Injection is a sterile suspension of recombinant human insulin and protamine containing antiseptic agent. It has a potency of not less than 90.0% and not more than 110.0% of the labelled potency of recombinant human insulin and contains not less than 80% and not more than 110% of the labelled amount of antiseptic agent.

Description A white or almost white suspension; dispersed uniformly on shaking. When examined under a microscope, the particles are seen to be rod-shaped crystals, the majority with a maximum diameter greater than 1 µm, but rarely exceeding 60 µm, free from aggregates.

Identification To each ml add 3 µl of 9.6 mol/L hydrochloric acid solution to obtain a clear solution, which complies with test (1) for Identification described under Recombinant Human Insulin.

pH value 6.9–7.8 (Appendix VI H).

Related proteins To each ml add 3 µl of 9.6 mol/L hydrochloric acid solution as a test solution, measure 50 µl and carry out the test for Related proteins described under Recombinant human insulin, the total related proteins are not more than 8.0%.

High molecular weight proteins To each ml add 3 µl of 9.6 mol/L hydrochloric acid solution as the test solution, measure 100 µl and carry out the test for High molecular weight proteins described under Recombinant human insulin. The percentage of high molecular weight proteins is not more than 3.0%.

Zinc Measure accurately a quantity equivalent to about 16 µg of zinc to a 10 ml volumetric flask, add 2 ml of boric acid potassium chloride BS (pH 9.0) and 0.4 ml of 0.01 mol/L hydrochloric acid solution containing 250 Units of trypsin per ml, allow to stand for 10 minutes, and then add 1 ml of zincous solution described under Recombinant Human Insulin; not less than 10 µg and not more than 40 µg of Zn per 100 Units of recombinant human insulin.

Recombinant human insulin in the supernatant Measure accurately 10 ml, centrifuge at the speed of 1500 g for 10 minutes, using the supernatant as the test solution. Measure accurately 1.0 ml of the reference solution of recombinant human insulin described under Assay to a 10 ml volumetric flask, dilute with 0.01 mol/L hydrochloric acid solution to volume, as the reference solution. Carry out the Assay described under Recombinant Human Insulin; not more than 2.5% of recombinant human insulin in supernatant.

Phenol or m-cresol Complies with the test for Phenol or m-cresol described under Recombinant Human Insulin Injection,

using the test solution obtained in test for Recombinant human insulin in the supernatant.

Sterility Complies with the test for sterility (Appendix IX H, membrane filtration method), using a clear solution prepared by mixing the content of each container with 90 ml of sterilized 1% aqueous ascorbic acid solution.

Bacterial endotoxin Carry out the test for bacterial endotoxin (Appendix XI E); not more than 2.5 EU per Unit of recombinant human insulin.

Other requirements Complies with the general requirements for injections (Appendix I B) except visible particles.

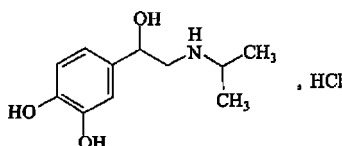
Assay Measure accurately a quantity, add 3 μ l of 9.6 mol/L hydrochloric acid solution per ml to obtain a clear solution. Dilute an accurately measured quantity with 0.01 mol/L hydrochloric acid solution to produce a solution of 10 Units per ml, carry out the Assay described under Recombinant Human Insulin.

Category As described under Recombinant Human Insulin.

Strength (1) 3 ml : 300 Units (2) 10 ml : 400 Units

Storage Preserve in tightly closed containers, stored in a cold place, avoid freezing.

Isoprenaline Hydrochloride



$C_{11}H_{17}NO_3 \cdot HCl$ 247.72

[51-30-9]

Isoprenaline Hydrochloride is 4- [1-hydroxyl-2-(1-methylethyl) amino]-1, 2-benzenediol hydrochloride. It contains not less than 98.5% of $C_{11}H_{17}NO_3 \cdot HCl$, calculated on the dried basis.

Description A white or almost white crystalline powder; odourless; taste, slightly bitter. Discoloured slowly on exposure to light and air, especially in alkali solution. Freely soluble in water; sparingly soluble in ethanol; insoluble in chloroform or ether.

Melting range 165.5-170°C, with decomposition (Appendix VI C).

Identification (1) Dissolve 20 mg in 2 ml of water, add 2 drops of ferric chloride TS; a deep green colour is produced, changing to blue and then to red on addition of a dropwise freshly prepared 5% sodium bicarbonate solution.

(2) Dissolve 10 mg in 10 ml of water. To 2 ml, add 0.1 ml of hydrochloric acid (0.1 mol/L) VS and 1 ml of 0.1 mol/L iodine solution, allow to stand for 5 minutes, then add 4 ml of 0.1 mol/L sodium thiosulfate solution; a pale red colour develops.

(3) A solution of 0.05 mg per ml in water only exhibits a maximum at 280 nm; the absorbance is about 0.50 (Appendix IV A).

(4) The infrared absorption spectrum (Appendix IV C) is concordant with the reference spectrum of isoprenaline hydrochloride (Appendix XVI).

(5) The aqueous solution yields the reactions characteristic of chlorides (Appendix III).

Acidity Dissolve 0.10 g in 10 ml of water, pH 4.5-5.5 (Appendix VI H).

Ketonic substance The absorbance of a solution of 2.0 mg per ml in water at 310 nm (Appendix IV A) is not greater than 0.15.

Loss on drying When dried to constant weight at 80°C, loses not more than 0.5% of its weight (Appendix VII L).

Residue on ignition Not more than 0.1% (Appendix VII N).

Assay Dissolve about 0.15 g, accurately weighed, in 30 ml of glacial acetic acid by warming, cool to room temperature, add 5 ml of mercuric acetate TS and 1 drop of crystal violet IS, titrate with perchloric acid (0.1 mol/L) VS until the colour changes to blue. Perform a blank determination and make any necessary correction. Each ml of perchloric acid (0.1 mol/L) VS is equivalent to 24.77 mg of $C_{11}H_{17}NO_3 \cdot HCl$.

Category β -Adrenergic receptor stimulating agent.

Storage Preserve in tightly closed containers, protected from light, stored in a dry place.

Preparation (1) Isoprenaline Hydrochloride Aerosol
(2) Isoprenaline Hydrochloride Injection

Isoprenaline Hydrochloride Aerosol

Isoprenaline Hydrochloride Aerosol contains not less than 90.0% and not more than 120.0% of the labelled amount of isoprenaline hydrochloride ($C_{11}H_{17}NO_3 \cdot HCl$). It contains 0.200%-0.325% (g/g) of isoprenaline hydrochloride in the inhalation.

Formula	Isoprenaline hydrochloride	2.5 g
	Ascorbic acid	1 g
	Ethanol	296.5 g
	Dichlorodifluoromethane	sufficient quantity
	To make	1000 g

Description A colourless or yellow, clear liquid in pressurized container; spray out as foggy particles on release of the delivery valve.

Identification (1) Dilute 1 drop of ferric chloride TS in a test tube with 5 ml of water, spray the liquid being examined for several times, a green colour is produced.

(2) Spray 3 times to 2 ml of 40% sodium acetate solution in a test tube, shake well, mix with 3 drops of mercuric chloride solution, a cherry red colour is produced.

Colour Remove the plastic coating of 3 containers. Mark the surface of liquid layer on the containers respectively. Punch a small hole on the aluminium cover and insert a needle for injection but does not contact the liquid surface. Remove the aluminium cover after complete evaporation of the propellant. Dilute to respective original volume with ethanol separately and shake well. Any colour produced is not more intense than that of reference solution Y_{10} (Appendix IX A, method 1). Repeat the test in the same manner with another 3 containers, if one container fails to pass the test. All comply with the requirements.

Other requirements Complies with the general requirements of aerosols (Appendix I L), except that the content in a unit spray is 80%-120% of the labelled amount.

Assay *Reference solution* Dissolve 35 mg, accurately weighed, of isoprenaline hydrochloride CRS in 0.005 mol/L sulfuric acid solution in 100 ml volumetric flask, dilute to volume and shake well.

Test solution Remove the plastic coating of 1 container,

accurately weighed, punch a small hole on the aluminium cover and insert a needle for injection without contact the surface of liquid. Connect the other end of the rubber tubing to a beaker containing 5 ml of ethanol, allow the propellant to evaporate slowly. Remove the aluminium cover, transfer the contents in the container with ethanol to a small beaker and evaporate to dryness over a water bath. Allow it to cool, dissolve the residue with a small quantity of 0.005 mol/L sulfuric acid solution in divided portions. Combine the aliquots of solution into 100 ml volumetric flask, dilute to volume with 0.005 mol/L sulfuric acid solution and shake well. Wash well the empty container, valve and aluminium cover, dry and weigh accurately. Calculate the concentration of isoprenaline hydrochloride in the aerosol being examined.

Procedure Filter the reference solution and the test solution respectively. Discard the initial filtrates and to 5 ml, accurately measured, of each the successive filtrates in 25 ml volumetric flask add 10 ml of 0.005 mol/L sulfuric acid solution, 5 ml of buffer solution (dissolve 5.04 g of sodium bicarbonate in 40 ml of a mixture of 1 ml of concentrate ammonia solution and 2.25 g of glycine and dilute with water to 50 ml), 1 ml of ferrous citrate solution (dissolve 1.5 g of ferrous sulfate in 200 ml of an aqueous solution containing 0.3 ml of dilute hydrochloric acid and 1 g of sodium bisulfite; dissolve 0.5 g of sodium citrate in 10 ml of the solution before use), dilute to volume with 0.005 mol/L sulfuric acid solution and shake well. Allow the solution to stand for 5 minutes, measure the absorbances of the resulting solutions at 530 nm (Appendix IV A) respectively. Calculate the content of $C_{11}H_{17}NO_3 \cdot HCl$.

Category As described under Isoprenaline Hydrochloride.

Strength 14 g per container, containing 35 mg of isoprenaline hydrochloride; 0.175 mg of isoprenaline hydrochloride in a unit spray.

Storage Preserve in well closed containers, protected from light, stored in a dark and cool place.

Isoprenaline Hydrochloride Injection

Isoprenaline Hydrochloride Injection is a sterile solution of Isoprenaline Hydrochloride in Water for Injection. It contains not less than 85.0% and not more than 110.0% of the labelled amount of isoprenaline hydrochloride ($C_{11}H_{17}NO_3 \cdot HCl$).

Description A clear, colourless liquid.

Identification (1) Dilute a quantity each of isoprenaline hydrochloride injection and isoprenaline hydrochloride CRS with 80% methanol to produce the solution of 0.2 mg per ml as the test solution and reference solution respectively. Carry out the method for thin-layer chromatography (Appendix V B), using silica gel as the coating substance and ethyl acetate-isopropanol-water-concentrated ammonia solution (50 : 30 : 16 : 4) as the mobile phase. Apply separately to the plate 10 μ l each of the two solutions. After developing and removal of the plate, dry it in air, place it in a chamber saturated with diethylamine vapors about a few minutes and spray with diazotized *p*-nitroaniline TS. The colour and position of the principal spot in the chromatogram obtained with the test solution correspond to the principal spot obtained with the reference solution.

(2) To 2 ml add 2 drops of ferric chloride TS, a deep green colour is produced, it turns to blue and then to red on adding dropwise freshly prepared 5% sodium bicarbonate solution.

pH value 2.5-4.5 (Appendix VI H).

Other requirements Complies with the general requirements for injections (Appendix I B).

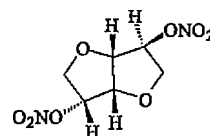
Assay Mix thoroughly an accurately measured quantity of the injection, equivalent to about 1 mg of isoprenaline hydrochloride, with 7 g of chromatographic kieselguhr and 2 ml of a buffer solution (dissolve 10.89 g of potassium dihydrogen phosphate and 3.48 g of dipotassium hydrogen phosphate in water and dilute with water to 100 ml) and transfer the mixture to a chromatographic column (25 mm \times 250 mm). Use 1 g of Kieselguhr to wash the container by means of dry cleaning and transfer it to the column. Pass 50 ml of ether saturated with water through the column and discard it, then elute with 50 ml of a solution of bis (α -ethyl hexyl) phosphoric acid in ether saturated with water (1 \rightarrow 50), and collect the eluate. Wash the bottom of the column with ether, combine the washings and eluate to a separator containing 10 ml of sulfuric acid solution (1 \rightarrow 350). Shake, transfer the acid layer to a 25 ml volumetric flask. Extract further with 10 ml of sulfuric acid solution (1 \rightarrow 350) from the ether layer. Combine the acid layers in the volumetric flask and dilute with sulfuric acid solution (1 \rightarrow 350) to volume and mix well. Measure the absorbance at 250 nm, 278 nm and 300 nm (Appendix IV A), calculate the correct absorbance at 278 nm on the baseline between the maxima at 250 nm and 300 nm. To a quantity of isoprenaline hydrochloride CRS, accurately weighed, add sulfuric acid solution (1 \rightarrow 350) to produce a solution of 0.5 mg per ml. Repeat the operation. Calculate the content of isoprenaline hydrochloride ($C_{11}H_{17}NO_3 \cdot HCl$) with reference to the ratio of the absorbance obtained from test solution to that obtained from the reference solution.

Category As described under Isoprenaline Hydrochloride.

Strength 2 ml : 1 mg

Storage Preserve in well closed containers, stored in a cool place and protected from light.

Isosorbide Dinitrate



$C_6H_8N_2O_8$ 236.14

[16051-77-7]

Isosorbide Dinitrate is 1, 4 : 3, 6-dianhydro-D-glucitol dinitrate. It contains not less than 97.0% and not more than 102.0% of $C_6H_8N_2O_8$, calculated on the dried basis.

Description A white crystalline powder; odourless. Freely soluble in acetone or chloroform; sparingly soluble in ethanol; slightly soluble in water.

Melting range 68-72°C (Appendix VI C).

Specific optical rotation +135° to +140° in a solution of 10 mg per ml in dehydrated ethanol (Appendix VI E).

Identification (1) Dissolve about 10 mg in a mixture of 1 ml of water and 2 ml of sulfuric acid in a test tube, cool and slowly add 3 ml of ferrous sulfate TS alongside the wall to form two layers; a brown colour is produced at the interface between the two layers.

(2) To 2 mg add 3 ml of freshly prepared 10% catechol solution, and mix well. Add 6 ml of sulfuric acid with caution; a dark green colour is produced.

(3) The infrared absorption spectrum (Appendix IV C) is concordant with the reference spectrum of isosorbide (Appendix XVI).

Nitrate To 0.25 g add 5 ml of water in a test tube, shake for 5 minutes. Filter and add 5 ml of sulfuric acid to the filtrate, mix and cool to room temperature. Slowly add 5 ml of ferrous sulfate TS alongside the wall to form two layers; no brown colour is produced immediately at the interface between the two layers.

Loss on drying When dried to constant weight in a desiccator using silica gel as desiccant, loses not more than 0.5% of its weight (Appendix VIII L).

Residue on ignition Not more than 0.1% (Appendix VIII N).

Assay Carry out the method for high performance liquid chromatography (Appendix V D), using a column packed with octadecylsilane bonded silica gel and a mixture of methanol-water (54 : 46) as the mobile phase. Detection wavelength is 230 nm and the number of the theoretical plates of the column is not less than 5000, calculated with reference to the peak of isosorbide dinitrate. The resolution factor between the peaks of isosorbide dinitrate and internal standard complies with the related requirements.

Internal standard solution Dissolve an accurately weighed quantity of hydrocortisone in the mobile phase to produce a solution of 80 µg per ml as the internal standard solution.

Procedure Dissolve about 25 mg of isosorbide dinitrate CRS, accurately weighed, with 27 ml of methanol in a 50 ml volumetric flask, add a quantity of water and allow to cool to room temperature, dilute with water to volume and mix well. Measure accurately 5 ml each of the reference solution and internal standard solution to a 25 ml volumetric flask, dilute with the mobile phase to volume and mix well. Inject 20 µl of the resulting solution into the column and calculate the correction factor. Repeat the operation, using 25 mg of the substance being examined instead of isosorbide dinitrate CRS, calculate the content of $C_6H_8N_2O_8$.

Category Vasodilator

Storage Preserve in tightly closed containers.

Preparation (1) Isosorbide Dinitrate Cream
(2) Isosorbide Dinitrate Spray
(3) Isosorbide Dinitrate Tablets

Isosorbide Dinitrate Cream

Isosorbide Dinitrate Cream contains not less than 90.0% and not more than 110.0% of the labelled amount of isosorbide dinitrate ($C_6H_8N_2O_8$).

Description White or creamy white cream.

Identification (1) Extract a quantity equivalent to about 15 mg of isosorbide dinitrate in a separator with a mixture of 10 ml of cyclohexane, 5 ml of methanol and 1 ml of saturated sodium chloride solution. Separate the methanol layer to another separator which contains 5 ml of 5% potassium aluminium sulfate solution, extract with 10 ml of chloroform. Filter the chloroform layer through anhydrous sodium sulfate. Evaporate the filtrate to dryness on a water bath, dissolve the residue on adding 1 ml of water and 2 ml of sulfuric acid, mix well, and transfer to a test tube, cool to room temperature and add alongside the wall 3 ml of ferrous sulfate TS to form a subjacent layer, a brown colour is produced at the junction of the liquids.

(2) To a quantity equivalent to about 2 mg of isosorbide

dinitrate add 3 ml of freshly prepared 10% catechol solution, mix well. Add dropwise 2 ml of sulfuric acid by shaking, a dark green colour is produced.

Other requirements Complies with the general requirements for cream (Appendix I F).

Assay Reference solution Weigh accurately 34.25 mg of potassium nitrate, previously dried at 105°C to constant weight, transfer it to a 200 ml volumetric flask and dissolve in 3 ml of water, dilute with glacial acetic acid to volume, mix well (Each ml is equivalent to 200 µg of $C_6H_8N_2O_8$).

Test solution Dissolve a quantity equivalent to 0.1 g of isosorbide dinitrate, accurately weighed, in 20 ml of glacial acetic acid in a 70°C water bath. Allow to stand for 30 minutes in a 15 °C water bath, filter through dry filter paper, wash the filter with glacial acetic acid. Combine the filtrate and the washings in a 50 ml volumetric flask, cool to room temperature, dilute with glacial acetic acid to volume and mix well. Measure accurately 5 ml of the solution to another 50 ml volumetric flask, dilute with glacial acetic acid to volume and mix well.

Procedure Measure accurately 1 ml each of above two solutions to separate 25 ml volumetric flasks. Take 1 ml of glacial acetic acid in another 25 ml volumetric flask as blank. Add accurately 2 ml of phenoldisulfonic acid TS to each flask and mix well, allow to stand for 15 minutes, add 10 ml of water, cool in an ice bath. Add slowly 8 ml of concentrated ammonia solution, cool to room temperature and dilute with water to volume, mix well. Measure the absorbance at 405 nm (Appendix IV A), calculate the content of $C_6H_8N_2O_8$.

Category As described under Isosorbide Dinitrate.

Strength 10 g : 1.5 g

Storage Preserve in tightly closed containers, stored in a cool place.

Isosorbide Dinitrate Spray

Isosorbide Dinitrate Spray contains not less than 80.0% and not more than 120.0% of labelled amount of isosorbide dinitrate ($C_6H_8N_2O_8$).

Description A clear, colourless or almost colourless liquid.

Identification (1) Transfer a quantity, equivalent to about 10 mg of isosorbide dinitrate, to a test tube, add 2 ml of sulfuric acid, mix well and cool to room temperature. Slowly add 3 ml of ferrous sulfate TS along the wall of test tube to form two layers; a brown colour is produced at the interface between the two layers.

(2) The retention time of the principal peak in the chromatogram of the test solution in the Assay is identical with that of the principal peak in the chromatogram of the reference preparation.

Total number of discharges per container Select 3 containers, actuate each valve continually in fume hood, until the container is empty. For each container containing 20 ml, the total number of discharges per container is not less than 180.

Related substances Measure accurately 1 ml of the substance being examined into a 10 ml volumetric flask, dilute with mobile phase to volume, mix well as test solution. Measure accurately 1 ml of the test solution, into a 100 ml volumetric flask, dilute with mobile phase to volume, mix well as reference solution. Carry out the method as described under Assay. Inject 20 µl of the reference solution into the column, adjust the attenuation so that the principal peak height in the chromatogram is 10%-20% full scale of the

chart. Inject separately 20 μ l each of the test solution and the reference solution into the column, record the chromatogram for twice of the retention time of the principal peak. The sum of the areas of the peaks other than the principal peak in the chromatogram obtained with the test solution is not greater than the area of the principle peak in the chromatogram obtained with the reference solution.

Other requirements Complies with the general requirements for aerosols except the content of active ingredient of each spray is not less than 70% and not more than 130% of the labelled amount of isosorbide dinitrate (Appendix I L).

Assay Measure accurately 2 ml of the substance being examined into a 50 ml volumetric flask, dilute with mobile phase to volume, mix well. Measure accurately 5 ml of the resulting solution and 5 ml of the internal standard solution obtained under Isosorbide Dinitrate for the Assay into a 25 ml volumetric flask, dilute with mobile phase to volume, mix well as test solution. Carry out the method as described under the Isosorbide Dinitrate for the Assay. Inject 20 μ l of the test solution into the column and record the peak area in the chromatogram. Calculate the content of $C_6H_8N_2O_8$ by the internal standard method.

Category As described under Isosorbide Dinitrate.

Strength (1) 10 ml : 0.125 g, containing 0.625 mg of isosorbide dinitrate of each spray
(2) 20 ml : 0.25 g, containing 1.4 mg of isosorbide dinitrate of each spray

Storage Preserve in well closed containers, protected from light, stored at a room temperature of 20°C.

Isosorbide Dinitrate Tablets

Isosorbide Dinitrate Tablets contain not less than 90.0% and not more than 110.0% of the labelled amount of isosorbide dinitrate ($C_6H_8N_2O_8$).

Description White tablets.

Identification To a quantity of powdered tablets, equivalent to about 20 mg of isosorbide dinitrate, add 10 ml of chloroform, shake thoroughly, and filter. Evaporate the filtrate on a water bath to dryness. The residue has a melting range of 67-72°C (Appendix VI C). The residue also complies with test (1) for Identification described under Isosorbide Dinitrate.

Content uniformity Comply with the requirement for content uniformity (Appendix X E). Triturate 1 tablet with the mobile phase and transfer to a 50 ml volumetric flask, add a quantity of the mobile phase, shake for 15 minutes to dissolve isosorbide dinitrate, dilute with mobile phase to volume and mix well. Filter, discard the initial filtrate. Carry out the method for high performance liquid chromatography (Appendix V D) described in Assay. Inject 20 μ l of the successive filtrate into the column, record the peak area obtained in the chromatogram. Dissolve an accurately weighed quantity of isosorbide dinitrate CRS, previously tested for Loss on drying, in the mobile phase to produce a solution of 0.1 mg per ml, repeat the operation. Calculate the content of $C_6H_8N_2O_8$ with the peak area obtained in the chromatogram by the external standard method.

Dissolution Comply with dissolution test (Appendix VI C, method 2), using 500 ml of water as the dissolution medium, adjust the rotational speed of the paddle to 75 rpm. Withdraw a quantity of the solution at exact 45 minutes, and

filter. Carry out the method for high performance liquid chromatography (Appendix V D), using a column packed with octadecylsilane bonded silica gel and a mixture of methanol-ammonium sulfate (0.1 mol/L) BS (pH 3.0 \pm 0.1) (53 : 47) as the mobile phase. Detection wavelength is 220 nm and the number of the theoretical plates of the column is not less than 3000, calculated with reference to peak of isosorbide dinitrate. Inject 100 μ l of the successive filtrate into the column, record the chromatogram. Dissolve 10 mg of isosorbide dinitrate CRS in 5 ml of methanol in a 100 ml volumetric flask, dilute with water to volume and mix well. Measure accurately 5 ml to a 50 ml volumetric flask (for strength 5 mg) or 25 ml volumetric flask (for strength 10 mg), dilute with water to volume and mix well, repeat the operation. Calculate the content of $C_6H_8N_2O_8$ with respect to the peak area obtained in the chromatogram by the external standard method, not less than 70% of the labelled amount is dissolved.

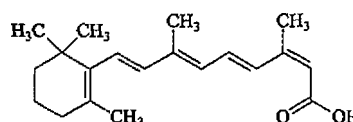
Other requirements Comply with the general requirements for tablets (Appendix I A).

Assay Weigh accurately and powder 10 tablets. Shake a quantity of the powder equivalent to about 5 mg of isosorbide dinitrate, accurately weighed, in a 50 ml volumetric flask with a quantity of the mobile phase for 15 minutes, add 10 ml, measured accurately, of the internal standard solution and dilute with the mobile phase to volume, mix well and filter. The successive filtrate is a test solution. Carry out the Assay described under Isosorbide Dinitrate.

Category, Storage As described under Isosorbide Dinitrate.

Strength (1) 5 mg (2) 10 mg

Isotretinoin



$C_{20}H_{28}O_2$ 300.44

Isotretinoin is 3, 7-dimethyl-9-(2, 6, 6-trimethylcyclohex-1-enyl)-2-cis-4-trans-6-trans-8-trans-nonatetraacenoic acid. It contains not less than 98.0% and not more than 102.0% of $C_{20}H_{28}O_2$, calculated on the dried basis.

Description A yellow to orange yellow crystalline powder. Soluble in chloroform or ether; slightly soluble in ethanol or isopropanol, practically insoluble in water.

Identification (1) To a quantity add acidified isopropanol solution (dilute 1 ml of 0.1 mol/L hydrochloric acid solution with isopropanol to 1000 ml) to produce a solution of 4 μ g per ml. The light absorption of the solution exhibits a maximum at 354 nm (Appendix IV A).

(2) The infrared absorption spectrum (Appendix IV C) is concordant with the spectrum of Isotretinoin (Appendix XI).

Tretinoin Protect from light throughout the procedure. Carry out the method for high performance liquid chromatography (Appendix V D), using a column packed with silica gel (5 μ m) and a mixture of isooctane-isopropanol-glacial acetic acid (99.65 : 0.25 : 0.1) as the mobile phase. Detection wavelength is 352 nm, and the number of the theoretical plates of the column is not less than 1000, calculated with reference to the peak of tretinoin. The resolution factor between the peaks of tretinoin and

isotretinoin is more than 1.0. Dissolve a quantity of tretinoin CRS, accurately weighed, in a quantity of dichloromethane, dilute with isooctane to produce a reference solution of 2.5 μg per ml. Repeat the operation, using isotretinoin instead of tretinoin CRS, to produce a test solution of 250 μg per ml. Separately inject 20 μl of reference solution and test solution into the column. The peak area of tretinoin in the chromatogram obtained with the test solution is not greater than that of principal peak obtained with the reference solution.

Loss on drying When dried at 105 °C for 3 hours, loses not more than 0.5% of its weight (Appendix VIII L).

Residue on ignition Not more than 0.1% (Appendix VIII N), using 1.0 g.

Heavy metals Carry out the limit test for heavy metals (Appendix VIII H, method 2), using the residue obtained in the test for Residue on ignition; not more than 0.002%.

Assay Dissolve about 0.24 g, accurately weighed, in 30 ml of dimethylformamide, add 3 drops of the solution of thymol blue in dimethylformamide (1 \rightarrow 100), titrate with sodium methoxide (0.1 mol/L) VS until the colour turns to green. Perform a blank determination and make any necessary correction. Each ml of sodium methoxide (0.1 mol/L) VS is equivalent to 30.04 mg of $\text{C}_{20}\text{H}_{28}\text{O}_2$.

Category Treatment of acne.

Storage Preserve in a tightly closed container, filled with inert gas, stored in a 0 to 5°C place and protected from light.

Preparation Isotretinoin Soft Capsules

Isotretinoin Soft Capsules

Isotretinoin Soft Capsules contain not less than 90.0% and not more than 110.0% of the labelled amount of Isotretinoin ($\text{C}_{20}\text{H}_{28}\text{O}_2$).

Description Dark brown capsules containing orange-yellow oily suspension.

Identification Dilute the content of the capsules with acidified isopropanol solution (dilute 1 ml of 0.1 mol/L hydrochloric acid solution with isopropanol to 1000 ml) to produce a solution of 4 μg per ml. The light absorption of the solution exhibits maximum at 354 nm (Appendix IV A).

Content uniformity Protect from light throughout the procedure. Comply with the requirements for content uniformity (Appendix X E). Carefully cut the top of 1 Capsule with scissors, transfer the content to a 50 ml volumetric flask and the opened empty shell to a 25 ml beaker respectively, wash the shell and the scissors with 10 ml of dichloromethane in portions, combine the washings to the 50 ml volumetric flask, shake thoroughly to dissolve, add isooctane to volume, mix well. Measure accurately 2 ml to another 100 ml volumetric flask, dilute to volume with isooctane, mix well. Measure the absorbances of the resulting solution and the reference solution obtained in the Assay at 361 nm (Appendix IV A). Calculate the content of isotretinoin ($\text{C}_{20}\text{H}_{28}\text{O}_2$).

Other requirements Comply with the general requirements for capsules (Appendix I E).

Assay Protect from light throughout the procedure. Transfer an accurately weighed quantity of the mixed contents of 20 Capsules equivalent to about 10 mg of isotretinoin to a 50 ml volumetric flask, add 5 ml of

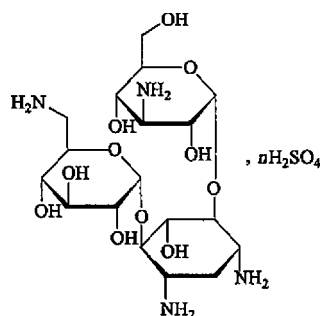
dichloromethane shake to dissolve, dilute with isooctane to volume, mix well. Transfer 2 ml, accurately measured, to another 100 ml volumetric flask, dilute with isooctane to volume, mix well. Measure the absorbance at 361 nm (Appendix IV A). Weigh accurately a quantity of isotretinoin CRS (calculated on the dried basis), proceed in the same manner. Calculate the content of $\text{C}_{20}\text{H}_{28}\text{O}_2$.

Category As described under Isotretinoin.

Strength 10 mg

Storage Preserve in tightly closed containers, stored in a cool and dry place.

Kanamycin Sulfate



[133-92-6]

Kanamycin Sulfate is O-3-amino-3-deoxy- α -D-glucopyranosyl-(1 \rightarrow 6)-O [6-amino-6-deoxy- α -D-glucopyranosyl-(1 \rightarrow 4)]-2-deoxy-D-stroptamine sulfate. It has not less than 67.0% of $\text{C}_{18}\text{H}_{36}\text{N}_4\text{O}_{11}$, calculated on the dried basis.

Description A white or almost white powder; odourless; hygroscopic.

Freely soluble in water; practically insoluble in ethanol, acetone chloroform or ether.

Specific optical rotation +102° to +110°, in a solution of 50 mg per ml in water (Appendix VI E).

Identification (1) Dissolve 1 mg in 2 ml of water, add 4 ml of a 0.2% solution of anthrone in sulfuric acid, heat on a water bath for 15 minutes and allow to cool; a bluish-purple colour is produced.

(2) The retention time of principal peak of the substance being examined in the chromatogram obtained in the Assay is identical with that of the principal peak of kanamycin sulfate CRS in the chromatogram of the reference solution.

(3) The infrared absorption spectrum (Appendix IV C) is concordant with the reference spectrum of kanamycin sulfate (Appendix XVI).

(4) The aqueous solution yields the reactions characteristic of sulfates (Appendix III).

Acidity or alkalinity Dissolve 3 g in 10 ml of water, pH 6.0-8.0 (Appendix VI H).

Clarity and colour of solution To 5 portions of 1.7 g each add 5 ml of water, the solutions are clear and colourless; any opalescence produced is not more pronounced than that of reference suspension I (Appendix IX B); any colour produced is not more intense than that of reference solution Y₄ or YG₄ (Appendix IX A, method 1).

Kanamycin B Dissolve an accurately weighed quantity of the substance being examined in water to produce solution of 2 mg of kanamycin per ml as the test solution; then dissolve

an accurately weighed quantity of the substance being examined in water to produce solution of 0.04 mg of kanamycin per ml as the reference solution. Carry out the method for Assay. Inject 20 μ l of the reference solution into the column, adjust the attenuation so that the principal peak height in the chromatogram is 20% full scale of the chart. Measure accurately 20 μ l of test solution and reference solution into the column respectively and record the chromatogram, the peak area of kanamycin B obtained from test solution is not greater than 2.0% of principal peak of reference solution.

Sulfates Dissolve about 0.18 g, accurately weighed, in 100 ml of water and adjust the solution to pH 11 using concentrated ammonia solution. Add 10 ml of barium chloride (0.1 mol/L) VS and 5 drops of phthalein purple IS. Titrate with disodium edetate (0.05 mol/L) VS, make sure to keep the pH value 11 during the titration, adding 50 ml of ethanol when the colour of the solution begins to change, and continue the titration until the bluish-purple colour disappears. Perform a blank determination and make any necessary correction. Each ml of barium chloride (0.1 mol/L) VS is equivalent to 9.606 mg of sulfate (SO_4). The content of SO_4 is 23.0%-26.0%, calculated on the dried basis.

Loss on drying When dried for 3 hours at 105°C, loses not more than 4.0% of its weight (Appendix VIII L).

Residue on ignition Not more than 0.5% (Appendix VIII N).

Bacterial endotoxin Carry out the test for bacterial endotoxin (Appendix XI E); less than 0.4 EU per ml.

Sterility Complies with the test for sterility (Appendix XI H, membrane filtration method), to each portion add not less than 500 ml of 0.9% sterile sodium chloride solution respectively. Meanwhile, transfer 0.25-0.5 ml of a solution of 30 mg per ml to each of six tubes containing 10 ml of a 0.5% glucose broth, allow three of tubes incubated at 30-35°C and the remainder incubated at 20-25°C. All the results comply with the requirement.

Assay Carry out the method for high performance liquid chromatography (Appendix V D), using a column packed with octadecylsilane bonded silica gel and a mixture of 0.2 mol/L trifluoroacetic acid-methanol (95 : 5) as the mobile phase; detected by ELSD (The flux is 0.3 L per minute; maintain the excursion column temperature at 110°C). Dissolve Kanamycin CRS and Kanamycin B CRS in water to produce a mixture solution containing 80 μ g per ml. Inject 20 μ l into the column, the resolution factor between Kanamycin and Kanamycin B is not less than 5.0; calculate the 5 times injection results, the relative standard derivation (RSD) for replicate injection is less than 2.0 %.

Procedure Dissolve an accurate quantity of Kanamycin CRS in water to produce the solution containing 0.10, 0.15, 0.20 mg per ml. Inject 20 μ l into the column, record the chromatogram. Calculate the regression equation, using the logarithm of reference solution concentration and corresponding peak area; correlation coefficient should be not less than 0.99; Dissolve an another accurate quantity of Kanamycin CRS in water to produce the solution containing 0.15 mg per ml, repeat the operation. Calculate the content of $\text{C}_{18}\text{H}_{36}\text{N}_4\text{O}_{11}$ using regression equation.

Category Aminoglycoside Antibiotics.

Storage Preserve in hermetically sealed containers, stored in a dry place.

Preparation (1) Kanamycin Sulfate Eye Drops
(2) Kanamycin Sulfate for Injection
(3) Kanamycin Sulfate Injection

Kanamycin Sulfate Eye Drops

Kanamycin Sulfate Eye Drops contain not less than 90.0% and not more than 110.0% of the labelled potency of Kanamycin ($\text{C}_{18}\text{H}_{36}\text{N}_4\text{O}_{11}$). It may contains suitable preservatives.

Description A clear, colourless to slightly yellow or slightly yellow green liquid.

Identification Comply with the tests (1), (2) and (4) for Identification described under Kanamycin Sulfate.

pH value 6.0-7.0 (Appendix VI H).

Colour The eye drops are colourless; any colour produced is not more intense than that of reference solution Y_3 or YG_3 (Appendix IX A, method 1).

Osmotic pressure Osmolar concentration is 260-320 mO₂/mol/kg (Appendix IX G).

Other requirements Comply with the general requirements for eye preparations (Appendix I G).

Assay Measure accurately a quantity, dilute to produce a solution of 0.15 mg per ml with water and carry out the Assay described under Kanamycin Sulfate.

Category As described under Kanamycin sulfate.

Strength 8 ml : 40 mg (calculated as $\text{C}_{18}\text{H}_{36}\text{N}_4\text{O}_{11}$)

Storage Preserve in tightly closed containers, stored in a cool and dark place.

Kanamycin Sulfate for Injection

Kanamycin Sulfate for Injection is a sterile powder of kanamycin sulfate. It contains not less than 65.0% of Kanamycin ($\text{C}_{18}\text{H}_{36}\text{N}_4\text{O}_{11}$), calculated on the dried basis. It contains not less than 93.0% and not more than 107.0% of the labelled potency of Kanamycin ($\text{C}_{18}\text{H}_{36}\text{N}_4\text{O}_{11}$), calculated on the basis of the average weight of contents.

Description A white or almost white powder.

Identification Comply with the tests (1), (2) and (4) for Identification described under Kanamycin Sulfate.

Clarity and colour of solution To each of 5 containers add water to produce solutions of 0.2 g per ml, the solutions are clear and colourless; any opalescence produced is not more pronounced than that of reference suspension 1 (Appendix IX B); Any colour produced is not more intense than that of reference solution Y_4 or YG_4 (Appendix IX A, method 1).

Kanamycin B Using the mixed contents obtained from the test for weight variation of the contents. Dissolve an accurately quantity of the substance being examined in water to produce solution containing 2 mg of Kanamycin per ml as the test solution; then dissolve an accurately weighed quantity of the substance being examined in water to produce solution containing 0.08 mg of Kanamycin per ml as the reference solution. Carry out the method for assay under Kanamycin Sulfate. The peak area of Kanamycin B obtained from test solution is not greater than the area of principal peak of reference solution (4.0%).

Loss on drying When dried for 3 hours at 105°C, loses not more than 5.0% of its weight (Appendix VIII L).

Acidity or alkalinity, Bacterial Endotoxin and Sterility Comply with the corresponding requirements described under Kanamycin Sulfate.

Other requirements Comply with the general requirements for injections (Appendix I B).

Assay Carry out the Assay described under Kanamycin Sulfate, using the mixed contents obtained from the test for weight variation of the contents.

Category As described under Kanamycin Sulfate.

Strength Calculated as $C_{18}H_{36}N_4O_{11}$ (1) 0.5 g (2) 1 g

Storage Preserve in tightly closed containers, stored in a dry place.

Kanamycin Sulfate Injection

Kanamycin Sulfate Injection is a sterile solution of kanamycin sulfate. It contains not less than 90.0% and not more than 110.0% of the labelled potency of Kanamycin ($C_{18}H_{36}N_4O_{11}$).

Description A clear, colourless to slightly yellow or yellowish-green liquid.

Identification Comply with the tests (1), (2) and (4) for Identification described under Kanamycin Sulfate.

pH value 4.5-7.5 (Appendix VI H).

Colour The solution is colourless; any colour produced is not more intense than that of reference solution Y_4 or YG_4 (Appendix IX A, method 1).

Kanamycin B Dissolve an accurately weighed quantity of the substance being examined in water to produce solution of 2 mg of Kanamycin per ml as the test solution; then dissolve an accurately weighed quantity of the substance being examined in water to produce solution of 0.08 mg of Kanamycin per ml as the reference solution. Carry out the method for assay under Kanamycin Sulfate. The peak area of Kanamycin B obtained from test solution is not greater than the area of principal peak of reference solution.

Sterility Comply with the test for sterility (Appendix XI H, membrane filtration method), dissolving each content in not less than 500 ml of 0.9% sterile sodium chloride solution respectively.

Bacterial endotoxin Complies with the corresponding requirements described under Kanamycin Sulfate.

Other requirements Complies with the general requirements for injections (Appendix I B).

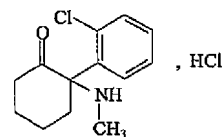
Assay Measure accurately a quantity and carry out the Assay described under Kanamycin Sulfate.

Category As described under Kanamycin Sulfate.

Strength 2 ml : 0.5 g (500000 Units)

Storage Preserve in well closed containers.

Ketamine Hydrochloride



$C_{13}H_{16}ClNO \cdot HCl$ 274.19

[1867-66-9]

Ketamine Hydrochloride is 2-(2-chlorophenyl)-2-methylamino-cyclohexanone hydrochloride. It contains not less than 99.0% of $C_{13}H_{16}ClNO \cdot HCl$, calculated on the dried basis.

Description A white crystalline powder; odourless. Freely soluble in water; soluble in hot ethanol; insoluble in ether or benzene.

Identification (1) Dissolve about 0.2 g in 4 ml of water, cool in an ice bath, add 10% potassium carbonate solution dropwise to about pH 10, allow to stand and filter. Wash the crystals with water, dry in vacuum over phosphorous pentoxide. The melting point is 91-94°C (Appendix VI C).

(2) The light absorption of a solution of 0.3 mg per ml in water exhibits maxima at 269 nm and 277 nm (Appendix IV A).

(3) The infrared absorption spectrum (Appendix IV C) is concordant with the reference spectrum of ketamine hydrochloride (Appendix XVI).

(4) The aqueous solution yields the reactions characteristic of chlorides (Appendix III).

Acidity Dissolve 0.10 g in 10 ml of water, pH 4.0-5.5 (Appendix VI H).

Clarity of Solution A solution of 1.0 g in 10 ml of water is clear, any opalescence produced is not more pronounced than that of reference suspension 1 (Appendix IX B).

Loss on drying When dried to constant weight at 105°C, loses not more than 0.5% of its weight (Appendix VIII L).

Residue on ignition Not more than 0.1% (Appendix VIII N); using 1.0g.

Heavy metals Carry out the limit test for heavy metals (Appendix VIII H, method 2), using the residue obtained in the test for Residue on ignition; not more than 0.001%

Assay Dissolve about 0.2 g, accurately weighed, in 20 ml of glacial acetic acid by warming, cool to room temperature, then add 5 ml of mercuric acetate TS and 1 drop of crystal violet IS and titrate with perchloric acid (0.1 mol/L) VS until the colour changes to blue. Perform a blank determination and make any necessary correction. Each ml of perchloric acid (0.1 mol/L) VS is equivalent to 27.42 mg of $C_{13}H_{16}ClNO \cdot HCl$.

Category General anaesthetic by intravenous injection.

Storage Preserve in tightly closed containers.

Preparation Ketamine Hydrochloride Injection

Ketamine Hydrochloride Injection

Ketamine Hydrochloride Injection is a sterile solution of Ketamine Hydrochloride in Water for Injections. It contains not less than 90.0% and not

more than 110.0% of the labelled amount of ketamine ($C_{13}H_{16}ClNO$).

Description A clear, colourless liquid.

Identification (1) To 2 drops add 4 ml of 0.5% sulfuric acid solution and 1 drop of potassium iodobismuthate TS; a reddish-brown precipitate is produced.
(2) Complies with test (2) for Identification described under Ketamine Hydrochloride.

pH value 3.5-5.5 (Appendix VI H).

Other requirements Complies with the general requirements for injections (Appendix I B).

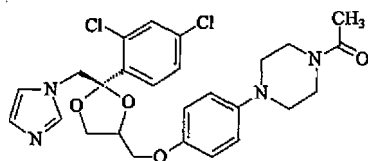
Assay To an accurately measured quantity equivalent to about 0.2 g of ketamine hydrochloride in a separator add sufficient water to produce 25 ml. Make alkaline with 1.5 ml of ammonia TS and extract with chloroform for four times (25, 20, 15 ml and 15 ml respectively). Wash the chloroform extracts with the same 15 ml of water and filter through cotton wool moistened with chloroform. Wash the cotton wool and the filter with 5 ml of chloroform. Combine the chloroform extracts and washings, evaporate to dryness on a water bath and cool. Dissolve the residue in a mixture of 2 ml of acetic anhydride and 20 ml of glacial acetic acid, add 1 drop of crystal violet IS, titrate with perchloric acid (0.1 mol/L) VS until the colour changes to pure blue. Perform a blank determination and make any necessary correction. Each ml of perchloric acid (0.1 mol/L) VS is equivalent to 23.77 mg of $C_{13}H_{16}ClNO$.

Category As described under Ketamine Hydrochloride.

Strength (1) 2 ml : 0.1 g (2) 10 ml : 0.1 g
(3) 20 ml : 0.2 g

Storage Preserve in well closed containers.

Ketoconazole



$C_{26}H_{28}Cl_2N_4O_4$ 531.44

Ketoconazole is \pm cis-1-acetyl-4-[4-[2-(2,4-dichlorophenyl)-2-(1H-imidazol-1-ylmethyl)-1,3-dioxolan-4-yl] methoxy] phenyl piperazine. It contains not less than 98.5% of $C_{26}H_{28}Cl_2N_4O_4$, calculated on the dried basis.

Description An almost white crystalline powder; odourless; tasteless.

Freely soluble in chloroform; soluble in methanol; slightly soluble in ethanol; practically insoluble in water.

Melting range 147-151°C (Appendix VI C).

Specific optical rotation -1° to $+1^\circ$, in a solution of 40 mg per ml in methanol (Appendix VI E).

Identification (1) Dissolve about 10 mg in 5 ml of 0.1 mol/L hydrochloric acid solution, add a few drops of potassium iodobismuthate TS, an orange-red precipitate is produced.
(2) Dissolve about 60 mg, accurately weighed, in 10 ml of 0.1 mol/L hydrochloric acid solution in a 100 ml volumetric flask, dilute with water to volume, mix well. Transfer 25 ml to a 100 ml volumetric flask, dilute with 0.01 mol/L

hydrochloric acid solution to volume, mix well. Transfer 10 ml to a 100 ml volumetric flask, dilute with 0.01 mol/L hydrochloric acid solution to volume. The light absorption of the resulting solution exhibits maxima at 221 nm and 269 nm, and a shoulder peak at 276 nm.

(3) The infrared absorption spectrum (Appendix IV C) is concordant with the reference spectrum of Ketoconazole (Appendix XVI).

Clarity and colour of chloroform solution Dissolve 0.30 g in 10 ml of chloroform, the solution is clear; any colour produced is not more intense than that of reference solution OY₅ (Appendix IX A, method 1).

Related substances Carry out the method for thin-layer chromatography (Appendix V B), using silica gel G as the coating substance and a mixture of *n*-hexane-ethyl acetate-methanol-water-glacial acetic acid (42 : 40 : 15 : 2 : 1) as the mobile phase. Apply separately to the plate 10 μ l of each of four solutions in chloroform containing (1) 10 mg per ml, (2) 50 μ g per ml, (3) 100 μ g per ml, (4) 150 μ g per ml of the substance being examined. After developing and removal of the plate, dry it in air and expose it to iodine vapour until the spots appear. The intensity of any secondary spot in the chromatogram obtained with solution (1) is compared with that of the principal spots obtained with solution (2), (3) and (4), the total impurity is not more than 1.5%.

Loss on drying When dried in vacuum at 80°C for 4 hours, loses not more than 0.5% of its weight (Appendix VIII L).

Residue on ignition Not more than 0.1% (Appendix VIII N), using 1.0 g.

Heavy metals Carry out the limit test for heavy metals (Appendix VIII H, method 2), using the residue obtained in the test for residue on ignition; not more than 0.002%.

Assay Dissolve about 0.2 g, accurately weighed, in 40 ml of glacial acetic acid. Carry out the method for potentiometric titration (Appendix VII A), titrate with perchloric acid (0.1 mol/L) VS, perform a blank determination and make any necessary correction. Each ml of perchloric acid (0.1 mol/L) VS is equivalent to 26.57 mg of $C_{26}H_{28}Cl_2N_4O_4$.

Category Antifungal.

Storage Preserve in tightly closed containers, protected from light.

Preparation (1) Ketoconazole Cream
(2) Compound Ketoconazole Cream

Ketoconazole Cream

Ketoconazole Cream contains not less than 90.0% and not more than 110.0% of the labelled amount of ketoconazole ($C_{26}H_{28}Cl_2N_4O_4$).

Description A creamy white or pale red cream.

Identification (1) To about 0.5 g, add 10 ml of 0.1 mol/L hydrochloric acid solution, heat in a water bath to dissolve ketoconazole, cool and filter, to the filtrate add few drops of potassium iodobismuthate TS, an orange-red precipitate is produced.
(2) The light absorption of the solution obtained in the Assay exhibits maximum at 244 nm (Appendix IV A).

Other requirements Complies with the general requirements for creams (Appendix I F).

Assay To about 2 g, accurately weighed, add 25 ml of 0.1 mol/L hydrochloric acid solution in a beaker, heat in a water

bath, stir thoroughly to dissolve ketoconazole, allow to cool. Filter, transfer the filtrate to a separator, repeat the operation three times, combine the filtrates, add ammonia TS to neutralize until a precipitate is just produced, add one drop of ammonia TS, extract with three 25 ml portions of chloroform, filter all the chloroform extracts into a 100 ml volumetric flask through a wad of absorbent cotton moistened with chloroform. Wash the cotton and filter with a quantity of chloroform, combine the filtrates and washings, dilute with chloroform to volume, mix well as test preparation. Dissolve an accurately weighed quantity of ketoconazole CRS previously dried in vacuum at 80°C for 4 hours to produce a solution of about 0.4 mg per ml as reference preparation. To 2 ml of each of the two preparations, accurately measured, in separate 50 ml volumetric flasks, add with dehydrated ethanol to volume, mix well. Measure the absorbance at 244 nm (Appendix IV A), calculate the content of $C_{25}H_{28}Cl_2N_4O_4$ S.

Category Antifungal.

Strength 10 g : 0.2 g

Storage Preserve in tightly closed containers, stored in a cool and dark place.

Compound Ketoconazole Cream

Compound Ketoconazole Cream contains not less than 90.0% and not more than 110.0% of the labelled amount of ketoconazole ($C_{26}H_{28}Cl_2N_4O_4$), not less than 85.0% and not more than 115.0% of the labelled amount of clobetasol propionate ($C_{25}H_{32}ClFO_5$), not less than 90.0% and not more than 120.0% of the labelled potency of neomycin sulfate.

Formula	Ketoconazole	10 g
	Clobetasol Propionate	0.25 g
	Neomycin Sulfate	5000000 Units
	Base	a quantity
	to make	1000 g

Description A white or almost white cream.

Identification (1) The retention time of two principal peaks in the chromatogram of the test preparation obtained under the Assay for ketoconazole and clobetasol propionate corresponds with that of the principal peaks in the chromatogram of the —————.

(2) Transfer about 1.5 g of cream, equivalent to about 7500 Units of neomycin sulfate, in a conical flask with stopper, add 10 ml of trichloromethane and 5 ml of water, shake thoroughly, centrifuge, take the supernate as test solution. Dissolve a quantity of neomycin sulfate CRS in water to produce a reference solution of 2 mg per ml. Carry out the thin-layer chromatography (Appendix V B), using silica gel G as the coating substance and a mixture of methanol-ammonia solution (13.5 mol/L)-trichloromethane (60 : 40 : 20) as the mobile phase. Apply separately to the plate 5 µl each of above two solutions, after developing and removal of the plate, dry it in air, spray with a solution of 1% ninhydrin in butanol, heat at 105°C for 2 minutes. The colour and position of the principal spot in the chromatogram obtained with the test solution correspond to the principal spot obtained with the reference solution.

Other requirements Comply with the general requirements for Cream (Appendix I F).

Assay Ketoconazole and Clobetasol Propionate Carry out the method for high performance liquid chromatography (Appendix V D), using a column packed with

octadecylsilane bonded silica gel and a mixture of methanol-water (74 : 26) as the mobile phase. Detection wavelength is 239 nm and the number of the theoretical plates of the column is not less than 2000, calculated with reference to the peak of ketoconazole. The resolution factor between the peaks of ketoconazole and clobetasol propionate is greater than 2.0.

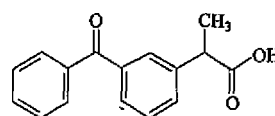
Procedure To about 4 g of cream, accurately weighed, add a quantity of anhydrous ethanol. Heat in a water bath at 80°C to dissolve ketoconazole and clobetasol propionate, transfer thoroughly to a 50 ml volumetric flask with anhydrous ethanol, cool to room temperature, dilute to volume with the same solvent, mix well. Cool in an ice bath for at least 2 hours, filter rapidly. Take the successive filtrate standing at room temperature for 15 minutes as test solution. Inject 10 µl of the test solution into the column, record the chromatogram. Weigh accurately a quantity of ketoconazole CRS and clobetasol propionate CRS, add anhydrous ethanol to produce a reference solution of 0.8 mg of ketoconazole CRS and 20 µg of clobetasol propionate CRS per ml. Repeat the operation, using the reference solution instead of the test solution. Calculate the content of $C_{26}H_{28}Cl_2N_4O_4$ and $C_{25}H_{32}ClFO_5$ respectively with respect to the peak areas obtained in the chromatogram by the external standard method.

Neomycin Sulfate Weigh accurately about 2 g into a 100 ml conical flask with stopper, add 50 ml of petroleum ether (boiling range: 90-120°C), treat with the aid of an ultrasonic bath for about 30 minutes to dissolve the base, transfer to a separator. Extract with 3% sodium chloride in phosphate BS (pH 7.8) for four times, each of 20 ml. Combine the extracts to a 100 ml volumetric flask, dilute with the same BS to volume, mix well. Carry out the Microbiological Assay of Antibiotics (Appendix XI A).

Category Antifungal.

Storage Preserve in tightly closed containers, stored in a cool place and protected from light.

Ketoprofen



$C_{16}H_{14}O_3$ 254.29

[22071-15-4]

Ketoprofen is α -methyl-3-benzoylbenzeneacetic acid. It contains not less than 98.5% of $C_{16}H_{14}O_3$, calculated on dried basis.

Description A white crystalline powder, odourless or almost odourless.

Very soluble in methanol; freely soluble in ethanol, acetone or ether, practically insoluble in water.

Melting point 93-96°C (Appendix VI C).

Identification (1) Dissolve about 50 mg in 1 ml of ethanol, add 1 ml of dinitrophenyldrazine TS and mix well. Heat to boiling, cool; an orange precipitate is produced.

(2) The infrared absorption spectrum (Appendix IV C) is concordant with the reference spectrum of ketoprofen (Appendix XVI).

Clarity and colour of methanol solution Dissolve 0.30 g in 25 ml of methanol, the solution is clear and colourless. Any opalescence produced is not more pronounced than that of

reference suspension 1 (Appendix IX B); any colour produced is not more intense than the mixture of reference solution Y₁ 10 ml and water 10 ml (Appendix IX A, method 1).

Related substances Carry out the method for thin-layer chromatography (Appendix V B), using silica gel GF₂₅₄ as the coating substance and toluene-isopropyl ether-formic acid (70 : 30 : 1) as the mobile phase. Apply separately to the plate 5 µl of each of three solutions in acetone containing (1) 100 mg per ml, (2) 0.5 mg per ml, (3) 0.2 mg per ml. After developing and removal of the plate, dry it in air, examine under ultraviolet light (254 nm). Any spot, other than the principal spot in chromatogram obtained with solution (1) is not more intense than the principal spot in the chromatogram obtained with solution (2) and not more than three spots are more intense than the principal spot in the chromatogram obtained with solution (3).

Loss on drying When dried in vacuum at 60°C over phosphorous pentoxide to constant weight, loses not more than 0.5% of its weight (Appendix VIII L).

Residue on ignition Not more than 0.1%; using 1.0 g (Appendix VIII N).

Heavy metals Carry out the limit test for heavy metals (Appendix VIII H, method 2), using the residue obtained in test for Residue on ignition: not more than 0.001%.

Assay Dissolve about 0.5 g, accurately weighed, in 25 ml of neutral ethanol (neutral to phenolphthalein IS) add 3 drops of phenolphthalein IS, titrate with sodium hydroxide (0.1 mol/L) VS. Each ml of sodium hydroxide (0.1 mol/L) VS is equivalent to 25.43 mg of C₁₆H₁₄O₃.

Category Anti-inflammatory and analgesic agent.

Storage Preserve in tightly closed containers, protected from light.

Preparation (1) Ketoprofen Enteric-coated Capsules
(2) Ketoprofen Liniment

Ketoprofen Enteric-coated Capsules

Ketoprofen Enteric-coated Capsules contain not less than 90.0% and not more than 110.0% of the labelled amount of ketoprofen (C₁₆H₁₄O₃).

Description Capsules with white powder contents.

Identification (1) Dissolve a quantity of the contents of capsules equivalent to 0.25 g of ketoprofen in 5 ml of ethanol by shaking, filter. The filtrate complies with the tests for Identification (1) described under Ketoprofen.

(2) Dissolve a quantity of the contents of capsules in 75% methanol to produce a solution of 10 µg per ml, filter. The light absorption of the successive filtrate exhibits a maximum at 258 nm. (Appendix IV A).

Drug Release Complies with the requirements for drug release test (Appendix X D method 2 (1)), with the apparatus of dissolution test method 1 and using 750 ml of 0.1 mol/L hydrochloric acid solution as the release medium and adjust the rotational speed of the paddle to 100 rpm. Withdraw 10 ml of solution after exactly 2 hours and filter. Take the successive filtrate as solution (1). Add 250 ml of 0.2 mol/L sodium phosphate solution (37°C) in the vessel, mix well (adjusting to pH 6.8 ± 0.05 with 2 mol/L hydrochloric acid or 2 mol/L sodium hydroxide solution if necessary). Withdraw 10 ml of solution after exactly 45 minutes and filter. Transfer 3 ml of the successive filtrate, accurately measured, in a 25 ml volumetric flask. Dilute to

volume with phosphate BS (pH 6.8) and mix well as solution (2). Empty a capsule, wash with methanol, and dry in air. Dissolve with the above phosphate BS (pH 6.8) and dilute to the same concentration of the capsule as that of the solution (2), as a blank solution. Measure the absorbances of the resulting solution at 260 nm (Appendix IV A), calculate the dissolution of C₁₆H₁₄O₃ from each capsule, taking 650 as the value of A (1%, 1 cm).

Other requirements Comply with the general requirements for capsules (Appendix I E).

Assay Dissolve a quantity of the mixed contents in the test for weight variation of contents equivalent to about 0.5 g of ketoprofen in 30 ml of neutral ethanol (neutral to phenolphthalein IS) and filter with a sintered glass filter. Wash the container and filter with four portions of neutral ethanol, each of 5 ml. Combine the filtrate and washings, add 3 drops of phenolphthalein IS, titrate with sodium hydroxide (0.1 mol/L) VS. Each ml of sodium hydroxide (0.1 mol/L) VS is equivalent to 25.43 mg of C₁₆H₁₄O₃.

Category As described under ketoprofen.

Strength (1) 25 mg (2) 50 mg

Storage Preserve in tightly closed containers, protected from light.

Ketoprofen Liniment

Ketoprofen Liniment contains not less than 90.0% and not more than 110.0% of the labelled amount of Ketoprofen (C₁₆H₁₄O₃).

Description A clear colourless or pale yellow solution.

Identification (1) To 1 ml add 1 ml of dinitro-phenyl hydrazine TS, mix well, heat until boil, cool, an orange-red precipitation is produced.

(2) The light absorption of a solution of 10 µg per ml in ethanol exhibits maximum at 255 nm (Appendix IV A).

pH value 5.6-7.0 (Appendix VI H).

Content of ethanol 65.0% to 75.0% (Appendix VII E).

Other requirements Complies with the general requirements for liniment (Appendix I T).

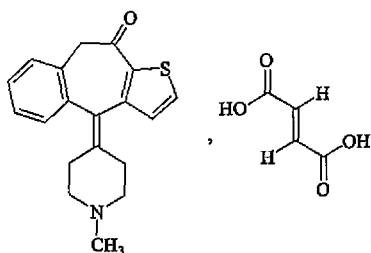
Assay Measure accurately 2 ml equivalent to about 60 mg of ketoprofen to a 100 ml brown volumetric flask, dilute with ethanol to volume, mix well. Measure accurately 2 ml to a 200 ml brown volumetric flask, dilute with ethanol to volume, mix well. Measure the absorbances at 255 nm (Appendix IV A). Repeat the operation, using about 60 mg of ketoprofen CRS, accurately weighed, instead of the substance being examined. Calculate the content of C₁₆H₁₄O₃.

Category As described under Ketoprofen.

Strength 30 ml : 0.9 g

Storage Preserve in tightly closed containers, protected from light.

Ketotifen Fumarate



$C_{19}H_{19}NOS \cdot C_4H_4O_4$ 425.50 [34580-14-8]

Ketotifen Fumarate is 4, 9-dihydro-4-(1-methyl-4-piperidinylidene)-10*H*-benzo [4,5] cyclohepta [1,2-*a*] thiophen-10-one (*E*)-butenedioate. It contains not less than 98.5% of $C_{19}H_{19}NOS \cdot C_4H_4O_4$, calculated on the dried basis.

Description An almost white crystalline powder; odourless; taste, bitter.

Soluble in methanol; slightly soluble in water or ethanol; very slightly soluble in acetone or chloroform.

Melting range 191-195°C, with decomposition (Appendix VI C).

Identification (1) To about 5 mg, add 1 drop of sulfuric acid; an orange-yellow colour is produced, and disappears on adding 1 ml of water.

(2) To about 5 mg add 1 ml of dinitrophenylhydrazine TS, heat on a water bath; a red loose precipitate is produced.

(3) To about 0.1 g add 5 ml of sodium carbonate TS, shake and filter. To the filtrate add 4 drops of potassium permanganate TS; the red colour disappears and a brown precipitate is produced.

(4) An aqueous solution of 10 µg per ml exhibits maximum at 301 nm (Appendix IV A).

(5) The infrared absorption spectrum (Appendix IV C) is concordant with the reference spectrum of Ketotifen Fumarate (Appendix XVI).

Related substances Carry out the method for thin-layer chromatography (Appendix V B), using silica gel G as the coating substance and a mixture of *n*-hexane-chloroform-methanol (6 : 3 : 1) as the mobile phase, and saturated the developing chamber with 5 ml of concentrated ammonia solution in a small beaker. Apply separately to the plate 10 µl each of two solution in ethanol containing (1) 10 mg per ml, (2) 0.1 mg per ml of the substance being examined. After developing and removal of the plate, dry it in air. Spray with dilute bismuth potassium iodide TS. Any spot other than the principal spot in the chromatogram obtained with solution (1) is not more intense than the principal spot obtained with solution (2).

Loss on drying When dried to constant weight at 105°C, loses not more than 0.5% of its weight (Appendix VII L).

Residue on ignition Not more than 0.1% (Appendix VII N).

Assay Dissolve about 0.3 g, accurately weighed, in 10 ml of glacial acetic acid, add 1 drop of crystal violet IS, titrate with perchloric acid (0.1 mol/L) VS until the solution changes to blue. Perform a blank determination and make any necessary correction. Each ml of perchloric acid (0.1 mol/L) VS is equivalent to 42.55 mg of $C_{19}H_{19}NOS \cdot C_4H_4O_4$.

Category Antihistaminic.

Storage Preserve in tightly closed containers, stored in cool and dark place.

Preparation (1) Ketotifen Fumarate Capsules
(2) Ketotifen Fumarate Eye Drops
(3) Ketotifen Fumarate Nasal Drops
(4) Ketotifen Fumarate Oral solution
(5) Ketotifen Fumarate Tablets

Ketotifen Fumarate Capsules

Ketotifen Fumarate Capsules contain not less than 90.0% and not more than 110.0% of the labelled amount of Ketotifen Fumarate, calculated on Ketotifen ($C_{19}H_{19}NOS$).

Description Capsules with white or almost white powder.

Identification (1) Dissolve a quantity of the finely powdered tablets equivalent to about 20 mg of ketotifen in 10 ml of water, stir thoroughly and filter. Concentrate 2 ml of the filtrate on a water bath to about 1 ml, cool, add 1 ml of sulfuric acid, a pale yellow colour is produced, and disappears on dilution with 2 ml of water.

(2) To 2 ml of the filtrate obtained under the Identification (1) add 1 ml of dinitrophenyl hydrazine TS, heat on a water bath, a red loose precipitate is produced gradually.

(3) The light absorption of the solution obtained under the Assay exhibits a maximum at 301 nm (Appendix IV A).

Content uniformity Transfer the content of 1 capsule to a 100 ml volumetric flask, wash the shell with water in divided portions, combine the washings to the same volumetric flask. Carry out the method described under the Assay, beginning at the words "shake to dissolve the Ketotifen Fumarate", the results comply with the requirements (Appendix X E).

Dissolution Carry out the dissolution test (Appendix X C, method 3), using 200 ml of water as the dissolution medium, adjust the rotational speed of the paddle to 75 rpm. Withdraw 10 ml after exactly 30 minutes and filter. Measure the absorbance of the successive filtrate at 301 nm (Appendix IV A). Calculate the dissolution of $C_{19}H_{19}NOS$ from each tablet, taking 465 as the value of *A* (1%, cm), Not less than 70% of the labelled amount is dissolved.

Other requirements Comply with the general requirements for capsules (Appendix I E).

Assay Weigh accurately 20 capsules, remove the contents, weigh accurately the shell of each capsule and mix well. Dissolve a quantity equivalent to about 1 mg of ketotifen in a 100 ml volumetric flask with water by shaking, dilute with water to volume, mix well and filter. Measure the absorbance of the successive filtrate at 301 nm (Appendix IV A), calculate the content of $C_{19}H_{19}NOS$, taking 465 as the value of *A* (1%, 1 cm).

Category As described under Ketotifen Fumarate.

Strength 1 mg (calculated as $C_{19}H_{19}NOS$)

Storage Preserve in tightly closed containers, protected from light.

Ketotifen Fumarate Eye Drops

Ketotifen Fumarate Eye Drops contain not less than 90.0% and not more than 110.0% of the

labelled amount of ketotifen fumarate, calculated with reference to ketotifen ($C_{19}H_{19}NOS$).

Description A clear, colourless or almost colourless liquid.

Identification (1) To about 5 ml add 1 ml of dinitrophenylhydrazine TS; a red curdy precipitate is produced on heating in a water bath.

(2) Dissolve a quantity of ketotifen fumarate CRS in ethanol to produce a solution of 0.5 mg per ml as reference solution. Use the eye drops as test solution. Carry out the method for thin-layer chromatography (Appendix V B), using silica gel G as the coating substance and a mixture of ethylacetate-methanol-strong ammonia solution (85 : 10 : 5) as the mobile phase. Apply separately to the plate 10 μ l each of above two solutions, after developing and removal of the plate, dry it in air and expose it to iodine vapours. The colour and position of principal spot in the chromatogram obtained with the test solution correspond to the principal spot obtained with the reference solution.

(3) The test solution obtained in Assay exhibits a maximum at 301 nm and a minimum at 256 nm (Appendix IV A).

pH value 4.8-5.8 (Appendix VI H).

Colour Any colour produced is not more intense than that of reference solution Y₂ (Appendix IX A, method 1).

Other requirements Comply with the general requirements for ophthalmic preparations (Appendix I G).

Assay Dilute a quantity, accurately measured, with water to produce a solution of 5 μ g of ketotifen per ml, measure the absorbance at 301 nm (Appendix IV A). Dissolve an accurately weighed quantity of ketotifen fumarate CRS in water to produce a solution of 7 μ g per ml, measure the absorbance in the same manner. Calculate the content of $C_{19}H_{19}NOS$, by multiplying by 0.7272.

Category As described under Ketotifen Fumarate.

Strength 5 ml : 2.5 mg (calculated with reference to $C_{19}H_{19}NOS$)

Storage Preserve in tightly closed containers, stored in a cool place and protected from light.

Ketotifen Fumarate Nasal Drops

Ketotifen Fumarate Nasal Drops contain not less than 90.0% and not more than 110.0% of the labelled amount of ketotifen fumarate ($C_{19}H_{19}NOS \cdot C_4H_4O_4$).

Description A clear, colourless to pale yellow liquid.

Identification (1) To about 3 ml, add 1 ml of dinitrophenylhydrazine TS, heat on a water bath, a red loose precipitate is produced.

(2) The light absorbance of the solution obtained under the Assay exhibits maximum at 301 nm (Appendix IV A).

pH value 4.0-6.0 (Appendix VI H).

Colour Colourless liquid; any colour produced is not more intense than that of reference solution Y₄ (Appendix IX A).

Other requirements Comply with the general requirements for nasal preparations (Appendix I R).

Assay Dilute a quantity, accurately measured, with water to produce a solution of 15 μ g per ml. Measure the absorbance of the solution at 301 nm (Appendix IV A). Repeat the operation, weigh a quantity of Ketotifen Fumarate CRS, calculate the content of $C_{19}H_{19}NOS \cdot$

$C_4H_4O_4$.

Category As described under Ketotifen Fumarate.

Strength 10 ml : 15 mg (calculated as $C_{19}H_{19}NOS$)

Storage Preserve in tightly closed containers, protected from light.

Ketotifen Fumarate Oral Solution

Ketotifen Fumarate Oral Solution is a solution of Ketotifen fumarate containing sugar. It contains not less than 90.0% and not more than 110.0% of the labelled amount of Ketotifen Fumarate, calculated on the basis of Ketotifen ($C_{19}H_{19}NOS$).

Description A yellow viscous liquid; taste, sweetish.

Identification (1) To 10 ml of the solution add 10 ml of 45% sodium hydroxide solution and 10 ml of *n*-hexane, shake thoroughly, allow to separate into two layers; transfer the *n*-hexane layer into a porcelain dish, evaporate to dryness on a water bath. Allow to cool and add 1 ml of dinitrophenylhydrazine TS, heat in a water bath, a red loose precipitate is produced gradually.

(2) The light absorption of the solution obtained under the Assay exhibits maximum at 294 nm (Appendix IV A).

Relative density 1.20-1.30 (Appendix VI A).

pH value 3.0-4.5 (Appendix VI H).

Other requirements Complies with the general requirements for oral solutions (Appendix I O).

Assay Weigh accurately a quantity of the solution equivalent to about 0.5 mg of ketotifen to a separator, add 10 ml of saturated sodium chloride solution and 10 ml of 45% sodium hydroxide solution, mix well. Add 50 ml of *n*-hexane accurately measured, shake for 30 minutes and allow to separate into two layers. Measure the absorbance of the supernatant at 294 nm (Appendix IV A). Dissolve a quantity of ketotifen fumarate CRS, accurately weighed in an amber coloured volumetric flask, dilute with water to produce a solution of 0.3 mg per ml. Measure accurately 2 ml, carry out the method as described above beginning at the words "to a separator", calculate the content of $C_{19}H_{19}NOS$. Then measure a quantity of the solution and determine the weight of per ml by a pycnometer, convert to the content of $C_{19}H_{19}NOS$ to per ml, calculate the percentage equivalent to that of the labelled amount.

Category As described under Ketotifen Fumarate.

Strength 5 ml : 1 mg (Calculated as $C_{19}H_{19}NOS$)

Storage Preserve in tightly closed containers, protected from light.

Ketotifen Fumarate Tablets

Ketotifen Fumarate Tablets contain not less than 90.0% and not more than 110.0% of the labelled amount of ketotifen fumarate, calculated on the basis of ketotifen ($C_{19}H_{19}NOS$).

Description White or almost white tablets.

Identification (1) Dissolve a quantity of the finely powdered tablets equivalent to about 20 mg of ketotifen in 10 ml of water, stir thoroughly and filter. Concentrate 2 ml of the filtrate on a water bath to about 1 ml, cool, add 1 ml of

sulfuric acid, a pale yellow colour is produced, and disappears on dilution with 2 ml of water.

(2) To 2 ml of the filtrate obtained under the Identification (1) add 1 ml of dinitrophenyl hydrazine TS, heat on a water bath, a red loose precipitate is produced gradually.

(3) The light absorption of the solution obtained under the Assay exhibits a maximum at 301 nm (Appendix IV A).

Content uniformity Use 1 tablets, carry out the method described under Assay beginning at the words "in a 100 ml volumetric flask". The results comply with the requirements (Appendix X E).

Dissolution Carry out the dissolution test (Appendix X C, method 3), using 200 ml of water as the dissolution medium, adjust the rotational speed of the paddle to 75 rpm. Withdraw 10 ml after exact 30 minutes and filter. Measure the absorbance of the successive filtrate at 301 nm (Appendix IV A). Calculate the dissolution of $C_{19}H_{19}NOS$ from each tablet, taking 465 as the value of A (1%, cm). Not less than 70% of the labelled amount is dissolved.

Other requirements Comply with the general requirements for tablets (Appendix I A).

Assay Weigh accurately and powder 20 tablets. Dissolve a quantity of the powdered tablets equivalent to about 1 mg of ketotifen in a 100 ml volumetric flask with water by shaking, dilute with water to volume, mix well and filter. Measure the absorbance of the successive filtrate at 301 nm (Appendix IV A), calculate the content of $C_{19}H_{19}NOS$, taking 465 as the value of A (1%, 1 cm).

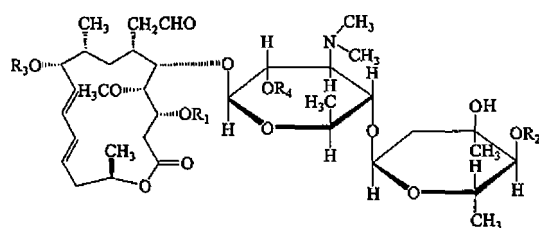
Category As described under Ketotifen Fumarate.

Strength 1 mg (Calculated as $C_{19}H_{19}NOS$)

Storage Preserve in tightly closed containers, protected from light.

Kitasamycin

(Leucomycin)



Kitasamycin A₁: R₁ = H R₂ = COCH₂CH(CH₃)₂

R₃ = H R₄ = H

Kitasamycin A₃: R₁ = COCH₃ R₂ = COCH₂CH(CH₃)₂

R₃ = H R₄ = H

Kitasamycin A₄: R₁ = H R₂ = COCH₂CH₂CH₃

R₃ = H R₄ = H

Kitasamycin A₅: R₁ = COCH₃ R₂ = COCH₂CH₂CH₃

R₃ = H R₄ = H

Kitasamycin A₆: R₁ = H R₂ = COCH₂CH₃

R₃ = H R₄ = H

Kitasamycin A₇: R₁ = COCH₃ R₂ = COCH₂CH₃

R₃ = H R₄ = H

Kitasamycin A₈: R₁ = COCH₃ R₂ = COCH₃

R₃ = H R₄ = H

Kitasamycin A₉: R₁ = H R₂ = COCH₃

R₃ = H R₄ = H

Kitasamycin A₁₃: R₁ = H R₂ = COCH₂CH₂CH₂CH₂CH₃

R₃ = H R₄ = H

Kitasamycin is a mixture mainly containing Kita-

samycin A₅, Kitasamycin A₄, Kitasamycin A₁ and Kitasamycin A₁₃. It has a potency of not less than 1300 Kitasamycin Units per mg, calculated on the anhydrous basis.

Description A white or almost white powder; taste; bitter. Very soluble in methanol, ethanol, acetone, chloroform or ether; Very slightly soluble in water; Insoluble in petroleum ether.

Identification (1) To about 10 mg add 5 ml of Sulphuric acid and shake slight, a reddish-brown colour is produced. (2) The retention time of the A₅, A₄, A₁₁, A₁₃ peaks of Kitasamycin in the substance being examined in the chromatogram obtained in the test for Kitasamycin components are identical with those of the four principal peaks of kitasamycin CRS in the chromatogram of the reference solution correspondingly.

Alkalinity Dissolve 0.1 g in 100 ml of water, shake and make it dissolve, pH 8.0-10.0 (Appendix VI H).

Water Not more than 3.0% (Appendix VII M, method 1 A).

Residue on ignition Not more than 0.5% (Appendix VII N), using 1.0 g.

Kitasamycin components Carry out the method for high performance liquid chromatography (Appendix V D), using a column packed with octadecylsilane bonded silica gel and a mixture of 0.1 mol/L ammonium acetate-methanol-acetonitrile (40 : 55 : 5) as the mobile phase. The column temperature is about 60°C, detection wavelength is 231 nm. The number of the theoretical plates of the column is not less than 3000, calculated with reference to the peak of kitasamycin A₅. The resolution factor between the adjacent peaks is not less than 1.0.

Procedure Dissolve an accurately weighed quantity in mobile phase to produce a solution containing 2 mg of kitasamycin per ml, mix well and filter. Inject 10 µl of the successive filtrate into the column and record the chromatogram. Dissolve an accurately weighed quantity in mobile phase to produce a solution containing 2 mg of kitasamycin CRS per ml, as reference solution (1); Transfer 5 ml of the solution into a 25 ml volumetric flask, dilute with mobile phase to volume and mix well, as reference solution (2). Repeat the operation, using reference solution (1) and reference solution (2) instead of the substance being examined. The retention times of kitasamycin active principal peaks are in this order: A₉, A₈, A₇, A₆, A₅, A₄, A₁, A₃ and A₁₃. Calculate the sum content of the main contents compare with the peak area of kitasamycin A₅ by the external standard method. The content of kitasamycin A₅ is 35%-70%, kitasamycin A₄ is 5%-25%, kitasamycin A₁, A₁₃ is 3%-15% respectively. The sum content of the kitasamycin A₉, A₈, A₇, A₆, A₅, A₄, A₁, A₃ and A₁₃ is not less than 85%.

Assay Dissolve an accurately weighed quantity in ethanol (using 1 ml of ethanol for 2 mg), dilute with sterile water to produce a solution of 1000 Units per ml. Carry out the microbiological assay of antibiotics (Appendix XI A).

Category Macrolide antibiotic.

Storage Preserve in tightly closed containers, stored in a dry place, protected from light.

Preparation Kitasamycin Tablet

Kitasamycin Tablets

... my i T bl ... o tai ... ot less than 90.0% and not more than 110.0% of the labelled amount of kitasamycin.

Description Sugar coated or film coated tablets with white or almost white core.

Identification (1) To a quantity of powdered tablets equivalent to about 10000 Units of kitasamycin, add 5 ml of Sulphuric acid and shake slightly, a reddish-brown colour is produced. (2) The retention times of the A_5 , A_4 , A_{11} , A_{13} peaks of Kitasamycin in the substance being examined in the chromatogram obtained in the test for kitasamycin components are identical with those of the four principal peaks of kitasamycin CRS in the chromatogram of the reference solution correspondingly.

Kitasamycin components Dissolve an accurately weighed quantity of powdered tablets in mobile phase to produce a solution of 2500 kitasamycin Units per ml, mix well and filter, carry out the test for Kitasamycin components described under Kitasamycin. The content of kitasamycin A_5 is 35%-70%, kitasamycin A_4 is 5%-25%, kitasamycin A_1 , A_{13} is 3%-15% respectively, calculated by the formula:
The content of Kitasamycin A_5 (A_4 , A_1 , A_{13})% =

$$\frac{A_T W_S \times \text{average weight} \times P \times \text{potency of kitasamycin CRS}}{A_S W_T \times \text{the labeled amount}} \times 100\%$$

Where A_T is the peak area of the kitasamycin A_5 (A_4 , A_1 , A_{13}) in the chromatogram;

A_S is the peak area of the kitasamycin A_5 CRS;

W_T is the weight of the substance being examined;

W_S is the weight of the kitasamycin CRS;

P is the percent content of the acetylspiramycin A_5 CRS.

Dissolution Carry out the dissolution test (Appendix X C, method 2), using 1000 ml of phosphate BS (pH 5.0) as the dissolution medium, adjust the rotational speed of the paddle to 75 rpm. Withdraw the solution at exact 45 minutes and filter. Dilute an accurately measured quantity of the successive filtrate with the dissolution medium to produce a solution of 20 μ g per ml. Triturate 10 tablets, to an accurately weighed quantity equivalent to about the average weight of one tablet add a quantity of ethanol (using 1 ml of ethanol for 2 mg of the labelled amount of kitasamycin) to make kitasamycin dissolve, dilute with the dissolution medium to produce a solution of 100 μ g per ml and filter. Dilute an accurately measured quantity of the successive filtrate with the dissolution medium to produce a solution of 20 μ g per ml. Measure the absorbance of the resulting solutions at 231 nm (Appendix IV A), calculate the dissolution of kitasamycin from each tablet. Not less than 80% is dissolved.

Other requirements Comply with the general requirements for tablets (Appendix I A).

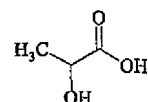
Assay Weigh accurately and triturate 10 tablets, weighed quantity in ethanol (using 1 ml of ethanol for 2 mg), dilute with sterile water to produce a solution of 1000 Units per ml, mix well and allow to stand. Measure accurately a quantity of the supernatant liquid and carry out the Assay described under Kitasamycin (Appendix VI A).

Category As described under Kitasamycin.

Strength 100000 units

Storage Preserve in tightly closed containers, stored in a dry place, protected from light.

Lactic Acid



$C_3H_6O_3$ 90.08

[50-21-5]

Lactic Acid is a mixture of 2-hydroxypropionic acid and its condensation products. It contains not less than 85.0% and not more than 90.0% of $C_3H_6O_3$ (g/g).

Description A clear colourless to pale yellow, viscous liquid; almost odourless; taste, slightly sour; hygroscopic. The aqueous solution exhibits acidic reaction. Miscible with water, ethanol or ether; insoluble in chloroform.

Relative density 1.20-1.21 (Appendix VI A).

Identification To the aqueous solution add potassium permanganate TS and heat, characteristic odour of acetaldehyde is evolved.

Chloride Carry out the limit test for chlorides (Appendix VIII A), using 3.0 g. Any opalescence produced is not more pronounced than that of a reference using 6.0 ml of sodium chloride standard solution (0.002%).

Sulfate Carry out the limit test for sulfates (Appendix VIII B), using 2.0 g. Any opalescence produced is not more pronounced than that of a reference using 2.0 ml of potassium sulfate standard solution (0.010%).

Citric, oxalic, phosphoric or tartaric acid To 0.5 g add a quantity of water to produce 5 ml, mix well, make it slightly alkaline with ammonia TS, add 1 ml of calcium chloride TS, heat in a water bath for 5 minutes. No opalescence is produced.

Readily carbonizable substances Transfer 5 ml of 95% (g/g) sulfuric acid to a clean test tube and add 5 ml of the substance being examined along the wall of test tube to form two layers, allow to stand for 15 minutes at 15°C. The colour of the interface between two layers is not more intense than pale yellow.

Reducing sugar Mix 0.5 g with 10 ml of water, neutralize with 20% sodium hydroxide solution, add 6 ml of alkaline cupric tartrate TS and boil for 2 minutes, no red precipitate is produced.

Residue on ignition Not more than 0.1% (Appendix VIII N).

Calcium salts Dissolve 1.0 g in 10 ml of water, neutralize the solution with ammonia TS, add a few drops of ammonium oxalate, no opalescence is produced.

Iron Carry out the limit test for iron (Appendix VIII G), using 1.0 g. Any colour produced is not more intense than that of a reference solution using 1.0 ml of iron standard solution (0.001%).

Heavy metals To 2.0 g add 10 ml of water and 1 drop of phenolphthalein IS, add dropwise ammonia TS until the colour of solution becomes pink, add 3 ml of dilute hydrochloric acid and sufficient water to produce 25 ml. Carry out the limit test for heavy metals (Appendix VIII H, method 1); not more than 0.001%.

Arsenic Dilute 2.0 g with 23 ml of water, add 5 ml of hydrochloric acid. Carry out the limit test for arsenic (Appendix

VIII J method 1); not more than 0.0001%.

Assay Weigh accurately about 1 g, add 50 ml of water and 25 ml of sodium hydroxide (1 mol/L) VS, accurately measured, boil for 5 minutes. Add 2 drops of phenolphthalein IS, titrate with sulfuric acid (0.5 mol/L) VS while hot. Perform a blank determination and make any necessary correction. Each ml of sodium hydroxide (1 mol/L) VS is equivalent to 90.08 mg of $C_6H_{13}O_2$.

Category Antiseptic, disinfectant.

Storage Preserve in tightly closed containers.

Lactulose Oral Solution

Lactulose Oral Solution is a sterile solution of lactulose. It contains not less than 90.0% and not more than 110.0% of the labelled amount of lactulose ($C_{12}H_{22}O_{11}$).

Description A clear, brownish-yellow viscous liquid.

Identification (1) To 5 ml of hot alkaline cupric tartrate TS add dropwise 5% aqueous solution, a red precipitate of cuprous oxide is produced.

(2) The retention time of principal peaks of the lactulose in the substance being examined in the chromatogram obtained in the Assay are identical with that the principal peak of lactulose CRS in the chromatogram of the reference solution.

Relative density 1.260-1.390 (Appendix VI A).

pH value 3.0-7.0 (Appendix VI H) after 15 minutes of contact with the electrodes.

Related substances Calculate the results from the Assay. It contains not more than 18.0% of lactose, not more than 12.0% of galactose and not more than 2.0% of fructose.

Residue on ignition Not more than 0.3% (Appendix VIII N); use 1.0 g.

Heavy metals Carry out the limit test for heavy metals (Appendix VIII H, method 1), using the residue obtained in the test for Residue on ignition; not more than 0.002%.

Other requirements Complies with the general requirements for oral solutions (Appendix I O), and the Salmonella is not detected.

Assay Carry out the method for high performance liquid chromatography (Appendix V D), using a column packed with aminopropylsilyl silica gel and a mixture of acetonitrile-water (77 : 23) as the mobile phase, detect with differential refractive index detector.

Procedure Transfer an accurately measured quantity of the oral solution equivalent to about 1 g of lactulose in a 50 ml volumetric flask by a "to contain" pipet. Wash the pipet and dilute to volume with water. Inject 10 μ l of the solution into the column, record the chromatogram. Weigh accurately about 500 mg of lactulose CRS, 180 mg of lactose CRS, 100 mg of galactose CRS and 20 mg of fructose CRS that previously dried at 60°C under reduced pressure for 16 hours. Transfer to a 25 ml volumetric flask, dissolve and dilute with water to volume, mix well. Repeat the operation, using these reference solutions, calculate the content of $C_{12}H_{22}O_{11}$ by the external standard method.

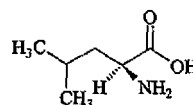
Category Hypoammoniaemic and laxative.

Strength (1) 10 ml : 5 g (2) 100 ml : 50 g
(3) 100 ml : 66.7 g

Storage Preserve in tightly closed containers, protected

from light.

Leucine



$C_6H_{13}NO_2$ 131.17

[61-90-5]

Leucine is (L)-2-amino-4-methylpentanoic acid. It contains not less than 98.5% of $C_6H_{13}NO_2$, calculated on the dried basis.

Description White crystals or a white crystalline powder; odourless; taste, slightly bitter. Freely soluble in formic acid; sparingly soluble in water; very slightly soluble in ethanol or ether.

Specific optical rotation +14.5° to +16.0°, in a solution of 40 mg per ml in 6 mol/L hydrochloric acid solution (Appendix VI E).

Identification The infrared absorption spectrum (Appendix IV C) is concordant with the reference spectrum of Leucine (Appendix XVI).

Acidity Heat to dissolve 0.50 g in 50 ml of water, cool to room temperature. pH 5.5-6.5 (Appendix VI H).

Transmittance of solution Heat to dissolve 0.50 g in 50 ml of water, cool to room temperature. The transmittance at 430 nm is not less than 98.0% (Appendix IV A).

Chloride Carry out the limit test for chloride (Appendix VIII A), using 0.25 g. Any opalescence produced is not more pronounced than that of a reference solution using 5.0 ml of sodium chloride standard solution (0.02%).

Sulfate Carry out the limit test for sulfate (Appendix VIII B), using 1.0 g. Any opalescence produced is not more pronounced than that of a reference solution using 2.0 ml of potassium sulfate standard solution (0.02%).

Ammonium Carry out the limit test for ammonium (Appendix VIII K), using 0.10 g. Any colour produced is not more intense than that of a reference solution using 2.0 ml of ammonium chloride standard solution (0.02%).

Other amino acids Carry out the method for thin-layer chromatography (Appendix V B), using silica gel G as the coating substance and a mixture of *n*-butanol-water-glacial acetic acid (3 : 1 : 1) as the mobile phase. Apply separately to the plate 5 μ l of each of two solutions of the substance being examined in water containing (1) 4 mg per ml, (2) 20 μ g per ml. After developing and removal of the plate, dry it in air and spray with ninhydrin solution (dissolve 1g ninhydrin in 50 ml of acetone) and heat at 80°C until the colour is produced and examine immediately. Any spot other than the principal spot in the chromatogram, obtained with solution (1) is not more intense than the principal spot obtained with solution (2).

Loss on drying When dried at 105°C for 3 hours, loses not more than 0.2% of its weight (Appendix VIII L).

Residue on ignition Not more than 0.1% (Appendix VIII N), using 1.0 g.

Iron Carry out the limit test for iron (Appendix VIII G), using 1.5 g. Any colour produced is not more intense than that of a reference solution using 1.5 ml of iron standard solution (0.001%).

Heavy metals Carry out the limit test for heavy metals (Appendix VIII H, method 2), using the residue obtained in the test for Residue on ignition; not more than 0.001%.

Arsenic Dissolve 2.0 g in 5 ml of water, add 1 ml of sulfuric acid and 10 ml of sulfite acid, evaporate to about 2 ml on a water bath, add 5 ml of water, add dropwise ammonia TS until phenolphthalein IS changes the colour. Add 5 ml of hydrochloric acid and sufficient water to produce 28 ml. Carry out the limit test for arsenic (Appendix VII J, method 1); not more than 0.0001%.

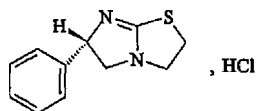
Bacterial endotoxin Carry out the test for bacterial endotoxin (Appendix XI E); less than 25 EU per g of leucine (for parenteral administration).

Assay Dissolve about 0.1 g, accurately weighed, in 1 ml of dehydrated formic acid, add 25 ml of glacial acetic acid. Carry out the method for potentiometric titration (Appendix VII A), titrate with perchloric acid (0.1 mol/L) VS. Perform a blank determination and make any necessary correction. Each ml of perchloric acid (0.1 mol/L) VS is equivalent to 13.12 mg of $C_{11}H_{12}N_2S$.

Category Amino acid.

Storage Preserve in tightly closed containers, protected from light.

Levamisole Hydrochloride



$C_{11}H_{12}N_2S \cdot HCl$ 240.76 [16595-80-5]

Levamisole Hydrochloride is (S)-(-)-6-phenyl-2,3,5,6-tetrahydroimidazo [2,1-b] thiazole hydrochloride. It contains not less than 98.5% of $C_{11}H_{12}N_2S \cdot HCl$, calculated on the dried basis.

Description White or almost white, needle crystals or a crystalline powder; odourless; taste, bitter. Very soluble in water; freely soluble in ethanol; slightly soluble in chloroform; very slightly soluble in acetone.

Melting range 225-230°C (Appendix VI C).

Specific optical rotation Not less than -121.5° , in a solution of 50 mg per ml in water (Appendix VI E).

Identification (1) Dissolve about 60 mg in 20 ml of water, add 2 ml of sodium hydroxide TS, boil for 10 minutes and cool, add a few drops of sodium nitroprusside TS; a red colour is produced, which fades on standing.

(2) The infrared absorption spectrum (Appendix IV C) is concordant with the reference spectrum of levamisole hydrochloride (Appendix XVI).

(3) The aqueous solution yields the reactions characteristic of chlorides (Appendix III).

Clarity of solution A solution of 2.0 g in 50 ml of freshly boiled and cooled (20-25°C) water is clear; any opalescence produced is not more pronounced than that of a reference suspension 2 (Appendix IX B).

Acidity The solution obtained in the test for Clarity of solution, pH 3.5-5.0 (Appendix VI H).

Light absorption The absorbance of a solution of 1 mg in 1 ml of methanolic hydrochloric acid (0.2 mol/L) VS (Appendix IV A) is not greater than 0.20, measured at 310

nm.

2-Iminothiazolidine derivatives Dissolve 50 mg in a mixture of 10 ml of dilute ethanol and 25 ml of water, add 5 ml of ammonia TS and heat at 50°C in a water bath for 5 minutes; Add 2 ml of silver nitrate TS and a sufficient quantity of water to produce 50 ml, mix well, heat at 50°C in a water bath for 10 minutes. Any opalescence produced is not more pronounced than that of a reference solution (to 2 ml of sodium chloride standard solution add water to produce 40 ml; add 1 ml of nitric acid and 1 ml of silver nitrate TS, dilute with water to 50 ml, mix well and allow to stand in a dark place for 5 minutes).

2,3-Dihydro-6-phenylimidazo [2,1-b] thiazole hydrochloride Carry out the method for thin-layer chromatography (Appendix V B), using silica gel G as the coating substance and a mixture of toluene-methanol-glacial acetic acid (45 : 8 : 4) as the mobile phase. Apply separately to the plate 5 μ l each of two solutions in methanol containing (1) 0.10 g per ml of the substance being examined, (2) 0.50 mg per ml of 2,3-dihydro-6-phenylimidazo [2,1-b] thiazole hydrochloride CRS. After developing and removal of the plate, dry it in air and visualize with iodine vapour. Any spot other than the principal spot in the chromatogram obtained with solution (1), is not more intense than that of the principal spot in the chromatogram obtained with solution (2) (0.5%).

Loss on drying When dried to constant weight at 105°C, loses not more than 0.5% of its weight (Appendix VIII L).

Residue on ignition Not more than 0.1% (Appendix VIII N).

Assay Dissolve about 0.2 g, accurately weighed, in 30 ml ethanol. Carry out the method for potentiometric titration (Appendix VII A), titrate with sodium hydroxide (0.1 mol/L) VS. Perform a blank determination and make any necessary correction. Each ml of sodium hydroxide (0.1 mol/L) VS is equivalent to 24.08 mg of $C_{11}H_{12}N_2S \cdot HCl$.

Category Anthelmintics. Biological response modifier.

Storage Preserve in tightly closed containers.

Preparation (1) Levamisole Hydrochloride Enteric-coated Tablets
(2) Levamisole Hydrochloride Granules
(3) Levamisole Hydrochloride Syrup
(4) Levamisole Hydrochloride Tablets

Levamisole Hydrochloride Enteric-coated Tablets

Levamisole Hydrochloride Enteric-coated Tablets contains not less than 90.0% and not more than 110.0% of the labelled amount of levamisole hydrochloride ($C_{11}H_{12}N_2S \cdot HCl$).

Description Enteric-coated tablets, with white core.

Identification A quantity of the powdered tablets with enteric-coating removed complies with the tests for Identification described under Levamisole Hydrochloride Tablets.

Drug Release Comply with the drug release test [Appendix X D method 2 (1)], using the apparatus of dissolution test method L. Adjust the rotational speed of the basket to 100 rpm. The rotational time in buffer solution is 60 minutes. To 3.0 ml of the filtrate accurately measured released in the acid solvent add 1.0 ml of 0.2 mol/L sodium phosphate solution, mix well, use as the test preparation (1), the filtrate released in the buffer solution as the test preparation (2). Weigh accurately a quantity of levamisole hydrochloride

CRS, dissolve in a phosphate BS ($\text{pH } 6.8 \pm 0.05$) [measure 750 ml of hydrochloric acid solution ($9 \rightarrow 1000$), add 250 ml of 0.2 mol/L sodium phosphate solution, adjust pH to 6.8 ± 0.05] to produce a solution of 25 μg per ml as the reference preparation. Transfer accurately 2 ml each of the above three solution to three separators. To each separator add 3.0 ml of bromocresol green solution [dissolve 50 mg of bromocresol green in 50 ml of 0.2 mol/L potassium hydrogen phthalate solution, adjust to pH 4.5 with 0.2 mol/L sodium hydroxide solution and dilute with water to 100 ml, mix well, filter if necessary], mix well, shake with 10 ml of chloroform for 1 minutes. Allow to stand until the mixture separates into two layers. Measure the absorbance of the chloroform layer at 420 nm (Appendix IV A). Calculate the amount of $\text{C}_{11}\text{H}_{12}\text{N}_2\text{S} \cdot \text{HCl}$ dissolved from each tablet, the results comply with the requirements.

Other requirements Comply with the general requirements for tablets (Appendix I A).

Assay Weigh accurately and powder 20 tablets with enteric-coating removed. Weigh accurately a quantity of the powder equivalent to about 0.2 g of levamisole hydrochloride to a separator, add 10 ml of water, shake to dissolve levamisole hydrochloride. Add 5 ml of sodium hydroxide TS and shake gently, extract with 50 ml of chloroform measured accurately, filter the chloroform layer with dry filter paper and discard the initial filtrate. To 25 ml of the successive filtrate, accurately measured, add 15 ml of glacial acetic acid and 1 drop of crystal violet IS. Titrate with perchloric acid (0.1 mol/L) VS until the colour changes to blue. Perform a blank determination and make any necessary correction. Each ml of perchloric acid (0.1 mol/L) VS is equivalent to 24.08 mg of $\text{C}_{11}\text{H}_{12}\text{N}_2\text{S} \cdot \text{HCl}$.

Category As described under Levamisole Hydrochloride.

Strength (1) 25 mg (2) 50 mg

Storage Preserve in tightly closed containers.

Levamisole Hydrochloride Granules

Levamisole Hydrochloride Granules contain not less than 90.0% and not more than 110.0% of the labelled amount of Levamisole Hydrochloride ($\text{C}_{11}\text{H}_{12}\text{N}_2\text{S} \cdot \text{HCl}$).

Description Water soluble granules.

Identification (1) Place a quantity of the powder equivalent to about 0.1 g levamisole hydrochloride in a separator, add 25 ml of water and shake to dissolve levamisole hydrochloride. Add 3 ml of sodium hydroxide TS and 10 ml of chloroform and shake gently. Separate the chloroform layer and evaporate it on a water bath to dryness. Dissolve the residue in 2 ml of dilute hydrochloric acid, add 20 ml of water and 3 ml of sodium hydroxide TS, boil for 10 minutes and allow to cool, add a few drops of sodium nitroprusside TS; a red colour is produced, which fades on standing. (2) Dissolve 1 g of the granules with 10 ml of water, the aqueous solution yields the reactions characteristic of chlorides (Appendix III).

Loss on drying When dried to constant weight at 105°C , losses not more than 2.0% of its weight (Appendix VIII L).

Other requirements Comply with the general requirements for granules (Appendix I N).

Assay Weigh accurately and powder a quantity of well mixed contents obtained in test for weight variation of contents equivalent to about 0.2 g of levamisole hydrochloride into a

separator. Add 10 ml of water, shake to dissolve levamisole hydrochloride. Add 5 ml of sodium hydroxide TS and shake gently, extract with 50 ml of chloroform measured accurately, filter the chloroform layer with dry filter paper and discard the initial filtrate. To 25 ml of the successive filtrate, accurately measured, add 15 ml of glacial acetic acid and 1 drop of crystal violet IS. Titrate with perchloric acid (0.1 mol/L) VS until the colour changes to blue. Perform a blank determination and make any necessary correction. Each ml of perchloric acid (0.1 mol/L) VS is equivalent to 24.08 mg of $\text{C}_{11}\text{H}_{12}\text{N}_2\text{S} \cdot \text{HCl}$.

Category As described under Levamisole Hydrochloride.

Strength 10 g : 50 mg

Storage Preserved in tightly closed containers, stored in a cool and dry place.

Levamisole Hydrochloride Syrup

Levamisole Hydrochloride Syrup contains not less than 90.0% and not more than 110.0% of the labelled amount of levamisole hydrochloride ($\text{C}_{11}\text{H}_{12}\text{N}_2\text{S} \cdot \text{HCl}$).

Description A clear, brown viscous liquid; taste, sweetish.

Identification To 10 ml of the syrup add 4 ml of sodium hydroxide TS and 30 ml of chloroform, shake thoroughly, allow to separate into two layers; evaporate the chloroform layer to dryness, dissolve the extract with water, add 2 ml of sodium hydroxide TS, boil for 10 minutes and cool (filter if necessary), add a few drops of sodium nitroprusside TS; a red colour is produced, which fades on standing.

Relative density 1.20-1.30 (Appendix VI A).

Other requirements Complies with the general requirements for syrups (Appendix I K).

Assay Measure accurately 25 ml of the syrup with a to contain pipet to a separator, wash the inner wall of the pipet with a quantity of water. Add 10 ml of water, shake to dissolve levamisole hydrochloride. Add 5 ml of sodium hydroxide TS and shake gently, extract with 50 ml of chloroform measured accurately, filter the chloroform layer with dry filter paper and discard the initial filtrate. To 25 ml of the successive filtrate, accurately measured, add 15 ml of glacial acetic acid and 1 drop of crystal violet IS. Titrate with perchloric acid (0.05 mol/L) VS or (0.02 mol/L) VS for strength (10 ml : 20 mg) until the colour changes to blue. Perform a blank determination and make any necessary correction. Each ml of perchloric acid (0.05 mol/L) VS or (0.02 mol/L) VS is equivalent to 12.04 mg or 4.815 mg of $\text{C}_{11}\text{H}_{12}\text{N}_2\text{S} \cdot \text{HCl}$.

Category As described under Levamisole Hydrochloride.

Strength (1) 10 ml : 20 mg (2) 100 ml : 0.8 g
(3) 500 ml : 4.0 g (4) 2000 ml : 16.0 g

Storage Preserved in tightly closed containers, protected from light.

Levamisole Hydrochloride Tablets

Levamisole Hydrochloride Tablets contain not less than 90.0% and not more than 110.0% of the labelled amount of levamisole hydrochloride

($C_{11}H_{12}N_2S \cdot HCl$).

Description White tablets or sugar-coated tablets.

Identification To a quantity of the powder equivalent to about 0.15 g of levamisole hydrochloride add 50 ml of water, shake to dissolve levamisole hydrochloride and filter; the filtrate complies with tests (1) and (3) for Identification described under Levamisole Hydrochloride.

Dissolution Comply with the dissolution test (Appendix X C, method 1), using 900 ml of water as dissolution medium, adjust the rotational speed of the paddle to 100 rpm. Withdraw 10 ml of the solution after exactly 30 minutes and filter. The successive filtrate is used as the test solution. Dissolve a quantity of levamisole hydrochloride CRS, weighed accurately, in water to produce a reference solution of 0.4 mg per ml. Measure accurately 1.0 ml, 2.0 ml, 3.0 ml, 4.0 ml and 5.0 ml of the reference solution to 100 ml volumetric flasks separately, dilute with 0.1 mol/L sodium hydroxide solution to their volumes and mix well. Measure the primary derivative curves of the resulting solutions at 220–250 nm and the value D on zero-amplitude of the peaks separately and perform a blank measure with 0.1 mol/L sodium hydroxide. Calculate the regression equation between the value D and the concentration C. Measure accurately 5.0 ml of the test solution to 10 ml (for strength 25 mg) or 20 ml (for strength 50 mg) volumetric flask, dilute to volume with 0.2 mol/L sodium hydroxide solution and mix well. Measure the primary derivative curve of the resulting solution and the value D on zero-amplitude of the peak, and calculate the dissolution of $C_{11}H_{12}N_2S \cdot HCl$ from each tablet with the regression equation. Not less than 80% of the labelled amount is dissolved.

Other requirements Comply with the general requirements for tablets (Appendix I A).

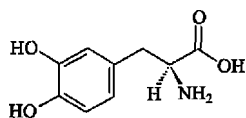
Assay Weigh accurately and powder finely 20 tablets. Weigh accurately a quantity of the powder equivalent to about 0.2 g of levamisole hydrochloride to a separator, add 10 ml of water, shake to dissolve levamisole hydrochloride; add 5 ml of sodium hydroxide TS and shake gently. Extract with 50 ml of chloroform measured accurately, filter the chloroform layer with dry filter paper and discard the initial filtrate. To 25 ml of the successive filtrate, accurately measured, add 15 ml of glacial acetic acid and 1 drop of crystal violet IS. Titrate with perchloric acid (0.1 mol/L) VS until the colour changes to blue. Perform a blank determination and make any necessary correction. Each ml of perchloric acid (0.1 mol/L) VS is equivalent to 24.08 mg of $C_{11}H_{12}N_2S \cdot HCl$.

Category As described under Levamisole Hydrochloride.

Strength (1) 25 mg (2) 50 mg

Storage Preserve in tightly closed containers.

Levodopa



$C_9H_9NO_4$ 197.19

[59-92-7]

Levodopa is 3-hydroxy-L-tyrosine. It contains not less than 98.0% of $C_9H_9NO_4$, calculated on the dried basis.

Description A white or almost white crystalline powder, odourless; tasteless.

Slightly soluble in water; insoluble in ethanol, chloroform or ether; freely soluble in dilute acids.

Specific optical rotation -159° to -168° (Appendix VI E). To about 0.2 g, accurately weighed, in a 25 ml amber coloured volumetric flask, add 5 g of urotropin and dissolve in a quantity of hydrochloric acid solution (9→100), make up to volume and mix well. Allow the solution to stand for 3 hours, protected from light before the measurement.

Specific absorbance Measure the absorbance of a solution of 30 μ g per ml in hydrochloric acid solution (9→1000) at 280 nm (Appendix IV A), the value of A (1%, 1 cm) is 136–146.

Identification (1) Dissolve about 5 mg in 5 ml of hydrochloric acid solution (9→1000), add 2 drops of ferric chloride TS; a green colour is produced. To 2.5 ml of the solution add an excess of dilute ammonia solution; a purple colour is produced. To the remainder of the solution add an excess of sodium hydroxide TS; a red colour is produced.

(2) Dissolve about 5 mg in 5 ml of water, add 1 ml of 1% ninhydrin solution and warm in a water bath; the solution becomes purple gradually.

(3) The infrared absorption spectrum (Appendix IV C) is concordant with the reference spectrum of levodopa (Appendix XVI).

Clarity and colour of acid solution A solution of 0.4 g in 10 ml of hydrochloric acid solution (9→100) is clear. Any colour produced is not more intense than that of reference solution YG₂ or Y₂ (Appendix IX A, method 1).

Chloride Carry out the limit test for chlorides (Appendix VIII A), using 0.30 g. Any opalescence produced is not more pronounced than that of a reference using 6.0 ml of sodium chloride standard solution (0.02%).

Foreign amino acids Carry out the method for thin-layer chromatography (Appendix V B), using microcrystalline cellulose (0.15 g/10 cm²) as the coating substance and nbutanol-glacial acetic acid-water (2 : 1 : 1) as the mobile phase. Apply separately to the plate 10 μ l each of three solutions in hydrochloric acid solution (9→1000) containing (1) 10 mg per ml, (2) 0.10 mg per ml of the substance being examined and (3) 10 mg of the substance being examined and 0.10 mg of L-tyrosine per ml. After developing and removal of the plate, dry it in air and spray with a mixture of 10% ferric chloride solution and 5% potassium ferricyanide solution (1 : 1), freshly prepared. Any spot in the chromatogram other than the principal spot obtained with solution (1) is not more intense than the principal spot obtained with solution (2), while spots corresponding to levodopa and tyrosine are both present in the chromatogram obtained with solution (3).

Loss on drying When dried to constant weight at 105°C loses not more than 1.0% of its weight (Appendix VIII L).

Residue on ignition Not more than 0.1% (Appendix VIII N) using 1.0 g.

Heavy metals Carry out the limit test for heavy metals (Appendix VIII H, method 2), using the residue obtained in the test for Residue on ignition; not more than 0.001%.

Assay Dissolve about 0.15 g, accurately weighed, in 2 ml of anhydrous formic acid, add 20 ml of glacial acetic acid and mix well, add 2 drops of crystal violet IS, titrate with perchloric acid (0.1 mol/L) VS until a green colour is obtained. Perform a blank determination and make any necessary correction. Each ml of perchloric acid (0.1 mol/L) VS is equivalent to 19.72 mg of $C_9H_9NO_4$.

Category Anti-Parkinsonian agent.

Storage Preserve in tightly closed containers, protected from light.

Preparation (1) Levodopa Capsules
(2) Levodopa Tablets

Levodopa Capsules

Levodopa Capsules contain not less than 90.0% and not more than 110.0% of the labelled amount of levodopa ($C_9H_{11}NO_4$).

Description Capsules containing white or almost white granules or powder.

Identification The contents of capsules comply with the test (1) and (2) for Identification described under Levodopa.

Dissolution Carry out the dissolution test (Appendix X C, method 1), using 900 ml of hydrochloric acid solution (9→1000) as the dissolution medium, adjust the rotational speed of the basket to 100 rpm. Withdraw 10 ml of the solution after exactly 30 minutes and filter. Measure accurately 5 ml of the successive filtrate to a 50 ml volumetric flask, dilute with the same dissolution medium to volume and mix well. Measure the absorbance of the resulting solution at 280 nm (Appendix IV A) and calculate the dissolution of $C_9H_{11}NO_4$ from each capsule, taking 141 as the value of A (1%, 1 cm). Not less than 80% of the labelled amount is dissolved.

Other requirements Comply with the general requirements for capsules (Appendix I E).

Assay Weigh accurately a quantity of mixed contents obtained in the test for weight variation of contents equivalent to about 30 mg of levodopa and carry out the Assay described under Levodopa Tablets beginning at the words "to a 100 ml volumetric flask . . .", calculate the content of $C_9H_{11}NO_4$.

Category As described under Levodopa.

Strength 0.25 g

Storage Preserve in tightly closed containers, protected from light.

Levodopa Tablets

Levodopa Tablets contain not less than 95.0% and not more than 105.0% of the labelled amount of levodopa ($C_9H_{11}NO_4$).

Description White or almost white tablets or film coated tablets with white or almost white core.

Identification Comply with tests (1) and (2) for Identification described under Levodopa, using a quantity of the powdered tablets.

Dissolution Carry out the dissolution test (Appendix X C, method 1), using 900 ml of hydrochloric acid solution (9→1000) as the dissolution medium, adjust the rotational speed of the basket to 100 rpm. Withdraw 10 ml of the solution after exactly 30 minutes and filter. Transfer 5 ml of the successive filtrate, accurately measured, to a 10 ml volumetric flask (for strength 50 mg), to a 25 ml volumetric flask (for strength 125 mg) or to a 50 ml volumetric flask (for strength 250 mg). Dilute with the same dissolution medium to volume and mix well. Measure the absorbance of the resulting solution at 280 nm (Appendix IV A). Calculate the

dissolution of $C_9H_{11}NO_4$ from each tablet, taking 141 as the value of A (1%, 1 cm). Not less than 80% of the labelled amount is dissolved.

Other requirements Comply with the general requirements for tablets (Appendix I A).

Assay Weigh accurately and powder 10 tablets. To an accurately weighed quantity equivalent to about 30 mg of levodopa in a 100 ml volumetric flask add a quantity of hydrochloric acid solution (9→1000), shake well and then add hydrochloric acid solution (9→1000) to volume, mix well and filter. Discard the initial filtrate, measure accurately 10 ml of the successive filtrate to another 100 ml volumetric flask, add hydrochloric acid solution (9→1000) to volume and mix well. Measure the absorbance of the resulting solution at 280 nm (Appendix IV A), calculate the content of $C_9H_{11}NO_4$, taking 141 as the value of A (1%, 1 cm).

Category As described under Levodopa.

Strength (1) 50 mg (2) 125 mg (3) 250 mg

Storage Preserve in tightly closed containers, protected from light.

Levodopa and Benserazide Hydrochloride Capsules

Levodopa and Benserazide Hydrochloride Capsules contain not less than 90.0% and not more than 110.0% of the labelled amount of levodopa ($C_9H_{11}NO_4$) and benserazide hydrochloride ($C_{10}H_{15}N_3O_5 \cdot HCl$) respectively.

Identification (1) Shake about 0.5 g of the contents with 10 ml of water, filter. The filtrate complies with tests (1) for Identification described under Benserazide Hydrochloride. The residue complies with tests (2) for Identification described under Levodopa.

(2) The retention time of principal peaks of the benserazide hydrochloride and levodopa in the substance being examined in the chromatogram obtained in the Assay are identical with that of the principal peaks of benserazide hydrochloride CRS and levodopa CRS in the chromatogram of the reference solution correspondingly.

Loss on drying When dried to constant weight under reduced pressure in a desiccator over phosphorus pentoxide, the contents of the capsules being examined lose not more than 1.0% of their weight (Appendix VIII L).

Other requirements Comply with the general requirements for capsules (Appendix I E).

Assay Carry out the method for high performance liquid chromatography (Appendix V D), using a column packed with octadecylsilane bonded silica gel and a mixture of trifluoroacetic acid-methanol-water (1 : 20 : 1000) as the mobile phase. Detection wavelength is 220 nm and the number of theoretical plates of the column is not less than 1000, calculated with reference to the peak of benserazide hydrochloride. The resolution factor between the peaks of levodopa and benserazide hydrochloride complies with the related requirements.

Procedure Dissolve a quantity of the mixed contents obtained in weight variation equivalent to 15 mg of benserazide hydrochloride and 20 mg of levodopa respectively, accurately weighed, in a 50 ml amber coloured volumetric flask with mobile phase and dilute to volume, shake well. Filter and inject 10 μ l of the successive filtrate into the column, record the peak areas

correspondingly obtained in the chromatogram. Repeat the operation, using benserazide hydrochloride CRS and levodopa CRS instead of the substance being examined. Calculate the contents of $C_9H_{11}NO_4$ and $C_{10}H_{15}N_3O_5 \cdot HCl$ respectively with respect to the peak area obtained in the chromatogram by the external standard method.

Category As described under Levodopa.

Strength (1) levodopa 100 mg and benserazide 25 mg (equivalent to 28.5 mg of benserazide hydrochloride)
(2) levodopa 200 mg and benserazide 50 mg (equivalent to 57 mg of benserazide hydrochloride)

Storage Preserve in tightly closed containers, protected from light, stored in a cool and dry place.

Levodopa and Benserazide Hydrochloride Tablets

Levodopa and Benserazide Hydrochloride Tablets contain not less than 90.0% and not more than 110.0% of the labelled amounts of levodopa ($C_9H_{11}NO_4$) and benserazide hydrochloride ($C_{10}H_{15}N_3O_5 \cdot HCl$).

Description Pale red tablets (containing colouring matter).

Identification (1) Triturate 1 tablet with 10 ml of water, shake well and filter. To 2 ml of the filtrate in a clean test tube, add 1 ml of ammoniacal silver nitrate TS, a brown colour is produced; silver is reduced and deposited as a mirror on the wall of tube when heated in a water bath. Dilute another 1 ml of the filtrate with water to 20 ml. To 5 ml of the solution add 1 ml of 1% ninhydrin solution and warm in a water bath, the solution becomes purple gradually.

(2) ... e. n. n. ... e. ... p. n. c. p. ... e. n. e. ... hydrochloride and levodopa in the substance being examined in the chromatogram obtained in the Assay are identical with those of the principal peaks of benserazide hydrochloride CRS and levodopa CRS in the chromatogram of the reference solution correspondingly.

DL-Serinhydrazide hydrochloride an DL-2-amino-N', N'- is (2,3,4-trihydroxybenzyl) hydracrylohydrazide hydrochloride Proceed as described in the Assay. Calculate the contents of DL-serinhydrazide hydrochloride (impurity A) and DL-2-amino-N', N'-bis (2,3,4-trihydroxybenzyl) hydracrylohydrazide hydrochloride (impurity B) respectively with respect to the peak height of impurity A and the peak area of impurity B obtained in the chromatogram by the external standard method. Impurity A and impurity B are not more than 2.0% and 3.0% of the labelled amount of benserazide hydrochloride ($C_{10}H_{15}N_3O_5 \cdot HCl$) respectively.

Other requirements Comply with the general requirements for tablets (Appendix I A).

Assay Carry out the method for high performance liquid chromatography (Appendix V D), using a column packed with octylsilane bonded silica gel and a mixture of 0.05 mol/L potassium dihydrogen phosphate-methanol-acetonitrile (70.5 : 25 : 4.5) (containing 0.005 mol/L sodium decane-sulfonate, adjusted to pH 3.5 with phosphoric acid) as the mobile phase. Detection wavelength is 270 nm for levodopa, and then changed to 220 nm after elution of levodopa peak. The number of theoretical plates of the column is not less than 1000, calculated with reference to the peak of benserazide hydrochloride. The resolution factor among the peaks of levodopa, impurity A, benserazide hydrochloride and impurity

B complies with the related requirements.

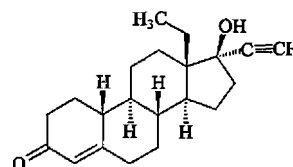
Procedure Weigh accurately and powder 10 tablets. Weigh accurately a quantity of the powdered tablets equivalent to 100 mg of levodopa and 28.5 mg of benserazide hydrochloride into a 200 ml volumetric flask, add 180 ml of mobile phase, treat in an ultrasonic bath for 2 minutes, shake for 15 minutes, dilute with mobile phase to volume, mix well and filter. Use the successive filtrate as test solution. Inject 20 μ l of the test solution into the column immediately, and record the chromatogram. Dissolve separately a quantity of impurity A CRS and impurity B CRS, both accurately weighed, in mobile phase to produce solutions both of 0.285 mg per ml as impurity A reference solution and impurity B reference solution. Weigh accurately about 100 mg of levodopa CRS and about 28.5 mg CRS of benserazide hydrochloride CRS into the same 200 ml volumetric flask, add a quantity of mobile phase, shake until dissolved, add 2 ml of impurity A reference solution and 3 ml of impurity B reference solution, both accurately measured, dilute with mobile phase to volume and mix well. Use the resulting solution as reference solution. Inject 20 μ l of the reference solution into the column immediately, and record the chromatogram. Calculate the contents of $C_9H_{11}NO_4$ and $C_{10}H_{15}N_3O_5 \cdot HCl$ respectively with respect to the peak area obtained in the chromatogram by the external standard method.

Category As described under Levodopa.

Strength levodopa 200 mg and benserazide 50 mg (equivalent to benserazide hydrochloride 57 mg)

Storage Preserve in tightly closed containers, stored in a cool and dry place and protected from light.

Levonorgestrel



$C_{21}H_{28}O_2$ 312.47

[797-63-7]

Levonorgestrel is D (-)-13-ethyl-17 β -hydroxy-18, 19-dinor-17 α -pregn-4-en-20-yn-3-one. It contains not less than 97.0% and not more than 103.0% of $C_{21}H_{28}O_2$.

Description A white or almost white crystalline powder; odourless; tasteless. Soluble in chloroform; slightly soluble in methanol; insoluble in water.

Melting range 233-239°C, melting within 5°C (Appendix VI C).

Specific optical rotation -30°C to -35°C in a solution of 20 mg per ml in chloroform (Appendix VI E).

Identification (1) The retention time of principal peak of the substance being examined is identical with that of principal peak of the reference solution in the chromatogram obtained in Assay.

(2) The infrared absorption spectrum (Appendix IV C) is concordant with the reference spectrum of Levonorgestrel (Appendix XVI).

Related substances Carry out the method as described under

Assay. Dissolve a quantity of the substance being examined in the mobile phase to produce a solution of about 75 µg per ml (solution 1), and dilute accurately 2 ml to 100 ml with the mobile phase as solution 2. Inject 20 µl of solution 2 into the column. Adjust the attenuation so that the principal peak height in the chromatogram is 20% full scale of the chart. And then inject separately 20 µl each of solution 1 and 2 into the column, and record the chromatogram for twice the retention time of the principal peak. The sum of the areas of all peaks other than the principal peak in the chromatogram obtained with solution 1 is not greater than the area of the principal peak obtained with solution 2.

Ethinyl group Dissolve about 100 mg, accurately weighed, in 40 ml of tetrahydrofuran, add 10 ml of 5% silver nitrate solution. Carry out the method for potentiometric titration (Appendix VI A), titrate with sodium hydroxide (0.1 mol/L) VS. Each ml is equivalent to 2.503 mg of ethinyl group ($-\text{C}\equiv\text{CH}$), it contains not less than 7.81% and not more than 8.18% of ethinyl group.

Assay Carry out the method for high performance liquid chromatography (Appendix V D), using a column packed with octadecylsilane bonded silica gel and a mixture of acetonitrile-water (70 : 30) as the mobile phase. Detection wavelength is 240 nm and the number of the theoretical plates of the column is not less than 2000, calculated with reference to the peak of levonorgestrel. The resolution factor between the peaks of levonorgestrel and internal standard complies with the related requirements.

Internal standard solution Dissolve a quantity of megestrol acetate with acetonitrile to produce a solution of about 1 mg per ml.

Procedure Dissolve about 7.5 mg of Levonorgestrel CRS, accurately weighed, in the mobile phase in a 50 ml volumetric flask and dilute to volume, mix well. Measure accurately 2 ml each of the above solution and the internal standard solution, mix well. Inject 20 µl of resulting solution into the column. Repeat the operation, using the substance being examined instead of Levonorgestrel CRS, calculate the content of $\text{C}_{21}\text{H}_{28}\text{O}_2$.

Category Progesteroïd.

Storage Preserve in tightly closed containers, protected from light.

Preparation (1) Compound Levonorgestrel Pills
(2) Compound Levonorgestrel Tablets
(3) Levonorgestrel and Quinestrol Tablets
(4) Levonorgestrel Tablets

Levonorgestrel Tablets

Levonorgestrel Tablets contain not less than 90.0% and not more than 110.0% of the labelled amount of levonorgestrel ($\text{C}_{21}\text{H}_{28}\text{O}_2$).

Description White tablets.

Identification (1) To the powder equivalent to 37.5 mg of levonorgestrel add 200 ml of chloroform in portions, stir thoroughly, filter with a sintered glass filter (G_4), wash the residue and the filter with chloroform, combine the filtrates, evaporate the filtrate on a water bath to dryness and allow to cool. Dissolve the residue in 5 ml of chloroform and determine the optical rotation (Appendix VI E). It should be levorotatory, not lower than 0.18° .

(2) The retention time of principal peak of the substance being examined is identical with that of principal peak of the

reference solution in the chromatogram obtained in Assay.

Content uniformity Comply with the requirements for content uniformity (Appendix X E). Dissolve 1 tablet in the volumetric flask (0.75 mg in 5 ml volumetric flask, 1.5 mg in 10 ml volumetric flask). Carry out the method as described under Assay, beginning at the words "dilute with the mobile phase to volume," and calculate the content of $\text{C}_{21}\text{H}_{28}\text{O}_2$.

Other requirements Comply with the general requirements for tablets (Appendix I A).

Assay Carry out the method for high performance liquid chromatography (Appendix V D), using a column packed with octadecylsilane bonded silica gel and a mixture of acetonitrile-water (70 : 30) as the mobile phase. Detection wavelength is 240 nm and the number of the theoretical plates of the column is not less than 2000, calculated with reference to the peak of levonorgestrel. The resolution factor between the peaks of levonorgestrel and internal standard complies with the related requirements.

Internal standard solution Dissolve a quantity of megestrol acetate, accurately weighed, in acetonitrile to produce a solution of about 1 mg per ml.

Procedure Dissolve a quantity of levonorgestrel CRS, accurately weighed, in acetonitrile to produce a solution of 0.15 mg per ml as reference solution. Mix 2 ml each of the reference solution and the internal standard solution, both measured accurately, shake well. Inject 20 µl of the resulting solution into the column. Weigh accurately and powder 20 tablets. Weigh accurately a quantity of the powder equivalent to about 1.5 mg of levonorgestrel into a 10 ml volumetric flask, add a quantity of the mobile phase, dissolve levonorgestrel by ultrasonic treatment, cool, dilute with the mobile phase to volume, shake well and filter. Mix 2 ml each of the successive filtrate and the internal standard solution, both measured accurately and shake well. Inject 20 µl of the resulting solution into the column, calculate the content of $\text{C}_{21}\text{H}_{28}\text{O}_2$.

Category Progesteroïd.

Strength (1) 0.75 mg (2) 1.5 mg

Storage Preserve in tightly closed containers, protected from light.

Levonorgestrel and Quinestrol Tablets

Levonorgestrel and Quinestrol Tablets contain not less than 90.0% and not more than 115.0% of the labelled amount of levonorgestrel ($\text{C}_{21}\text{H}_{28}\text{O}_2$), and not less than 94.0% and not more than 115.0% of the labelled amount of quinestrol ($\text{C}_{25}\text{H}_{32}\text{O}_2$).

Formula	Levonorgestrel	6 g
	Quinestrol	3 g

To make	1000 tablets
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Description Film coated tablets with white or almost white core.

Identification (1) To a quantity of powdered tablets equivalent to about 150 mg of levonorgestrel, add about 200 ml of chloroform in portions, stir thoroughly, filter in vacuum using G_4 funnel, wash the residue and the filter, combine the filtrate and washings, evaporate on a water bath to dryness, cool, add accurately 20 ml of chloroform, the optical rotation of the resulting solution should be

levorotatory, not lower than 0.18° (Appendix VI E).

(2) The retention time of principal peak of the substance being examined is identical with that of principal peak of the reference solution in the chromatogram obtained in Assay.

Related substances Measure 2 ml of quineestrol CRS solution obtained in Assay, evaporate on a water bath to dryness, cool, add 2.5 ml of chloroform as solution (1). Measure 2 ml of levonorgestrel CRS solution obtained in Assay, evaporate on a water bath to dryness, cool, add 1 ml of chloroform, as solution (2). Measure 2 ml of the solution obtained in test (1) for Identification, evaporate on a water bath to 1 ml as solution (3). Carry out the method for thin-layer chromatography (Appendix V B), using silica gel G as the coating substance and a mixture of chloroform-methanol (96 : 4) as the mobile phase. Apply separately to the plate 15 μ l each of solution (1) and (2), and 12.5 μ l of solution (3), after developing and removal of the plate, dry it in air, spray with a freshly prepared 10% solution of phosphomolybdic acid in ethanol, dry it at 105°C for 10 minutes and examine immediately. Any spot other than the principal spots obtained with solution (3) is not more intense than the principal spot obtained with solution (1) and (2). The colour and position of the two principal spots in the chromatogram obtained with solution (3) correspond to the principal spot obtained with solutions (1) and (2).

Content uniformity Comply with the requirements for content uniformity (Appendix X E).

Carry out the method for Assay, using 1 tablet and beginning at the words "to a 50 ml volumetric flask". Calculate the contents of $\text{C}_{21}\text{H}_{28}\text{O}_2$ and $\text{C}_{25}\text{H}_{32}\text{O}_2$ respectively with respect to the peak area obtained in the chromatogram by the internal standard method.

Dissolution Carry out the dissolution test (Appendix X C, method 2), using 900 ml of 0.8% lauryl sodium sulfate solution as the dissolution medium, adjust the rotational speed of the paddle to 100 rpm. Withdraw a quantity of the solution after exactly 60 minutes and filter. Take the successive filtrate as the test solution. Dissolve about 30 mg of levonorgestrel CRS and 15 mg of quineestrol CRS, weighed accurately, with mobile phase into a 50 ml volumetric flask and dilute with mobile phase to volume, mix well. Measure accurately 1 ml of the solution into a 100 ml volumetric flask, dilute with the dissolution medium to volume, mix well as the reference solution. Carry out the method as described under Assay. Inject separately 20 μ l of the test solution and the reference solution and record the chromatogram. Calculate the dissolution of $\text{C}_{21}\text{H}_{28}\text{O}_2$ and $\text{C}_{25}\text{H}_{32}\text{O}_2$ from each tablet with respect to the peak area obtained in the chromatogram by the external standard method. The dissolution of $\text{C}_{21}\text{H}_{28}\text{O}_2$ and $\text{C}_{25}\text{H}_{32}\text{O}_2$ is separately not less than 60% and 80% of the labelled amount.

Other requirements Comply with the general requirements for tablets (Appendix I A).

Assay Carry out the method for high performance liquid chromatography (Appendix V D), using a column packed with octadecylsilane bonded silica gel and a mixture of acetonitrile-water (80 : 20) as the mobile phase. Detection wavelength is 220 nm and the number of the theoretical plates of the column is not less than 3000, calculated with reference to the peak of levonorgestrel. The resolution factor between the peaks complies with the related requirements.

Internal standard solution Dissolve a quantity of progesterone caproate in acetonitrile to produce a solution of about 0.12 mg per ml.

Procedure Weigh accurately and powder 10 tablets. Dissolve an accurately weighed quantity of the powder equivalent to about 6 mg of levonorgestrel in the mobile phase in a 50 ml

volumetric flask by ultrasonication, cool, dilute with the mobile phase to volume, mix well and filter. Measure accurately 1 ml each of the successive filtrate and the internal standard solution and mix well. Inject 20 μ l into the column, and record the chromatogram. Separately dissolve an accurately weighed quantity of levonorgestrel CRS and quineestrol CRS in the mobile phase to produce a solution of 0.12 mg of levonorgestrel per ml and a solution of 0.06 mg of quineestrol per ml. Measure accurately 1 ml each of the resulting solutions and mix well. Inject 20 μ l into the column and record the chromatogram. Calculate the contents of $\text{C}_{21}\text{H}_{28}\text{O}_2$ and $\text{C}_{25}\text{H}_{32}\text{O}_2$ respectively with respect to the peak area obtained in the chromatogram by the internal standard method.

Category Progesteroide.

Storage Preserve in tightly closed containers, protected from light.

Compound Levonorgestrel Pills

Compound Levonorgestrel Pills contain not less than 90.0% and not more than 115.0% of the labelled amount of levonorgestrel ($\text{C}_{21}\text{H}_{28}\text{O}_2$) and ethinylestradiol ($\text{C}_{20}\text{H}_{24}\text{O}_2$) respectively.

Formula	Levonorgestrel	150 mg
	Ethinylestradiol	30 mg
	To make	1000 pills

Description Sugar coated dripping pills.

Identification (1) Remove the sugar coating of 1 pill, allow to disintegrate by warming with about 2 ml of ethanol in water bath and cool. Add 2 ml of alkaline trinitrophenol solution (mix equal amounts of ethanolic solution of 0.6% trinitrophenol, 7% sodium hydroxide solution and dilute ethanol TS before use), allow to stand for 30 minutes, a brownish-yellow colour is produced.

(2) Remove the sugar coating of 100 pills, allow to disintegrate by warming with 20 ml of water in a conical flask. Cool and transfer to a separator and wash the flask twice with water, 5 ml each. Combine the washings to the separator, extract with 3×40 ml of ether. Discard the aqueous layer. Wash the combined ether extract with 2×25 ml of water. Filter the ether extract through anhydrous sodium sulfate on cotton wool pad, vaporize the solvent, dissolve the residue in chloroform. Transfer it to a 2 ml volumetric flask, dilute to volume with chloroform, shake well, filter, if necessary. Determine the optical rotation with 1 dm micropolarimeter (Appendix VI E). It should be levorotatory, not lower than 0.18° .

(3) Remove the sugar coating of 10 pills, allow to disintegrate by warming with about 4 ml of water in a small beaker. Cool and transfer to a separator, extract with 20 ml of ether, discard the aqueous layer, wash the ethereal layer with water and filter through a layer of anhydrous sodium sulfate on a pad of cotton wool. Vaporize ether on an evaporating dish, dissolve the residue in 0.3 ml of chloroform, used as the test solution. Use the chloroform solutions of 1 mg of ethinylestradiol CRS per ml and 0.5 mg of levonorgestrel per ml, respectively, as the reference solutions. Carry out the test for thin-layer chromatography (Appendix V B), using silica gel G as the coating substance and chloroform-methanol (9 : 1) as the mobile phase. Apply 30 μ l each of the above three solutions to the same plate, after developing and removal of the plate, dry in air, spray with sulfuric acid-dehydrated ethanol (1 : 1), heat at

105°C until the colour of spots develop. The positions and colours of the two principal spots of the test solution are identical with that of the reference solutions accordingly.

Other requirements Comply with the general requirements for the pills (Appendix I H).

Assay Carry out the method for high performance liquid chromatography (Appendix V D), using a column packed with octadecylsilane bonded silica gel and a mixture of acetonitrile-water (60 : 40) as the mobile phase. Detection wavelength is 220 nm and the number of the theoretical plates of the column is not less than 5000, calculated with reference to the peak of levonorgestrel. The resolution factor between the peaks of levonorgestrel and internal standard complies with the related requirements.

Internal Standard Solution Dissolve a quantity of megestrol acetate with acetonitrile to produce a solution of about 1 mg per ml.

Procedure Weigh accurately and powder finely 20 pills. Weigh accurately a quantity equivalent to about 0.75 mg of levonorgestrel to a 10 ml volumetric flask, adding 1 ml of internal standard solution, measured accurately, and a quantity of the mobile phase and dissolve by ultrasonic generator, cool, dilute to volume with the mobile phase, mix well, filter. Inject 20 µl of the successive filtrate into the column. And then dissolve a quantity of levonorgestrel CRS and ethinylestradiol CRS with acetonitrile to produce a solution of 0.75 mg of levonorgestrel and 0.15 mg of ethinylestradiol per ml. Measure accurately 1 ml each of the solution and the internal standard solution to a 10 ml volumetric flask, dilute with the mobile phase, mix well. Inject 20 µl of the resulting solution into the column, calculate the content of $C_{21}H_{28}O_2$ and $C_{20}H_{24}O_2$.

Category Contraceptive.

Storage Preserve in tightly closed containers, protected from light.

Compound Levonorgestrel Tablets

Compound Levonorgestrel Tablets contain 0.135-0.1725 mg of levonorgestrel ($C_{21}H_{28}O_2$) and 27.0-34.5 µg of ethinylestradiol ($C_{20}H_{24}O_2$) in each tablet.

Formula	Levonorgestrel	150 mg
	Ethinylestradiol	30 mg

To make	1000 tablets
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Description Sugar coated or film coated tablets with white or almost white core.

Identification (1) Powder 5 tablets, add 10 ml of chloroform, stir thoroughly and filter. To 2 ml of successive filtrate add 2 ml of alkaline trinitrophenol solution (mix equal amounts of ethanolic solution of 0.6% trinitrophenol, 7% sodium hydroxide solution and dilute ethanol TS before use), allow to stand for 30 minutes, a brownish-yellow colour is produced.

(2) To the powder equivalent to 15 mg of levonorgestrel add 200 ml of chloroform in portions, stir thoroughly, filter with a sintered glass filter (G_4), wash the residue and the filter with chloroform, combine the filtrates, evaporate the filtrate on a water bath to dryness and allow to cool. Dissolve the residue in 2 ml of chloroform and determine the optical rotation (Appendix VI E). It should be levo-rotatory, not lower than 0.18°.

(3) Powder 5 tablets, add 10 ml of chloroform, stir thoroughly and filter. Evaporate the filtrates on a water bath to dryness. Dissolve the residue in 1 ml of chloroform as test solution. Evaporate 1 ml of the reference solution obtained in Assay on a water bath to dryness and cool. Dissolve the residue in 1 ml of chloroform as reference solution. Carry out the thin-layer chromatography (Appendix V B), using silica gel G as the coating substance and a mixture of chloroform-methanol (9 : 1) as the mobile phase. Apply separately to the plate 30 µl each of above two solutions, after developing and removal of the plate, dry it in air, spray with sulfuric acid-ethanol (1 : 1), heat at 105°C. The colour and position of the two principal spots in the chromatogram obtained with the test solution correspond to that obtained with reference solutions.

Other requirements Comply with the general requirements for tablets (Appendix I A).

Assay Reference preparation Weigh accurately about 15 mg of levonorgestrel CRS to a 50 ml volumetric flask, add ethanol to volume and shake thoroughly as solution (1). Weigh accurately about 15 mg of ethinylestradiol CRS to a 100 ml volumetric flask, add ethanol to volume and shake thoroughly as solution (2). Measure accurately 25 ml of solution (1) and 10 ml of solution (2) to a 100 ml volumetric flask. Dilute with ethanol to volume and shake well.

Test preparation Transfer 5 tablets into a separator, add 6 ml of water, shake to disintegrate, extract with six 7-8 ml portions of chloroform, filter the extracts into the 50 ml volumetric flask using a wad of absorbent cotton, dilute with chloroform to volume and shake well.

Procedure Levonorgestrel: Measured accurately 10 ml of the test solution in a 50 ml conical flask with stopper, evaporate on a water bath to dryness and dissolve the residue in 5 ml of ethanol. Measured accurately 2 ml of the reference solution in a conical flask with stopper, add 3 ml of ethanol. To above two solution add 4 ml of alkaline trinitrophenol solution separately, allow to stand in dark place for 40 minutes and measure the absorbance at 490 nm (Appendix IV A). Calculate the content of $C_{21}H_{28}O_2$.

Ethinylestradiol: Measured accurately 10 ml of the test solution in a 50 ml conical flask with stopper, evaporate on a water bath to dryness and dissolve the residue in 5 ml of ethanol. Measured accurately 2 ml of the reference solution in a conical flask with stopper, add 3 ml of ethanol. Cool above two solution on ice bath for 30 seconds, add 6 ml of sulfuric acid when shaking, cool on ice bath for 30 seconds, allow to stand in room temperature for 20 minutes and measure the absorbance at 530 nm (Appendix IV A). Calculate the content of $C_{20}H_{24}O_2$.

Category Contraceptive.

Storage Preserve in tightly closed containers, protected from light.

Lidocaine Carbonate Injection

Lidocaine Carbonate Injection is a sterile solution made by lidocaine hydrochloride and sodium bicarbonate under saturated of CO_2 in Water for Injection. It contains not less than 95.0% and not more than 105.0% of the labelled amount of lidocaine carbonate, calculated on the lidocaine ($C_{14}H_{22}N_2O$).

Description A clear, colourless liquid.

Identification (1) To 10 ml of the injection, add 10 ml of

trinitrophenol TS, a precipitate is produced, filter, wash with water and dry, it melts at 228-232°C with decomposition (Appendix VI C).

(2) To 2 ml of the injection add 0.2 ml of cupric sulfate TS and 1 ml of sodium carbonate TS; a bluish-violet colour is produced. Shake the solution with 2 ml of chloroform, the chloroform layer exhibits a yellow colour on standing.

(3) Yields the reactions characteristic of carbonates and bicarbonates (Appendix III).

pH value 6.0-7.5 (Appendix VI H).

Other requirements Complies with the general requirements for injection (Appendix I B).

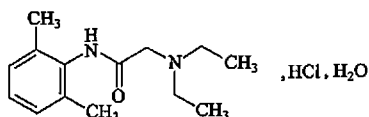
Assay Measure accurately a quantity equivalent to about 0.172 g of lidocaine in a separator, make alkaline with ammonia TS and extract with four 20 ml portions of chloroform. Combine the chloroform layers, evaporate to almost dryness on a water bath. To the residue add accurately 30 ml of sulfuric acid (0.05 mol/L) VS, heat to evaporate the chloroform. Cool, add a few drops of methyl red-bromocresol green IS and titrate with sodium hydroxide (0.1 mol/L) VS. Perform a blank determination and make any necessary correction. Each ml of sulfuric acid (0.05 mol/L) VS is equivalent to 23.43 mg of $C_{14}H_{22}N_2O$.

Category Local anesthetic.

Strength (1) 5 ml : 86.5 mg
(2) 10 ml : 0.173 g (calculated on the lidocaine)

Storage Preserve in well closed containers.

Lidocaine Hydrochloride



$C_{14}H_{22}N_2O \cdot HCl \cdot H_2O$ 288.82 [6108-05-0]

Lidocaine Hydrochloride is *N*-(2,6-dimethylphenyl)-2-(diethylamino)-acetamide hydrochloride monohydrate. It contains not less than 99.0% of $C_{14}H_{22}N_2O \cdot HCl$, calculated on the anhydrous basis.

Description A white crystalline powder; odourless; taste, bitter with numbing.

Freely soluble in water or ethanol; soluble in chloroform; insoluble in ether.

Melting range 75-79°C (Appendix VI C).

Identification Dissolve 0.2 g in 20 ml of water and carry out the following tests: (1) To 10 ml of the solution, add 10 ml of trinitrophenol TS, a precipitate is produced, filter, wash with water and dry, it melts at 228-232°C with decomposition (Appendix VI C).

(2) To 2 ml of the solution add 0.2 ml of cupric sulfate TS and 1 ml of sodium carbonate TS; a bluish-violet colour is produced. Shake the solution with 2 ml of chloroform, the chloroform layer exhibits a yellow colour on standing.

(3) The infrared absorption spectrum (Appendix IV C) is concordant with the reference spectrum of lidocaine hydrochloride (Appendix XVI).

(4) The aqueous solution yields the reactions characteristic of chlorides (Appendix III).

Acidity Dissolve 0.20 g in 40 ml of water, pH 4.0-5.5 (Appendix VI H).

Clarity of solution A solution of 1.0 g in 10 ml of water is clear. Any opalescence produced is not more pronounced than that of reference suspension 1 (Appendix IX B).

Water 5.0%-7.5% (Appendix VIII M, method 1 A).

Residue on ignition Not more than 0.1% (Appendix VIII N).

Heavy metals Dissolve 2.0 g in 2 ml of acetate BS (pH 3.5) and sufficient water to produce 25 ml. Carry out the limit test for heavy metals (Appendix VIII H, method 1): not more than 0.001%.

Assay Dissolve about 0.2 g, accurately weighed, in 10 ml of glacial acetic acid, add 5 ml of mercuric acetate TS and 1 drop of crystal violet IS, titrate with perchloric acid (0.1 mol/L) VS until the colour changes to green. Perform a blank determination and make any necessary correction. Each ml of perchloric acid (0.1 mol/L) VS is equivalent to 27.08 mg of $C_{14}H_{22}N_2O \cdot HCl$.

Category Local anesthetic and antiarrhythmic agent.

Storage Preserve in tightly closed containers.

Preparation (1) Lidocaine Hydrochloride Injection
(2) Lidocaine Hydrochloride Mucilage (I)

Lidocaine Hydrochloride Injection

Lidocaine Hydrochloride Injection is a sterile solution of lidocaine hydrochloride in Water for Injection. It contains not less than 95.0% and not more than 105.0% of the labelled amount of lidocaine hydrochloride ($C_{14}H_{22}N_2O \cdot HCl$).

Description A clear, colourless liquid.

Identification Complies with the tests (1), (2) and (4) for Identification described under Lidocaine Hydrochloride.

pH value 3.5-5.5 (Appendix VI H).

Other requirements Complies with the general requirements for Injections (Appendix I B).

Assay Carry out the method for high performance liquid chromatography (Appendix V D), using a column packed with octadecylsilane bonded silica gel and a mixture of phosphate BS (measure 1.3 ml of 1 mol/L sodium dihydrogen phosphate solution and 32.5 ml of 0.5 mol/L disodium hydrogen phosphate solution into 1000 ml volumetric flask, dilute with water to the volume and mix well)-acetonitrile (50 : 50) (adjust with phosphoric acid to pH 8.0) as the mobile phase. Detection wavelength is 254 nm. The number of theoretical plates of the column is not less than 2000, calculated with reference to the peak of lidocaine.

Procedure Dilute an accurately measured volume of the injection equivalent to about 100 mg of lidocaine hydrochloride in a 50 ml volumetric flask with the mobile phase to volume and mix well. Inject 20 μ l of the resulting solution into the column, record the peak area correspondingly obtained in the chromatogram. Dissolve about 85 mg of lidocaine CRS, accurately weighed, in 0.5 ml of 1 mol/L hydrochloric acid in a 50 ml volumetric flask, dilute with the mobile phase to volume and mix well, use the resulting solution as reference solution. Repeat the operation, using the reference solution instead of test solution. Calculate the content of $C_{14}H_{22}N_2O \cdot HCl$ with respect to the peak area obtained in the chromatogram by the external standard method and by multiplying by 1.156.

Category As described under Lidocaine Hydrochloride.

Strength (1) 5 ml : 50 mg (2) 5 ml : 0.1 g

(3) 10 ml : 0.2 g (4) 20 ml : 0.4 g

Storage Preserve in well closed containers.

Lidocaine Hydrochloride Mucilage (I)

Lidocaine Hydrochloride Mucilage is a sterile mucilage of lidocaine hydrochloride. It contains not less than 95.0% and not more than 105.0% of the labelled amount of lidocaine hydrochloride ($C_{14}H_{22}N_2O \cdot HCl$).

Description A colourless to slightly yellow, viscous liquid.

Identification (1) Dilute about 20 g with 20 ml of water in a separator, make alkaline with ammonia TS and extract with 20 ml of chloroform. To the chloroform layers add 20 ml of water, make acidic with dilute hydrochloric acid, shake and filter the acid layers. To the filtrate add 10 ml of trinitrophenol TS, a yellow precipitate is produced.

(2) Dilute about 10 g with 20 ml of water, to 2 ml of the solution add 0.2 ml of cupric sulfate TS and 1 ml of sodium carbonate TS, a bluish-purple colour is produced. Mix the solution with 2 ml of chloroform, the chloroform layer exhibits a yellow colour on standing.

(3) The aqueous solution obtained in (2) yields the reactions characteristic of chlorides (Appendix III).

pH value 6.0-7.0 (Appendix VI H).

Fill Complies with the test for minimum fill (Appendix X F).

Sterility Complies with the test for sterility (Appendix XI H).

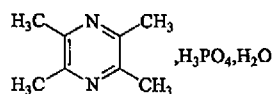
Assay Weigh accurately a quantity equivalent to about 20 mg of lidocaine hydrochloride to a separator containing 10 ml of water, make alkaline with ammonia TS and extract with four 20 ml portions of chloroform. Combine the chloroform layers, evaporate on a water bath to almost dry, add accurately 20 ml of sulfuric acid (0.005 mol/L) VS, evaporate again on a water bath to remove chloroform, cool. Carry out the method for potentiometric titration (Appendix VII A), titrate with sodium hydroxide (0.01 mol/L) VS, perform a blank determination and make any necessary correction. Each ml of sulfuric acid (0.005 mol/L) VS is equivalent to 2.708 mg of $C_{14}H_{22}N_2O \cdot HCl$.

Category As described under Lidocaine Hydrochloride.

Strength (1) 10 g : 0.2 g (2) 20 g : 0.4 g

Storage Preserve in tightly closed containers.

Ligustrazine Phosphate



$C_8H_{12}N_2 \cdot H_3PO_4 \cdot H_2O$ 252.20

Ligustrazine Phosphate is 2,3,5,6-tetramethyl pyrazine phosphate, monohydrate. It contains not less than 98.0% and not more than 102.0% of $C_8H_{12}N_2 \cdot H_3PO_4$, calculated on anhydrous basis.

Description A white or almost white crystalline powder; stinking slightly; taste bitter.

Soluble in water or ethanol, insoluble in chloroform.

Identification (1) To about 10 mg, add 5 ml of water to dissolve ligustrazine phosphate, add 2 drops of dilute nitric acid, shake well, add 2 drops of potassium iodobismuthate TS; an orange red precipitate is produced.

(2) The light absorption of a solution of 15 μ g per ml in water exhibits a maximum at 295 nm (Appendix IV A).

(3) Yield the reactions characteristic of phosphate (Appendix III).

Acidity Dissolve 0.20 g in 20 ml of water, pH 2.4-3.2 (Appendix VI H).

Related substance Carry out the method for high performance liquid chromatography (Appendix V D), using a column packed with octadecylsilane bonded silica gel and a mixture of methanol-water (3 : 2) as the mobile phase. Detection wavelength is 295 nm and the number of theoretical plates of the column is not less than 2000, calculated with reference to the peak of ligustrazine phosphate. Prepare a solution of 0.5 mg per ml of the substance being examined in water as test solution; and measure accurately 1 ml of the test solution into a 100 volumetric flask and add water to volume as reference solution. Inject 20 μ l of the reference solution into the column. Adjust the attenuation so that the principal peak height in the chromatogram is about 20% of full scale. Inject separately 20 μ l each of the resulting solutions into the column, and record the chromatogram for triple the retention time of the principal peak. The sum of the areas of all peaks other than the principal peak is not greater than the area of the principal peak in the chromatogram obtained from the reference solution.

Residual solvent Carry out the method for residual solvent (Appendix VIII P, method 2), using a quartz capillary column packed with bonded polyethyleneglycol as the stationary phase; a flame ionization detector is used. The temperature of vaporizer is 200°C, the temperature of detector is 250°C; maintain the column temperature at 50°C for 5 minutes, then raise the temperature to 190°C by 50°C per minute, maintain for 5 minutes. The resolution factor between the peaks of ethanol, acetone and solvent complies with the related requirements, the number of theoretical plates of the column is not less than 1000, calculated with reference to the peak of acetone. To a quantity of the substance being examined, weigh accurately, add dimethyl sulfoxide to produce a solution of 0.1 g per ml as test solution; measure accurately 2 ml of the test solution into a headspace vial, and maintain the temperature at 75°C for 20 minutes. Withdraw accurately 1 ml of the gas from headspace vial and inject into the column, record the chromatogram. Weigh accurately each quantity of ethanol and acetone, add dimethyl sulfoxide to produce a solution of 0.5 mg each ethanol and acetone per ml as reference solution. Measure accurately 2 ml into the headspace vial, and repeat the operation as described above. Calculate the content of ethanol and acetone, complies with the requirements.

Water 6.0%-8.0% (Appendix VIII M, method 1).

Heavy metals To 0.5 g add 23 ml of water, heat to dissolve ligustrazine phosphate, add 2 ml dilute acetic acid. Carry out the limit test for heavy metals (Appendix VIII H, method 1); not more than 0.002%.

Assay Dissolve about 0.2 g, accurately weighed, in 30 ml of glacial acetic acid. Carry out the method for potentiometric titration (Appendix VII A), titrate with perchloric acid (0.1 mol/L) VS. Perform a blank determination and make any necessary correction. Each ml of perchloric (0.1 mol/L) VS is equivalent to 23.42 mg of $C_8H_{12}N_2 \cdot H_3PO_4$.

Category Vasodilator.

Storage Preserve in tightly closed containers, protected from light.

Preparation (1) Ligustrazine Phosphate Tablets
(2) Ligustrazine Phosphate Injection
(3) Ligustrazine Phosphate Capsules

Ligustrazine Phosphate Capsules

Ligustrazine Phosphate Capsules contain not less than 90.0% and not more than 110.0% of the labelled amount of ligustrazine phosphate ($C_8H_{12}N_2 \cdot H_3PO_4 \cdot H_2O$).

Description Capsules containing white or almost white powder.

Identification To a quantity of the contents, equivalent to about 0.2 g of ligustrazine phosphate, add 20 ml of water, shake and filter. The filtrate complies with the tests for Identification described under Ligustrazine Phosphate.

Dissolution Carry out the method for dissolution test (Appendix X C, method 1), using 900 ml of water as the dissolution medium and adjust the rotation speed of the basket to 100 rpm. Withdraw 10 ml of the solution at exact 20 minutes and filter. Transfer 3 ml of the successive filtrate, accurately measured, to a 10 ml volumetric flask and dilute with water to volume. Measure the absorbance of the resulting solution at 295 nm (Appendix IV A). Calculate the dissolution of $C_8H_{12}N_2 \cdot H_3PO_4 \cdot H_2O$ from each capsule, taking 326 as the value of A (1%, 1 cm); not less than 70% of the labelled amount is dissolved.

Other requirements Comply with the general requirements for capsules (Appendix I E).

Assay Weigh accurately a quantity of the mixed contents obtained in the test for weight variation of contents, equivalent to about 50 mg of ligustrazine phosphate, to a 100 ml volumetric flask, add 60 ml of water, shake thoroughly to dissolve ligustrazine phosphate, dilute with water to volume and mix well, filter. Transfer 3 ml of the successive filtrate, accurately measured, to another 100 ml volumetric flask, dilute with water to volume and mix well. Measure the absorbance of the resulting solution at 295 nm (Appendix IV A). Calculate the content of $C_8H_{12}N_2 \cdot H_3PO_4 \cdot H_2O$, taking 326 as the value of A (1%, 1 cm).

Category As described under Ligustrazine Phosphate.

Strength 50 mg

Storage Preserve in tightly closed containers, protected from light.

Ligustrazine Phosphate Injection

Ligustrazine Phosphate Injection is a sterile solution of Ligustrazine Phosphate in Water for injection. It contains not less than 90.0% and not more than 110.0% of the labelled amount of ligustrazine phosphate ($C_8H_{12}N_2 \cdot H_3PO_4 \cdot H_2O$).

Description A clear, colourless liquid.

Identification Dilute about 0.4 ml with 5 ml of water. The resulting solution complies with the tests for Identification described under ligustrazine phosphate.

pH value 2.0-3.0 (Appendix VI H).

Pyrogens Complies with the test for pyrogens (Appendix XI D), using 5 ml of a solution of 2 mg of ligustrazine phosphate per ml in Sodium chloride injection per kg of the rabbit's weight.

Other requirements Complies with the general requirements for injection (Appendix I B).

Assay Measure accurately 2 ml to a 100 ml volumetric flask, dilute with water to volume and mix well, then measure accurately 3 ml of the diluted solution to another 100 ml volumetric flask, dilute with water to volume and mix well. Measure the absorbance of the resulting solution at 295 nm (Appendix IV A), calculate the content of $C_8H_{12}N_2 \cdot H_3PO_4 \cdot H_2O$, taking 326 as the value of A (1%, 1 cm).

Category As described under Ligustrazine Phosphate.

Strength 2 ml : 50 mg

Storage Preserve in well closed containers, protected from light.

Ligustrazine Phosphate Tablets

Ligustrazine Phosphate Tablets contain not less than 90.0% and not more than 110.0% of the labelled amount of ligustrazine phosphate ($C_8H_{12}N_2 \cdot H_3PO_4 \cdot H_2O$).

Description Sugar coated tablets with white or almost white core.

Identification To a quantity of powdered tablets, equivalent to about 0.2 g of ligustrazine phosphate, add 20 ml of water, shake to dissolve ligustrazine phosphate, filter. The filtrate complies with the tests for Identification described under Ligustrazine Phosphate.

Dissolution Carry out the method for dissolution test (Appendix X C, method 1), using 900 ml of water as the dissolution medium and adjust the rotation speed of the basket to 100 rpm. Withdraw 10 ml of the solution after exact 45 minutes and filter. Transfer 3 ml of the successive filtrate, accurately measured, to a 10 ml volumetric flask and dilute with water to volume. Measure the absorbance of the resulting solution at 295 nm (Appendix IV A). Calculate the dissolution of $C_8H_{12}N_2 \cdot H_3PO_4 \cdot H_2O$ from each tablet, taking 326 as the value of A (1%, 1 cm); not less than 80% of the labelled amount is dissolved.

Other requirements Comply with the general requirements for tablets (Appendix I A).

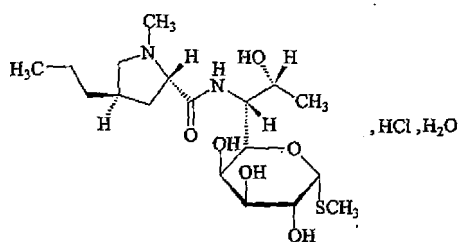
Assay Weigh accurately and powder 20 tablets with coating removed. Transfer an accurately weighed quantity of the powder, equivalent to about 50 mg of ligustrazine phosphate, in a 100 ml volumetric flask, add 60 ml of water, shake thoroughly to dissolve ligustrazine phosphate, dilute with water to volume and mix well, filter. Transfer 3 ml of the successive filtrate, accurately measured, to another 100 ml volumetric flask, dilute with water to volume and mix well. Measure the absorbance of the resulting solution at 295 nm (Appendix IV A). Calculate the content of $C_8H_{12}N_2 \cdot H_3PO_4 \cdot H_2O$, taking 326 as the value of A (1%, 1 cm).

Category As described under Ligustrazine Phosphate.

Strength 50 mg

Storage Preserve in tightly closed containers, protected from light.

Lincomycin Hydrochloride



$C_{18}H_{34}N_2O_6S \cdot HCl \cdot H_2O$ 461.02 [7179-49-9]

Lincomycin Hydrochloride is (2*S*-trans) methyl 6,8-dideoxy-6-[[[1-methyl-4-propyl-2-pyrrolidinyl] carbonyl] amino]-1-thio-*D*-erythro- α -*D*-galacto-octopyranoside monohydrochloride monohydrate. It contains not less than 82.5% of $C_{18}H_{34}N_2O_6S$, calculated on the anhydrous basis.

Description A white crystalline powder; odour, slight or characteristic; taste, bitter. Freely soluble in water or methanol; sparingly soluble in ethanol.

Identification (1) The infrared absorption spectrum (Appendix IV C) is concordant with the spectrum of lincomycin hydrochloride CRS.

(2) The retention time of the principal peak of the substance being examined in the chromatogram obtained in the Assay is identical with the principal peak in the chromatogram of lincomycin CRS.

(3) The aqueous solution yields the reactions characteristic of chlorides (Appendix III).

Crystallinity Complies with the test for Crystallinity (Appendix IX D).

Acidity To a quantity add water to produce a solution of 0.1 g per ml, pH 3.0-5.5 (Appendix VI H).

Clarity and colour of solution To each of 5 portions add water to produce a solution of 0.4 g of $C_{18}H_{34}N_2O_6S$ per ml, the solutions are clear. Any opalescence produced is not more pronounced than that of reference suspension 1 (Appendix IX B). Any colour produced is not more intense than that of reference solution Y₁ or YG₁ (Appendix IX A, method 1).

Water Not more than 6.0% (Appendix VIII M, method 1 A).

Residue on ignition Not more than 0.5% (Appendix VIII N).

Bacterial endotoxin Carry out the test for bacterial endotoxin (Appendix XI E); not more than 0.5 EU per mg (for parenteral administration).

Lincomycin B Carry out the method described under Assay. The peak area of lincomycin B is not greater than 5.0% of the sum of the peak areas of lincomycin and lincomycin B.

Assay Carry out the method for high performance liquid chromatography (Appendix V D), using a column packed with octadecylsilane bonded silica gel and a mixture of 0.05 mol/L borax solution (adjust to pH 6.0 with 85% phosphoric acid)-methanol (4 : 6) as the mobile phase. Detection wavelength is 214 nm and the number of theoretical plates of the column is not less than 1500, calculated with reference to the peak of lincomycin. The resolution factor between peaks of lincomycin and lincomycin B is not less than 2.6. The relative retention times for lincomycin B and

lincomycin are 0.5-0.7 and 1.0, respectively.

Procedure Dissolve about 50 mg, accurately weighed, with a quantity of the mobile phase in a 25 ml volumetric flask, add the mobile phase to volume, mix well. Inject 10 μ l of the resulting solution into the column. Repeat the operation, using lincomycin CRS instead of the substance being examined, calculate the content of $C_{18}H_{34}N_2O_6S$.

Category Antibiotic.

Storage Preserve in tightly closed containers.

Preparation (1) Lincomycin Hydrochloride Capsules
(2) Lincomycin Hydrochloride Injections
(3) Lincomycin Hydrochloride Tablets

Lincomycin Hydrochloride Capsules

Lincomycin Hydrochloride Capsules contain not less than 90.0% and not more than 110.0% of labelled amount of lincomycin hydrochloride, calculated with reference to lincomycin ($C_{18}H_{34}N_2O_6S$).

Description Capsules containing white crystalline powder.

Identification (1) The retention time of the principal peak of the substance being examined in the chromatogram obtained in the Assay is identical with the principal peak in the chromatogram of lincomycin hydrochloride CRS.

(2) The aqueous solution yields the reactions characteristic of chlorides (Appendix III).

Water Not more than 7.0% (Appendix VIII M, method 1 A), using the mixed contents.

Lincomycin B Carry out the method described under Assay, using 2 mg per ml of the solution containing the substance being examined. The peak area of lincomycin B is not greater than 5.0% of the sum of the peak areas of lincomycin and lincomycin B.

Other requirements Comply with the general requirements for capsules (Appendix I E).

Assay Dissolve an accurately weighed quantity (equivalent to about 0.25 g of lincomycin) of the mixed contents obtained from the test for weight variation of contents with the mobile phase to produce a solution of 2 mg per ml and filter. Carry out the Assay described under Lincomycin Hydrochloride, using the successive filtrate as the test solution.

Category As described under Lincomycin Hydrochloride.

Strength (1) 0.25 g (calculated as $C_{18}H_{34}N_2O_6S$)
(2) 0.5 g (calculated as $C_{18}H_{34}N_2O_6S$)

Storage Preserve in tightly closed containers.

Lincomycin Hydrochloride Injection

Lincomycin Hydrochloride Injection is a sterile solution of lincomycin hydrochloride in Water for Injection. It contains not less than 90.0% and not more than 110.0% of labelled amount of lincomycin ($C_{18}H_{34}N_2O_6S$).

Description A clear, colourless solution.

Identification (1) The retention time of the principal peak of the substance being examined in the chromatogram obtained in the Assay is identical with the principal peak in

the chromatogram of lincomycin hydrochloride CRS.

(2) The aqueous solution yields the reactions characteristic of chlorides (Appendix III).

pH pH 3.0-5.5 (Appendix VI H), using a solution of 0.1 g per ml in water.

Colour The solution is colourless; any colour produced is not more intense than that of reference solution Y₂ or YG₂ (Appendix IX A, method 1).

Sterility Carry out the test for sterility (Appendix XII H, membrane filtration method), dissolving each content in not less than 500 ml of 0.9% sterile sodium chloride solution respectively.

Bacterial endotoxin Complies with the corresponding requirements described under Lincomycin Hydrochloride.

Lincomycin B Carry out the method described under Assay. The peak area of lincomycin B is not greater than 5.0% of the sum of the peak areas of lincomycin and lincomycin B.

Other requirements Complies with the general requirements for injections (Appendix I B).

Assay Carry out the method for high performance liquid chromatography (Appendix V D), using a column packed with octadecylsilane bonded silica gel and a mixture of 0.05 mol/L borax solution (adjust to pH 5.0 with 85% phosphoric acid)-methanol-acetonitrile (60 : 36 : 4) as the mobile phase. Detection wavelength is 214 nm and the number of theoretical plates of the column is not less than 1500, calculated with reference to the peak of lincomycin.

Procedure Measure a quantity of the substance being examined accurately and dilute with the mobile phase to produce a solution of 2 mg per ml. Inject 10 µl of the resulting solution into the column. Repeat the operation, using lincomycin CRS instead of the substance being examined, calculate the content of C₁₈H₃₄N₂O₆S.

Category As described under Lincomycin Hydrochloride.

Strength (1) 1 ml : 0.2 g (calculated as C₁₈H₃₄N₂O₆S)
(2) 2 ml : 0.6 g (calculated as C₁₈H₃₄N₂O₆S)

Storage Preserve in well closed containers.

Lincomycin Hydrochloride Tablets

Lincomycin Hydrochloride Tablets contain not less than 90.0% and not more than 110.0% of labelled amount of lincomycin hydrochloride, calculated with reference to lincomycin (C₁₈H₃₄N₂O₆S).

Description White tablets or sugar coated tablets with white core.

Identification (1) The retention time of the principal peak of the substance being examined in the chromatogram obtained in the Assay is identical with the principal peak in the chromatogram of lincomycin hydrochloride CRS.

(2) The aqueous solution yields the reactions characteristic of chlorides (Appendix III).

Lincomycin B Carry out the method described under Assay. The peak area of lincomycin B is not greater than 5.0% of the sum of the peak areas of lincomycin and lincomycin B.

Other requirements Comply with the general requirements for tablets (Appendix I A).

Assay Weigh accurately and powder 10 tablets or 4 sugar coated tablets. To an accurately weighed quantity of powder equivalent to about 0.25 g of lincomycin add sufficient 80%

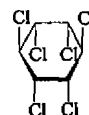
ethanol to produce a suspension containing about 10 mg per ml, shake thoroughly, allow it to stand. Measure accurately 5 ml of the supernatant liquid to a 25 ml volumetric flask, dilute with the mobile phase to volume and mix thoroughly. Filter through a 0.45 µm membrane, use the successive filtrate as test solution. Inject 10 µl to the column and proceed as described under Lincomycin Hydrochloride.

Category As described under Lincomycin Hydrochloride.

Strength (1) 0.25 g (calculated as C₁₈H₃₄N₂O₆S)
(2) 0.5 g (calculated as C₁₈H₃₄N₂O₆S)

Storage Preserve in tightly closed containers.

Lindane



C₆H₆Cl₆ 290.83

[58-89-9]

Lindane is γ-1,2,3,4,5,6-hexachlorocyclohexane. It contains not less than 99.0% of C₆H₆Cl₆.

Description A white crystalline powder; odour, slightly characteristic. Freely soluble in acetone or ether; soluble in dehydrated ethanol; insoluble in water.

Congealing point Not less than 112 °C (Appendix VI D).

Identification Transfer 1 ml of 0.5% lindane solution in ethanol to a test tube with stopper, add 3 ml of ethanol and 1 ml of ethanolic potassium hydroxide TS, allow to stand for 10 minutes. The solution yields the reactions characteristic of chlorides (Appendix III).

α-isomer Weigh accurately about 10 mg into a 100 ml volumetric flask. Add acetone to dissolve the substance being examined and dilute to volume. Use this solution as the test solution. Dissolve a quantity of lindane CRS, accurately weighed, in acetone to produce a solution of 1 µg per ml. Use this solution as the reference solution. Transfer respectively 1 ml each of the above two solutions, accurately measured, to two 50 ml volumetric flasks, dilute with cyclohexane to volume. Transfer respectively 1 ml of each solution, accurately measured, to two 10 ml volumetric flasks, dilute with cyclohexane to volume, and mix well. Carry out the method for gas chromatography (Appendix V E), using a glass column 2 m long coated with 2% of silicone (OV-17), maintain the column temperature at 190°C, and detect with an electron capture detector. Any peak area corresponding to α-isomer in the chromatogram obtained with the test solution is not greater than that of the principal peak in the chromatogram obtained with the reference solution.

Acidity Dissolve 10.0 g in 25 ml of acetone, add 75 ml of water and 1 drop of methyl red IS, and mix well. Titrate with sodium hydroxide (0.02 mol/L) VS until the colour changes to yellow. Perform a blank determination and make any necessary correction. Not more than 5.0 ml of sodium hydroxide (0.02 mol/L) VS is required.

Chloride Boil 0.75 g with 15 ml of water for 1 minute, cool, shake and filter. Add 3 ml of water and 2 ml of ethanol to 10 ml of the filtrate. Carry out the limit test for chlorides (Appendix VIII A). Any opalescence produced is not more pronounced than that of a reference solution using 5.0 ml of sodium chloride standard solution (0.01%).

Residue on ignition Not more than 0.1% (Appendix VIII N).

Assay Weigh accurately about 0.4 g, add 25 ml of ethanol, heat in a water bath to dissolve the substance being examined, cool. Add 10 ml of 1 mol/L ethanolic potassium hydroxide solution, shake, and allow to stand for 10 minutes. Add 100 ml of water, neutralise with 2 mol/L nitric acid solution, and add 10 ml in excess. Add 50 ml of silver nitrate (0.1 mol/L) VS, accurately measured, mix well. Add 2 ml of ferric ammonium sulfate IS, titrate with ammonium thiocyanate (0.1 mol/L) VS until the colour changes to pale brownish-red. Perform a blank determination and make any necessary correction. Each ml of silver nitrate (0.1 mol/L) VS is equivalent to 9.694 mg of $C_6H_6Cl_6$.

Category Parasiticide.

Storage Preserve in tightly closed containers, protected from light. Avoid connecting with ironware.

Preparation Lindane Cream

Lindane Cream

Lindane Cream contains not less than 90.0% and not more than 110.0% of the labelled amount of lindane ($C_6H_6Cl_6$).

Description A white cream.

Identification To about 1 g of the cream equivalent to 10 mg of lindane add 20 ml of chloroform, shake to dissolve the substance being examined, filter. Evaporate the filtrate to dryness. Dissolve the residue in 1 ml of acetone, and use the clear liquid as the test solution. Dissolve lindane CRS in acetone to produce a solution of about 10 mg per ml, and use this solution as the reference solution. Carry out the method for thin-layer chromatography (Appendix V B), using silica gel G as the coating substance and a mixture of butanone-*n*-hexane (7 : 93) as the mobile phase. Apply separately to the plate 5 μ l each of above two solutions. After developing and removal of the plate, dry it in air and spray the plate with a 0.5% solution of *o*-dianisidine in acetone. Place the plate under ultraviolet light for 10 minutes and examine in visible light. The colour and position of the principal spot in the chromatogram obtained with test solution correspond to those of the principal spot obtained with reference solution.

α -isomer Transfer a quantity of the cream equivalent to about 10 mg of Lindane, accurately weighed, to a 100 ml volumetric flask. Add acetone to dissolve the substance being examined and dilute to volume as the test solution. Carry out the test of α -isomer described under Lindane, beginning at the words "dissolve a quantity of lindane CRS...". It complies with the requirements.

Other requirements Complies with the general requirements for creams (Appendix I F).

Assay Carry out the method for gas chromatography (Appendix V E), using a glass column 2 m long coated with 2% of silicone (OV-17), maintain the column temperature at 190°C, and detect with an electron capture detector.

Procedure Transfer a quantity of the cream equivalent to about 10 mg of lindane, accurately weighed, to a 100 ml volumetric flask. Add acetone to dissolve the substance being examined and dilute to volume. Transfer 2 ml, accurately measured, to a 100 ml volumetric flask, dilute to volume with cyclohexane. Transfer 2 ml, accurately measured, to a 20 ml volumetric flask, dilute to volume with cyclohexane, mix well. Inject a quantity of the resulting solution, accurately

measured, into the column. Dissolve a quantity of Lindane CRS, accurately weighed, in acetone to produce a solution of about 0.2 μ g per ml, repeat the operation. Calculate the content of $C_6H_6Cl_6$ by the external standard method.

Category As described under Lindane.

Strength 1%

Storage Preserve in tightly closed containers, stored in a cool place.

Liquid Paraffin

Liquid Paraffin is a mixture of liquid hydrocarbons obtained from petroleum.

Description Colourless transparent oily liquid; odourless; tasteless; free from fluorescence in daylight. Soluble in chloroform, ether or volatile oils; insoluble in ethanol or water.

Relative density 0.845-0.890 (Appendix VI A).

Viscosity The kinematic viscosity (Appendix VI G, method 1) at 40°C (inner diameter of capillary tube is 1 mm) is not less than 36 mm²/s.

Acidity To 5.0 ml add 5 ml of neutralized ethanol (neutral to phenolphthalein I S) and boil. The solution yields a neutral reaction to moistened litmus paper.

Polycyclic aromatic compounds Measure 25 ml to a separator, add 25 ml of *n*-hexane, mix, add accurately 5 ml of dimethylsulfoxide, shake vigorously for 2 minutes and allow to separate. Transfer dimethylsulfoxide layer into another separator, wash with 2 ml of *n*-hexane, allow to centrifuge, if necessary. Measure the absorbances of dimethylsulfoxide layer in the range of 260-350 nm (Appendix IV A). The maximum absorbance is not greater than 0.10.

Solid paraffins Fill a stoppered test tube internal diameter about 25 mm with the substance being examined, previously dried at 105°C for 2 hours and cooled in a desiccator over sulfuric acid. Stopper the tube and cool at 0°C for 4 hours. Any opalescence produced is not more intense than that of an equal volume of reference solution [add 6 ml of dilute nitric acid and 1.0 ml of silver nitrate TS to 0.15 ml of 0.01 mol/L hydrochloric acid solution and dilute with water to 50 ml].

Readily carbonizable substances Add 5 ml of sulfuric acid (94.5%-95.5%) to 5 ml of the substance being examined in a stoppered test tube (about 160 mm \times 25 mm). Place the tube in a water bath for 30 seconds and draw out of the bath quickly. Stopper the test tube and shake vigorously in longitudinal direction 3 times with a finger tightly pressed on the stopper. The shaking amplitude is not less than 12 cm but the time is not exceeding 3 seconds. Place the tube again into the water bath and shake as above at intervals of 30 seconds. After a total of 10 minutes counted from the initial immersion of the test tube in the water bath, take it out from the bath and allow to stand. The paraffin layer is colourless. Any colour developed in the acid layer is not more intense than that of a reference solution prepared by mixing 1.5 ml of standard potassium dichromate CS, 1.3 ml of standard cobaltous chloride CS, 0.5 ml of standard copper sulfate CS and 1.7 ml of water with 5 ml of the substance being examined.

Category Cathartic.

Storage Preserve in tightly closed containers.

Lithium Carbonate

Li_2CO_3 73.89

[554-13-2]

Lithium Carbonate contains not less than 98.5% of Li_2CO_3 .

Description A white, crystalline powder; odourless; tasteless. The aqueous solution exhibits alkaline reaction. Slightly soluble in water; practically insoluble in ethanol.

Identification (1) Moisten a quantity on a platinum wire with hydrochloric acid. It imparts an intense crimson colour to a nonluminous flame.

(2) The aqueous solution yields the reactions characteristic of carbonates (Appendix III).

Chloride Carry out the limit test for chlorides (Appendix VII A), using 0.10 g. Any opalescence produced is not more pronounced than that of a reference using 7.0 ml of sodium chloride standard solution (0.07%).

Sulfate Carry out the limit test for sulfates (Appendix VII B), using 0.20 g. Any opalescence produced is not more pronounced than that of a reference using 2.0 ml of potassium sulfate standard solution (0.1%).

Aluminum and Iron To 0.5 g add 10 ml of water and a few drops of hydrochloric acid with stirring to dissolve. Heat to boiling and allow to cool. Make alkaline 5 ml of the solution with ammonia TS; no turbidity is produced.

Acid-insoluble substance To 10 g in a beaker add 50 ml of water, then add slowly 70 ml of hydrochloric acid solution (1→2). Cover the beaker with a watch glass and boil for 1 hour. Filter through a sintered glass filter previously dried to constant weight at 110°C. Wash the filtrate with hot water until the washing is free from chloride. Dry at 110°C for 1 hour; the residue is not more than 2 mg.

Calcium Mix 5.0 g with 50 ml of water and add an excess of dilute hydrochloric acid. Boil to expel carbon dioxide, cool, add 5 ml of ammonium oxalate TS, then neutralize with ammonia TS and allow to stand for 4 hours. Filter through a sintered glass filter and wash with water until the washing yields no turbidity with calcium chloride TS. Place the sintered glass filter in a beaker and cover with water, add 3 ml of sulfuric acid, heat to 70°C and titrate with potassium permanganate (0.02 mol/L) VS until a faint pink colour persists for 30 seconds. Not more than 3.8 ml of potassium permanganate (0.02 mol/L) VS is consumed (0.15%).

Magnesium Dissolve 1.0 g in 3 ml of water and about 2 ml of nitric acid. Neutralize with sodium hydroxide TS, dilute with water to produce 10 ml and mix well. To 0.70 ml of the solution add water to produce 9 ml, then add 1 ml of glycerin, 0.15 ml of 0.01% titan yellow solution, 0.25 ml of ammonium oxalate TS, 5 ml of sodium hydroxide TS and mix well. Any colour produced is not more intense than that of a reference solution prepared similarly using 1.0 ml of magnesium sulfate standard solution, measure accurately 1 ml of 1.01% magnesium sulfate solution, dilute with water to produce 100 ml and mix well (0.015%).

Potassium Dissolve 0.10 g in a 50 ml volumetric flask using 10 ml of hydrochloric acid solution (1→2) and dilute to volume with water (test preparation). Dissolve 0.10 g in another 50 ml volumetric flask using 10 ml of hydrochloric acid solution (1→2), add 3.0 ml of potassium chloride standard solution (transfer 191 mg of potassium chloride CRS previously dried at 105°C for 1 hour and accurately weighed, to a 1000 ml volumetric flask, add water to

volume and mix well. Measure accurately 10 ml of the solution into a 100 ml volumetric flask, dilute with water to volume and mix well), dilute with water to volume and mix well (reference preparation). Carry out the method for atomic absorption spectrophotometry (Appendix IV D) and measure the absorbances of the two solutions at 766.5 nm; not more than 0.030%.

Sodium Dissolve 0.50 g in a 50 ml volumetric flask using 10 ml of hydrochloric acid solution (1→2) and dilute with water to volume (test preparation), dissolve 0.50 g in another 50 ml volumetric flask in 10 ml of hydrochloric acid solution (1→2), add 23 ml of sodium chloride standard solution and dilute with water to volume (reference preparation). Carry out the method for atomic absorption spectrophotometry (Appendix IV D) and measure the absorbances of the two solutions at 589 nm; not more than 0.030%.

Heavy metals Dissolve 1.0 g in a quantity of hydrochloric acid, add a quantity of water, adjust pH to 3-4 with dilute acetic acid or ammonia TS and dilute with water to 25 ml. Carry out the limit test for heavy metals (Appendix VII H, method 1); not more than 0.002%.

Arsenic To 1.0 g add 22 ml of water and 5 ml of hydrochloric acid, carry out the limit test for arsenic (Appendix VII J); not more than 0.0002%.

Assay Weigh accurately about 1 g, add 50 ml of water, and 50 ml of sulfuric acid (0.5 mol/L) VS, accurately measured. Boil gently to expel carbon dioxide, cool, add phenolphthalein IS, and titrate with sodium hydroxide (1 mol/L) VS. Perform a blank determination and make any necessary correction. Each ml of sulfuric acid (0.5 mol/L) VS is equivalent to 36.95 mg of Li_2CO_3 .

Category Antimanic agent.

Storage Preserve in tightly closed containers, stored in a dry place.

Preparation (1) Lithium Carbonate Sustained-release Tablets
(2) Lithium Carbonate Tablets

Lithium Carbonate Sustained-release Tablets

Lithium Carbonate Sustained-release Tablets contain not less than 95.0% and not more than 105.0% of the labelled amount of lithium carbonate (Li_2CO_3).

Description White or almost white tablets.

Identification Comply with the tests for Identification described under lithium carbonate, Using a quantity of the powdered tablets.

Drug release Carry out the drug release test [Appendix X D (1)], with the apparatus of the dissolution test method I using 1 tablet. Using 1000 ml of 0.1 mol/L hydrochloric acid solution as the release medium and adjust the rotational speed of the basket to 150 rpm. Withdraw a quantity of the solution after exactly 3 hours and filter, collect the successive filtrate as the test solution (1). Carry out the test as described above using the remaining table with 1000 ml of Phosphate BS (pH 6.0) [Dissolve 107 g of sodium dihydrogen phosphate ($\text{NaH}_2\text{PO}_4 \cdot 2\text{H}_2\text{O}$) and 46g of disodium hydrogen phosphate ($\text{NaH}_2\text{PO}_4 \cdot 12\text{H}_2\text{O}$) in water to make 5000 ml and mix well] as the release medium. Withdraw a quantity of the solution after exactly 3 hours and filter, use the successive filtrate as the test solution (2).

Carry out the method for atomic absorption spectrophotometry (Appendix IV D, method 1), measure the absorbances of the solutions at 670.7 nm respectively, calculate the amount of lithium carbonate dissolved in the acid solvent and the buffer solvent separately. The amount of lithium carbonate dissolved per tablet in 3 hours is 45%-65% of the labelled amount; that dissolved per tablet in 6 hours is 65%-85% of the labelled amount.

Other requirements Comply with the general requirements for tablets (Appendix I A).

Assay Weigh accurately and powder finely 10 tablets. Boil gently a quantity of the powder equivalent to about 1 g of lithium carbonate accurately weighed with 50 ml of water and 50 ml of sulfuric acid (0.5 mol/L) VS, to expel carbon dioxide. Allow to cool, add phenolphthalein IS, titrate with sodium hydroxide (1 mol/L) VS. Perform a blank determination and make any necessary correction. Each ml of sulfuric acid (0.5 mol/L) VS is equivalent to 36.95 mg of Li_2CO_3 .

Category As described under lithium carbonate.

Strength 0.3 g

Storage Preserve in tightly closed containers.

Lithium Carbonate Tablets

Lithium Carbonate Tablets contain not less than 95.0% and not more than 105.0% of the labelled amount of lithium carbonate (Li_2CO_3).

Description White tablets.

Identification Comply with the tests for Identification described under Lithium Carbonate, using a quantity of powdered tablets.

Dissolution Carry out the dissolution test (Appendix X C, method 1), using 900 ml of water as dissolution medium and the rotational speed of the basket to 100 rpm. Withdraw 25 ml of the solution after exactly 30 minutes and filter. Measure accurately 20 ml of the successive filtrate, add 5 drops of the methyl red-bromocresol green IS, and titrate with hydrochloric acid (0.01 mol/L) VS until a dark purple colour produced. Each ml of hydrochloric acid (0.01 mol/L) VS equivalent to 0.3695 mg of Li_2CO_3 . Calculate the dissolution of Li_2CO_3 . Not less than 65% of the labelled amount is dissolved.

Other requirements Comply with the general requirements for tablets (Appendix I A).

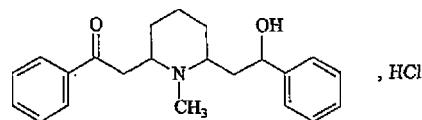
Assay Weigh accurately and powder 10 tablets. Weigh accurately a quantity of the powder equivalent to about 1 g of lithium carbonate. Proceed as described in the Assay described under Lithium Carbonate, beginning at the words "add 50 ml of water". Each ml of sulfuric acid (0.5 mol/L) VS is equivalent to 36.95 mg of Li_2CO_3 .

Category As described under Lithium Carbonate.

Strength 0.25 g

Storage Preserve in tightly closed containers.

Lobeline Hydrochloride



$\text{C}_{22}\text{H}_{27}\text{NO}_2 \cdot \text{HCl}$ 373.92

Lobeline Hydrochloride is 2- [1-methyl-6-(β -hydroxyphenethyl)-2-piperidyl] acetophenone hydrochloride. It contains not less than 99.0% of $\text{C}_{22}\text{H}_{27}\text{NO}_2 \cdot \text{HCl}$, calculated on the dried basis.

Description White crystals or a granular powder; odourless; taste, bitter. The aqueous solution exhibits weak acid reaction.

Freely soluble in ethanol or chloroform, soluble in water.

Specific optical rotation -56° to -58° , in a solution of 20 mg per ml in water (Appendix VI E).

Specific absorbance Measure the absorbance of a solution of 10 μg per ml in water at 249 nm (Appendix IV A), the value of A (1%, 1 cm) is 360-390.

Identification (1) Dissolve 0.1 g in 10 ml of water and boil, the characteristic odour of acetophenone is perceptible and more intense on adding 1 drop of 20% sodium hydroxide solution.

(2) Dissolve 10 mg in 1 ml of sulfuric acid, add 1 drop of formaldehyde solution, a red colour is produced.

(3) Dissolve 0.1 g in 5 ml of water, add dropwise ammonia TS to make the solution alkaline. Allow to stand until precipitate is produced, filter, wash the precipitate with water and dry it over phosphorous pentoxide for 24 hours. It melts at about 120°C (Appendix VI C).

(4) The aqueous solution yields the reactions characteristic of chlorides (Appendix III).

Clarity of chloroform solution A solution of 0.5 g in 10 ml of chloroform is clear.

Loss on drying When dried over phosphorous pentoxide to constant weight, loses not more than 1.0% of its weight (Appendix VIII L).

Residue on ignition Not more than 0.1% (Appendix VIII N).

Assay Dissolve about 0.2 g, accurately weighed, in 10 ml of glacial acetic acid, add 5 ml of mercuric acetate TS and 1 drop of crystal violet IS. Titrate with perchloric acid (0.1 mol/L) VS until the colour changes to bluish-green. Perform a blank determination and make any necessary correction. Each ml of perchloric acid (0.1 mol/L) VS is equivalent to 37.39 mg of $\text{C}_{22}\text{H}_{27}\text{NO}_2 \cdot \text{HCl}$.

Category Respiratory stimulant.

Storage Preserve in tightly closed containers, stored in a cool place and protected from light.

Preparation Lobeline Hydrochloride Injection

Lobeline Hydrochloride Injection

Lobeline hydrochloride Injection is a sterile solution of lobeline hydrochloride in Water for Injection.

tion. It contains not less than 90.0% and not more than 110.0% of the labelled amount of lobeline hydrochloride ($C_{22}H_{27}NO_2 \cdot HCl$).

Description A clear, colourless or almost colourless liquid.

Identification (1) Complies with test (1) for Identification described under Lobeline Hydrochloride.

(2) The light absorption of a solution obtained in the Assay exhibits a maximum at 249 nm and a minimum at 222 nm (Appendix IV A).

pH value 2.7-4.5 (Appendix VI H).

Colour Carry out the method for colour of solution (Appendix IX A): any colour produced is not more intense than that of reference solution Y_2 .

Other requirements Complies with the general requirements for injections (Appendix I B).

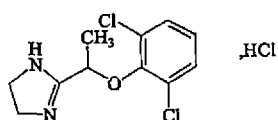
Assay Dilute an accurately measured quantity with water to produce a solution of 10 μ g per ml, measure the absorbance of the solution at 249 nm (Appendix IV A). Calculate the content of $C_{22}H_{27}NO_2 \cdot HCl$, taking 375 as the value of A (1%, 1 cm).

Category As described under Lobeline Hydrochloride.

Strength (1) 1 ml : 3 mg (2) 1 ml : 10 mg

Storage Preserve in well closed containers, protected from light.

Lofexidine Hydrochloride



$C_{11}H_{12}Cl_2N_2O \cdot HCl$ 295.60 [21498-08-08]

Lofexidine Hydrochloride is 2-[1-(2,6-dichlorophenoxy)-ethyl]-2-imidazoline monohydrochloride. It contains not less than 99.0% of $C_{11}H_{12}Cl_2N_2O \cdot HCl$, calculated on the dried basis.

Description A white or almost white crystalline powder; odourless.

Freely soluble in water or ethanol; slightly soluble in chloroform; very slightly soluble in acetone; practically insoluble in ether.

Melting range 224-229°C (Appendix VI C).

Identification (1) Dissolve about 1 mg in 2 ml of water, add 1 ml of 5% sodium nitroprusside solution freshly prepared, 2 ml of sodium hydroxide TS and 1 g of sodium bicarbonate, shake, a purple colour is produced. The colour of solution turns to dark after standing.

(2) Dissolve separately the substance being examined and lofexidine hydrochloride CRS in methanol to produce two solutions of 2 mg per ml. Carry out the method for thin-layer chromatography (Appendix V B), using silica gel G as the coating substance and a mixture of dehydrated ethanol-chloroform-ammonia concentrated TS (70 : 50 : 2) as the mobile phase. Apply separately to the plate 10 μ l each of above two solutions. After developing and removal of the plate, dry it in air and expose the plate to iodine vapour. The colour and position of the principal spot in the chromatogram obtained with the substance being examined correspond to that of the principal spot obtained with lofexidine

hydrochloride CRS.

(3) The infrared absorption spectrum (Appendix IV C) is concordant with the reference spectrum of lofexidine hydrochloride (Appendix XVI).

(4) The aqueous solution yields the reactions characteristic of chloride (Appendix III).

Acidity Dissolve 0.10 g in 10 ml of water, pH 5.0-6.5 (Appendix VI H).

Clarity of solution Dissolve 0.10 g in 10 ml of water, the solution is clear.

Related substances Dissolve a quantity of the substance being examined in mobile phase to produce a test solution of 0.5 mg per ml. Transfer 1 ml of the test solution, measured accurately, in a 100 ml volumetric flask, dilute with mobile phase to volume, mix well, to produce a reference solution. Carry out the method for high performance liquid chromatography (Appendix V D), using a column packed with octadecylsilane bonded silica gel and a mixture of methanol-0.27% potassium dihydrogen phosphate solution (65 : 35) as the mobile phase. Detection wavelength is 210 nm and the number of the theoretical plates of the column is not less than 600, calculated with reference to the peak of lofexidine. Inject 10 μ l of the reference solution into the column, adjust the attenuation so that the principal peak height in the chromatogram is 20% of the full scale of the chart. Inject separately 10 μ l each of the test solution and the reference solution into the column and record the chromatograms for three times the retention time of the principal peak. The sum of the areas of all peaks other than the principal peak is not greater than the area of the principal peak in chromatogram obtained with the reference solution.

Loss on drying When dried to constant weight at 105°C, loses not more than 0.5% of its weight (Appendix VIII L).

Assay Weigh accurately 0.2 g, add 15 ml of glacial acetic acid and 3 ml of mercuric acetate TS, warm slightly to dissolve, cool, add 1 drop of crystal violet IS. Titrate with perchloric acid (0.1 mol/L) VS until the colour changes to pure blue. Perform a blank determination and make any necessary correction. Each ml of perchloric acid (0.1 mol/L) VS is equivalent to 29.56 mg of $C_{11}H_{12}Cl_2N_2O \cdot HCl$.

Category Antihypertensive.

Storage Preserve in tightly closed containers, protected from light.

Preparation Lofexidine Hydrochloride Tablets

Lofexidine Hydrochloride Tablets

Lofexidine Hydrochloride Tablets contain not less than 90.0% and not more than 110.0% of the labelled amount of lofexidine hydrochloride ($C_{11}H_{12}Cl_2N_2O \cdot HCl$).

Description White tablets.

Identification (1) Triturate 10 tablets, add 10 ml of water, stir thoroughly and with the aid of an ultrasonic bath for 5 minutes to dissolve lofexidine hydrochloride. Filter, transfer the filtrate to a separator, adjust to alkaline with ammonia concentrated TS, add 20 ml of chloroform and shake to extract. Evaporate the chloroform extract to dryness and dissolve the residue in 1 ml of methanol. Use this solution as test solution. Dissolve a quantity of lofexidine hydrochloride CRS in methanol to produce a reference solution of 2 mg per ml. Carry out the method for thin-layer chromatography (Appendix V B), using silica

gel GF₂₅₄ as the coating substance and a mixture of dehydrated ethanol-chloroform-ammonia concentrated TS (70 : 30 : 2) as the mobile phase. Apply separately on the plate 10 µl each of the above two solutions. After developing and removal of the plate, dry it in air, examine under ultraviolet light (254 nm) and spray with dilute potassium iodobismuthate TS. The colour and position of the principal spot in the chromatogram obtained with test solution corresponds to that of the principal spot obtained with reference solution.

(2) To the above test solution, add 1 ml of water, mix well, add 1 ml of freshly prepared 5% sodium nitroprusside solution, 2 ml of sodium hydroxide TS and 1 g of sodium bicarbonate, shake, a purple colour is produced. The colour of solution turns to dark after standing.

Content uniformity Comply with the requirements for content uniformity (Appendix X E). Triturate 1 tablet, transfer to a 10 ml volumetric flask with water, add water to volume, mix well, filter. Use the successive filtrate as test solution and carry out the procedure described under the Assay.

Dissolution Carry out the dissolution test (Appendix X C, method 3), using 150 ml of water as the dissolution medium, adjust the rotational speed of the paddle to 100 rpm. Place 2 tablets in each of 6 vessels. Withdraw 5 ml of the solution after exactly 60 minutes and filter. Use the successive filtrate as test solution. Dissolve an accurately weighed quantity of lofexidine hydrochloride CRS in water to produce a reference solution of 2.6 µg per ml. Carry out the procedure described under the Assay and calculate the dissolution of C₁₁H₁₂Cl₂N₂O · HCl from each tablet. Not less than 70% of the labelled amount is dissolved.

Other requirements Comply with the general requirements for tablets (Appendix I A).

Assay Carry out the method for high performance liquid chromatography (Appendix V D), using a column packed with octylsilane bonded silica gel and a mixture of 0.02 mol/L potassium dihydrogen phosphate solution (adjust to pH 3.2 with phosphoric acid)-acetonitrile (4 : 1) as the mobile phase. Detection wavelength is 210 nm and the number of the theoretical plates of the column is not less than 1000, calculated with reference to the peak of lofexidine hydrochloride.

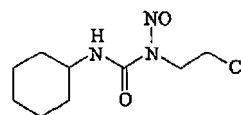
Procedure Weigh accurately and powder 20 tablets. To an accurately weighed quantity of the powdered tablets equivalent to about 0.2 mg of lofexidine hydrochloride in a 10 ml volumetric flask, add 5 ml of water and with the aid of an ultrasonic bath for 10 minutes to dissolve lofexidine hydrochloride, dilute with water to volume, mix well, filter. Inject 10 µl of the successive filtrate into the column and record the chromatogram. Dissolve lofexidine hydrochloride CRS in water to produce a solution of 0.02 mg per ml. Repeat the operation, using lofexidine hydrochloride CRS instead of the substance being examined. Calculate the content of C₁₁H₁₂Cl₂N₂O · HCl with respect to the peak area obtained in the chromatogram by the external standard method.

Category As described under Lofexidine Hydrochloride.

Strength 0.2 mg

Storage Preserve in tightly closed containers, stored in a dry place and protect from light.

Lomustine



C₉H₁₆ClN₃O₂ 233.70

[13010-47-4]

Lomustine is N-(2-chloroethyl)-N'-cyclohexyl-N-nitroso-urea. It contains not less than 97.0% and not more than 103.0% of C₉H₁₆ClN₃O₂, calculated on the dried basis.

Description A pale yellow crystalline powder; odourless. Freely soluble in chloroform; soluble in carbon tetrachloride or ethanol; sparingly soluble in cyclohexane; practically insoluble in water.

Melting point 88-91°C (Appendix VI C).

Identification (1) Dissolve 10-20 mg in 1 ml of ethanol, add 1 ml of a 1% solution of sulfanilamide in dilute hydrochloric acid. Heat in a water bath for 10 minutes, cool, add 2 ml of alkaline β-naphthol TS, an orange-red colour is produced.

(2) The light absorption of the solution obtained in the Assay exhibits a maximum at 232 nm (Appendix IV A).

(3) The infrared absorption spectrum (Appendix IV C) is concordant with the reference spectrum of lomustine (Appendix XVI).

(4) Heat about 10 mg with 5 ml of sodium hydroxide TS in a water bath for 5 minutes, acidify with nitric acid, the solution yields the reactions characteristic of chlorides (Appendix III).

Chloride shake thoroughly 0.40 g with 40 ml of water and filter. Carry out the limit test for chlorides (Appendix VIII A), using 20 ml of the filtrate. Any opalescence is not more pronounced than that of a reference using 4.0 ml of sodium chloride standard solution (0.02%).

Related substances Protect from light throughout the procedure. Carry out the method for thin layer chromatography (Appendix V B), using silica gel GF₂₅₄ as the coating substance and toluene as the mobile phase. Apply separately to the plate 20 µl each of two solutions in chloroform containing (1) 10 mg per ml, (2) 0.10 mg per ml of the substance being examined. After developing and removal of the plate, dry it in air and examine under ultraviolet light (254 nm). No spot other than the principal spot in the chromatogram obtained with solution (1) is more intense than the principal spot obtained with solution (2).

Loss on drying When dried to constant weight in vacuum over phosphorous pentoxide, loses not more than 0.5% of its weight (Appendix VII L).

Assay Protect from light throughout the procedure. Dissolve an accurately weighed quantity in cyclohexane to produce a solution of about 15 µg per ml. Measure the absorbance at 232 nm (Appendix IV A) and calculate the content of C₉H₁₆ClN₃O₂, taking 263 as the value of A (1%, 1 cm).

Category Antineoplastic.

Storage Preserve in tightly closed containers, stored in a cold place and protected from light.

Preparation Lomustine Capsules

Lomustine Capsules

Lomustine Capsules contain not less than 90.0% and not more than 110.0% of the labelled amount of lomustine ($C_9H_{16}ClN_3O_2$).

Identification Comply with the tests (1), (2) and (4) for Identification described under Lomustine, using the contents of the capsules.

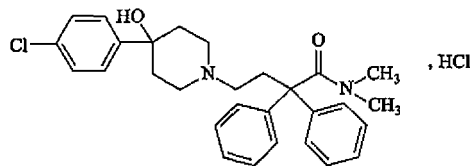
Other requirements Comply with the general requirements for capsules (Appendix I E).

Assay Protect from light throughout the procedure. Carry out the Assay described under Lomustine, using an accurately weighed quantity of the well mixed contents obtained in the test for weight variation of content.

Category, Storage As described under Lomustine.

Strength (1) 40 mg (2) 100 mg

Loperamide Hydrochloride



$C_{29}H_{33}ClN_2O_2 \cdot HCl$ 513.51

[34552-83-5]

Loperamide Hydrochloride is 4-(*p*-chlorophenyl)-4-hydroxy-*N*, *N*-dimethyl- α , α -diphenyl-1-piperidinebutyramide monohydrochloride. It contains not less than 98.0% and not more than 102.0% of $C_{29}H_{33}ClN_2O_2 \cdot HCl$, calculated on the dried basis.

Description A white or almost white crystalline powder; almost odourless; taste, bitter. Freely soluble in ethanol or glacial acetic acid; slightly soluble in water.

Identification (1) The light absorption of a solution of 0.4 mg per ml in methanol exhibits maxima at 265 nm, 259 nm and 253 nm.

(2) The infrared absorption spectrum (Appendix IV C) is concordant with the reference spectrum of loperamide hydrochloride (Appendix XVI).

Chloride content Weigh accurately about 15 mg, carry out the method for oxygen flask combustion (Appendix VII C), using 20 ml of 1 mol/L sodium hydroxide solution as the absorbing liquid. When the combustion is complete, shake the flask vigorously for 15 minutes, rinse the stopper and platinum wire with a small amount of water and add washings to the absorbing liquid. Add 1 drop of bromophenol blue IS, adjust with diluted nitric acid until the colour of the solution changes to yellow. Add 1 ml of diluted nitric acid, 20 ml of ethanol and 5 to 10 drops of a 1% solution of diphenylcarbazine in ethanol. Titrate with mercuric nitrate (0.005 mol/L) VS and shake vigorously towards the end point until the colour changes to pale rose-red. Perform a blank determination and make any necessary correction. Each ml of mercuric nitrate (0.005 mol/L) VS is equivalent to 0.3545 mg of chloride. The chloride content is not less than 13.52% and not more than 14.20%.

Related substances Carry out the method for thin-layer chromatography (Appendix V B), using silica gel G as the coating substance and a mixture of chloroform-methanol-formic acid (85 : 10 : 5) as the mobile phase. Apply separately to the plate 10 μ l each of two solutions of the substance being examined in chloroform containing (1) 10 mg per ml, (2) 0.05 mg per ml. After developing and removal of the plate, dry it in air and expose it to iodine vapour until the spots appear. Any spot in the chromatogram other than the principal spot obtained with solution (1) is not more intense than the principal spot obtained with solution (2).

Loss on drying When dried to constant weight at 105°C, loses not more than 0.5% of its weight (Appendix VIII L).

Residue on ignition Not more than 0.2% (Appendix VIII N), using 1.0 g.

Heavy metals Carry out the limit test for heavy metals (Appendix VIII H, method 2), using the residue obtained in the test for Residue on ignition; not more than 0.002%.

Assay Dissolve 0.3 g, accurately weighed, in 20 ml of glacial acetic acid and 10 ml of mercuric acetate TS, add 2 drops of naphtholbenzein IS. Titrate with perchloric acid (0.1 mol/L) VS until the colour changes to green. Perform a blank determination and make any necessary correction. Each ml of perchloric acid (0.1 mol/L) VS is equivalent to 51.35 mg of $C_{29}H_{33}ClN_2O_2 \cdot HCl$.

Category Antidiarrheal.

Storage Preserve in tightly closed containers, protected from light.

Preparation Loperamide Hydrochloride Capsules

Loperamide Hydrochloride Capsules

Loperamide Hydrochloride Capsules contain not less than 90.0% and not more than 110.0% of the labelled amount of loperamide hydrochloride ($C_{29}H_{33}ClN_2O_2 \cdot HCl$).

Description Capsules containing a white or yellowish-white powder.

Identification The retention time of principal peak of the substance being examined is identical with that of principal peak of the reference solution in the chromatogram obtained in the Assay.

Content uniformity Comply with the requirements for content uniformity (Appendix X E). Transfer the contents and shell of 1 capsule to a 50 ml conical flask with stopper, add 20 ml of methanol, accurately measured, shake for 30 minutes. Centrifuge, use the supernatant liquid as the test solution. Carry out the procedure as described under the Assay. Calculate the content of $C_{29}H_{33}ClN_2O_2 \cdot HCl$.

Dissolution Carry out the dissolution test (Appendix X C, method 3), using 150 ml of 0.004 mol/L hydrochloric acid solution as the dissolution medium, adjust the rotational speed of the paddle to 100 rpm. Withdraw the solution after exactly 45 minutes and filter. Use the successive filtrate as the test solution. Transfer 3 ml of reference solution obtained under the Assay, accurately measured, to a 25 ml volumetric flask, dilute with 0.004 mol/L hydrochloric acid solution to volume, mix well. Use this solution as the reference solution. Carry out the procedure as described under the Assay, calculate the dissolution of $C_{29}H_{33}ClN_2O_2 \cdot HCl$ from each capsule. Not less than 75 % of the labelled amount is dissolved.

Other requirements Comply with the general requirements for capsules (Appendix I E).

Assay Carry out the method for high performance liquid chromatography (Appendix V D), using a column packed with octadecylsilane bonded silica gel and a mixture of 0.01 mol/L tetrabutylammonium hydrogen sulfate solution-acetonitrile-methanol (63 : 26 : 11) as the mobile phase. Detection wavelength is 220 nm and the number of theoretical plates of the column is not less than 3000, calculated with reference to the peak of loperamide hydrochloride.

Reference solution Dissolve a quantity of loperamide hydrochloride CRS, accurately weighed, in methanol to produce a solution of 0.1 mg per ml.

Test solution Transfer the content and shells of 5 capsules to a conical flask with stopper, add 100 ml of methanol, accurately measured, shake for 30 minutes. Centrifuge at 3500 rpm for 5 minutes, use the supernatant liquid as the test solution.

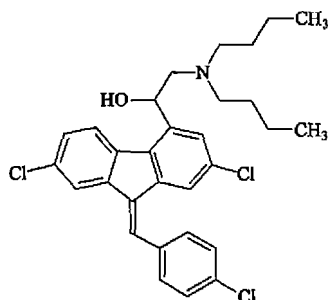
Procedure Inject respectively 20 μ l of the reference solution and the test solution, accurately measured, into the column. Calculate the content of $C_{29}H_{33}ClN_2O_2 \cdot HCl$.

Category As described under Loperamide Hydrochloride.

Strength 2 mg

Storage Preserve in tightly closed containers, stored in a dry place.

Lumefantrine



$C_{30}H_{32}Cl_3NO$ 528.94

Lumefantrine is α -(dibutylamino methyl)-2,7-dichloro-9-(*p*-chlorobenzene methylene)-4-fluorene methanol. It contains not less than 98.0% of $C_{30}H_{32}Cl_3NO$, calculated on the dried basis.

Description A yellow crystalline powder; odour, almond smell; tasteless. Freely soluble in chloroform; sparingly soluble in acetone, practically insoluble in ethanol or water.

Melting range 125-131°C (Appendix V C).

Identification (1) Transfer about 5 mg to a test tube, add 1 ml of citric-acetic anhydride TS, heat on a water bath, a violet colour is produced.

(2) Dissolve a quantity, accurately weighed, in ethanol on warming in a water bath to produce a solution of 10 μ g per ml. The light absorption of the solution exhibits four maxima at 234 nm, 266 nm, 301 nm and 335 nm (Appendix IV A).

(3) The infrared absorption spectrum (Appendix IV C) is concordant with the reference spectrum of lumefantrine (Appendix XVI).

Related substances Carry out the method for thin-layer

chromatography (Appendix V B), using silica gel GF₂₅₄ as the coating substance and a mixture of *n*-hexane-acetone-diethylamine (80 : 14 : 6) as the mobile phase. Apply separately to the plate 10 μ l each of two solutions of the substance being examined in chloroform containing (1) 10 mg per ml (2) 50 μ g per ml. After developing and removal of the plate, dry it in air and examine under ultra-violet light (254 nm). Any spot in the chromatogram other than the principal spot obtained with solution (1) is not more intense than the principal spot obtained with solution (2) and not more than four spots are observed.

Loss on drying When dried to constant weight at 105°C, loses not more than 0.2% of its weight (Appendix VIII L).

Residue on ignition Not more than 0.2% (Appendix VIII N), using 1.0 g.

Heavy metals Carry out the limit test for heavy metals (Appendix VIII H, method 2), using the residue obtained in test for Residue on ignition; not more than 0.002%.

Assay To about 0.5 g, accurately weighed, add 20 ml of acetic anhydride, shake to dissolve, add 1 drop of crystal violet IS, titrate with perchloric acid (0.1 mol/L) VS until the colour changes to pure blue. Perform a blank determination and make any necessary correction. Each ml of perchloric acid (0.1 mol/L) VS is equivalent to 52.89 mg of $C_{30}H_{32}Cl_3NO$.

Category Antimalarial agent.

Storage Preserve in tightly closed containers.

Lyophilizing Thrombin Powder

Lyophilizing Thrombin Powder is a sterile, lyophilized thrombin powder prepared by cativation of prothrombin extracted from bovine or porcine plasma for oral or local hemostases. It has a potency of not less than 10 Units per mg and contains not less than 80% of labelled amount of thrombin.

Description A white or almost white lyophilized mass or powder. A solution of 500 Units per ml in 0.9% sodium chloride solution is slightly opaque.

Loss on drying When dried in vacuum over phosphorus pentoxide in desiccator for four hours, loses not more than 3.0% of its weight, (Appendix VIII L).

Sterility Dissolve a quantity in 5 ml of 0.9% Sterile sodium chloride solution. Complies with the test for sterility (Appendix XI H).

Assay Preparation of fibrinogen solution Dissolve about 30 mg, accurately weighed, of the fibrinogen in 1.5 ml of 0.9% sodium chloride solution, add 0.1 ml of thrombin solution (about 3 Units), shake immediately and allow to stand at room temperature for 1 hour until coagulate completely. Take out the clot and wash it with water until the washing is clear with the addition of silver nitrate TS. Dry the clot at 105°C for 3 hours, weigh and calculate the percentage content of the clot in the fibrinogen. Prepare a fibrinogen solution containing 0.2% of clot with 0.9% sodium chloride solution, adjust to pH 7.0-7.4 with disodium hydrogen phosphate solution (0.05 mol/L), or sodium dihydrogen phosphate solution (0.05 mol/L), dilute with 0.9% sodium chloride solution to produce a solution containing 0.1% of clot.

Preparation of standard curve Dissolve a quantity of the thrombin RS in 0.9% sodium chloride solution to produce

solutions containing 5.0, 6.4, 8.0, 10.0 Units per ml. To each of 4 test tubes (10 mm × 100 mm) add, accurately measured, 0.9 ml of fibrinogen solution, and place the tubes in a water bath at $37^{\circ}\text{C} \pm 0.5^{\circ}\text{C}$ for 5 minutes. Add, accurately measured, 0.1 ml of the standard solutions of the four different concentrations to the test tubes, respectively. Place the tubes in a water bath at $37^{\circ}\text{C} \pm 0.5^{\circ}\text{C}$ immediately after shake. Record the initial clotting time. For each concentration, repeat the test five times and calculate the average clotting time (the test is fail if the deviation between the maximum and minimum of five determinations is more than 10% of the average value and repeat experiment again). Prepare standard solution of suitable concentration with reference to clotting time in a range of 14-60 seconds. Calculate the regression equation between logarithms of RS Units and logarithms of clotting time.

Procedure To each of accurately weighed contents of three containers according to the labelled amount, add 0.9% sodium chloride solution respectively, to produce test solutions with concentrations equivalent to the standard solutions. Measure accurately 0.1 ml of the test solution, and treated in the same manner as described under preparation of standard curve and calculate average clotting time (the requirement of deviation between the maximum and minimum is the same as described above). The thrombin Units is obtained from regression equation. Calculate thrombin Units per mg or per container of substance being examined as follows:

$$\begin{aligned}\text{thrombin Units/mg} &= U \times 10 \times V / W \\ \text{thrombin Units/container} &= U \times 10 \times V\end{aligned}$$

Where U is the real Units of 0.1 ml substance being examined obtained from standard curve;

V is the volume of dissolved contents in one container (ml);

W is the weight of the substance being examined in one container (mg);

10 is the factor from 0.1 ml to 1.0 ml.

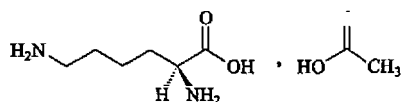
Calculate the percentage of labelled potency of each container. If one container doesn't comply with the requirement (more than 80% of labelled potency), repeat the test using other three containers.

Category Local hemostat.

Strength available (1) 200 Units (2) 500 Units
(3) 1000 Units (4) 2000 Units
(5) 5000 Units (6) 10000 Units

Storage Preserve in tightly closed containers at a temperature not exceeding 10°C .

Lysine Acetate



$\text{C}_6\text{H}_{14}\text{N}_2\text{O}_2 \cdot \text{C}_2\text{H}_4\text{O}_2$ 206.24

Lysine Acetate is (S)-2,6-diaminohexanoic acid acetate. It contains not less than 98.5% of $\text{C}_6\text{H}_{14}\text{N}_2\text{O}_2 \cdot \text{C}_2\text{H}_4\text{O}_2$, calculated on the dried basis.

Description White crystals or crystalline powder; practically odourless.

Freely soluble in water, practically insoluble in ethanol.

Specific optical rotation $+8.5^{\circ}$ to $+10.0^{\circ}$, in a solution of about 0.10 g per ml in water (Appendix VI E).

Identification The infrared absorption spectrum (Appendix IV C) is concordant with the spectrum of lysine acetate CRS (Appendix XVI).

Acidity or alkalinity Dissolve 0.10 g in 10 ml of water, pH 6.5-7.5 (Appendix VI H).

Transmittance of solution Dissolve 1.0 g in 10 ml of water, the transmittance at 430 nm is not less than 98.0% (Appendix IV A).

Chloride Carry out the limit test for chloride (Appendix VII A), using 0.50 g. Any opalescence produced is not more pronounced than that of a reference solution using 10.0 ml of sodium chloride standard solution (0.02%).

Sulfate Carry out the limit test for sulfate (Appendix VII B), using 1.0 g. Any opalescence produced is not more pronounced than that of a reference solution using 2.0 ml of potassium sulfate standard solution (0.02%).

Ammonium Carry out the limit test for ammonium (Appendix VII K), using 0.25 g. Any colour produced is not more intense than that of a reference solution using 5.0 ml of ammonium chloride standard solution (0.02%).

Other amino acids Carry out the method for thin-layer chromatography (Appendix V B), using silica gel G as the coating substance and propanol-concentrated ammonia solution (67 : 33) as the mobile phase. Apply separately to the plate 5 μl each of two solutions of substance being examined in water containing (1) 20 mg per ml, (2) 40 μg per ml. After developing and removal of the plate, dry it in air and spray with ninhydrin acetone solution (1 → 50), heat at 80°C until the colour is produced and examine immediately. Any spot, other than the principal spot in the chromatogram, obtained with solution (1) is not more intense than the principal spot obtained with solution (2) (0.2%).

Loss on drying When dried at 80°C for 3 hours, loses not more than 0.5% of its weight (Appendix VIII L).

Residue on ignition Not more than 0.1% (Appendix VIII N).

Iron Carry out the limit test for iron (Appendix VIII G), using 2.0 g. Any colour produced is not more intense than that of a reference solution using 2.0 ml of iron standard solution (0.001%).

Heavy metals Dissolve 2.0 g in 23 ml of water, add 2 ml of acetate BS (pH 3.5). Carry out the limit test for heavy metals (Appendix VIII H, method 1); not more than 0.001%.

Arsenic Dissolve 2.0 g in 23 ml of water, add 5 ml of hydrochloric acid, carry out the limit test for arsenic (Appendix VIII J, method 1); not more than 0.0001%.

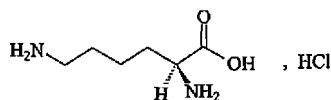
Bacterial endotoxin Carry out the test for bacterial endotoxin (Appendix XI E); less than 0.01 EU per mg of 'lysine ace a e' (for paren'era' a 'mini tra' i n).

Assay Dissolve about 0.1 g, accurately weighed, in 3 ml of dehydrated acetic acid, add 30 ml of glacial acetic acid. Carry out the method for potentiometric titration (Appendix VII A), titrate with perchloric acid (0.1 mol/L) VS. Perform a blank determination and make any necessary correction. Each ml of perchloric acid (0.1 mol/L) VS is equivalent to 10.31 mg of $\text{C}_6\text{H}_{14}\text{N}_2\text{O}_2 \cdot \text{C}_2\text{H}_4\text{O}_2$.

Category Amino acid.

Storage Preserve in tightly closed containers, protected from light.

Lysine Hydrochloride



$C_6H_{14}N_2O_2 \cdot HCl$ 182.65 [657-27-27]

Lysine is (L)-2,6-diamino caproic acid hydrochloride. It contains not less than 98.5% of $C_6H_{14}N_2O_2 \cdot HCl$, calculated on the dried basis.

Description White crystals or a white crystalline powder; odourless.

Freely soluble in water; very slightly soluble in ethanol, practically insoluble in ether.

Specific optical rotation $+20.0^\circ$ to $+21.5^\circ$, in a solution of 80 mg per ml in 6 mol/L hydrochloric acid solution (Appendix VI E).

Identification (1) The infrared absorption spectrum (Appendix IV C) is concordant with the reference spectrum of Lysine hydrochloride (Appendix XVI).

(2) Yields the reactions characteristic of chlorides (Appendix III).

Acidity Dissolve 1.0 g in 10 ml of water, pH 5.0-6.0 (Appendix VI H).

Transmittance of solution Dissolve 0.5 g in 10 ml of water, t_{40} is t_{10} than 9.0 Ap. ndix IV A).

Sulfate Carry out the limit test for sulfates (Appendix VIII B), u.i.g 1.0 g. Any colour produced is not more pronounced than that of a reference solution using 2.0 ml of potassium sulfate standard solution (0.02%).

Ammonium Carry out the limit test for ammonium (Appendix VII K), using 0.10 g. Any colour produced is not more intense than that of a reference solution using 2.0 ml of ammonium chloride standard solution (0.02%).

Other amino acids Carry out the method for thin-layer chromatography (Appendix V B), using silica gel G as the coating substance and a mixture of *n*-propanol-ammonium solution (2 : 1) as the mobile phase. Apply separately to the plate 5 μ l of each of two solutions of the substance being examined in water containing (1) 16 mg per ml, (2) 80 μ g per ml. After developing and removal of the plate, dry it in air and spray with ninhydrin solution (dissolve 1 g ninhydrin in 50 ml of acetone), heat at $80^\circ C$ until the colour is produced and examine immediately. Any spot, other than the principal spot in the chromatogram obtained with solution (1) is not more intense than the principal spot obtained with solution (2) (0.5%).

Loss on drying When dried to the constant weight at $105^\circ C$ for 3 hours, loses not more than 0.4% of its weight (Appendix VII L).

Residue on ignition Not more than 0.1% (Appendix VII N).

Iron Carry out the limit test for iron (Appendix VII G), using 0.50 g. Any colour produced is not more intense than that of a reference solution using 1.5 ml of iron standard solution (0.003%).

Heavy metals Dissolve 2.0 g in 23 ml of water, add 2 ml of acetate BS (pH3.5). Carry out the limit test for heavy metals (Appendix VII H, method 1); not more than 0.001%.

Arsenic Dissolve 2.0 g in 23 ml of water, add 5 ml of hydrochloric acid. Carry out the limit test for arsenic (Appendix VII J, method 1); not more than 0.0001%.

Bacterial endotoxin Carry out the test for bacterial endotoxin (Appendix XI E); less than 10 EU per g of lysine hydrochloride (for parenteral administration).

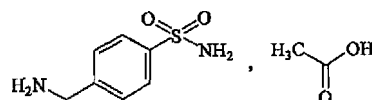
Chloride Content Dissolve about 0.35 g, accurately weighed, in 20 ml of water, add 2 ml of dilute acetate acid and 8 to 10 drops of bromophenol blue IS, titrate with silver nitrate (0.1 mol/L) VS until the colour becomes to blue-violet. Perform a blank determination and make any necessary correction. Each ml of silver nitrate (0.1 mol/L) VS is equivalent to 3.545 mg of Cl. It contains not less than 19.0% and not more than 19.6% of chloride, calculated on the dried basis.

Assay Weigh accurately about 80 mg, add 5 ml of mercuric acetate TS and 25 ml of glacial acetic acid, heat at $60-70^\circ C$ to dissolve, Carry out the method for potentiometric titration (Appendix VII A). Titrate with perchloric acid (0.1 mol/L) VS, perform a blank determination and make any necessary correction. Each ml of perchloric acid (0.1 mol/L) VS is equivalent to 9.133 mg of $C_6H_{14}N_2O_2 \cdot HCl$.

Category Amino acid.

Storage Preserve in tightly closed containers, protected from light.

Mafenide Acetate



$C_7H_{10}N_2O_2S \cdot C_2H_4O_2$ 246.29 [13009-99-9]

Mafenide Acetate is α -amino-*p*-toluenesulfonamide monoacetate, it contains not less than 98.0% of $C_7H_{10}N_2O_2S \cdot C_2H_4O_2$.

Description White to pale yellow crystals or a crystalline powder; odour, acetic; the aqueous solution exhibits weak acidic reaction.

Freely soluble in water.

Melting point $163-167^\circ C$, determined as such without drying (Appendix VI C).

Identification (1) To 5 ml of the aqueous solution (1 \rightarrow 1000) add 5 ml of sodium hydroxide TS, mix, add 0.5 ml of freshly prepared 5% potassium naphthoquinone sulfonate solution; a yellowish-red colour is produced. Allow it to stand for 10 minutes, the solution turns to bluish-green on addition of 0.2 g of ammonium chloride (Distinction from other sulfonamides).

(2) Dissolve 0.2 g in 1 ml of water, add 0.5 ml of ammonia TS; white crystals are produced. Filter, wash the crystals with a small quantity of water and dry at $105^\circ C$ for 2-3 hours, it has a melting point of $151-154^\circ C$ (Appendix VI C). The filtrate yields the reactions characteristic of acetates (Appendix III).

(3) The infrared absorption spectrum (Appendix IV C) is concordant with the reference spectrum of mafenide acetate (Appendix XVI).

Acidity Dissolve 1.0 g in 10 ml of water, add 1 drop of methyl red IS; no red colour is produced.

Ammonium To the remaining solution obtained in the test

for Acidity add 5 ml of sodium hydroxide TS, heat in a water bath, the vapour evolved does not change a moistened red litmus paper to blue.

Residue on ignition Not more than 0.1% (Appendix VIII N); using 1.0 g.

Heavy metals Carry out the limit test for heavy metals (Appendix VIII H, method 2), using the residue obtained in the test for residue on ignition; not more than 0.0015%.

Assay Dissolve about 0.2 g, accurately weighed, in 20 ml of glacial acetic acid, add 1 drop of crystal violet IS, titrate with perchloric acid (0.1 mol/L) VS until the colour changes to bluish-green. Perform a blank determination and make any necessary correction. Each ml of perchloric acid (0.1 mol/L) VS is equivalent to 24.63 mg of $C_7H_{10}N_2O_2S \cdot C_2H_4O_2$.

Category Sulfonamide.

Storage Preserve in tightly closed containers, stored in a cool place and protected from light.

Magnesium Oxide

MgO 40.30 [1309-48-4]

Magnesium Oxide contains not less than 96.5% of MgO, calculated with reference to substance freshly ignited to constant weight.

Description A white powder, odourless; tasteless; gradually absorbs carbon dioxide from the air. Practically insoluble in water; insoluble in ethanol; soluble in dilute acids.

Identification Its solution in dilute hydrochloric acid yields the reactions characteristic of magnesium salts (Appendix III).

Alkalinity Boil 1.0 g with 50 ml of water for 5 minutes. Filter while hot, wash the residue with a quantity of water. Combine the washings with the filtrate, add a few drops of methyl red IS and 2.0 ml of sulfuric acid (0.05 mol/L) VS, a red colour is produced.

Calcium oxide To about 0.5 g, accurately weighed after freshly ignited and cooled, add 6 ml of dilute hydrochloric acid, heat to dissolve and allow to cool. Add 300 ml of water and 5 ml of tartaric acid solution (1→5), then 10 ml of triethanolamine solution (3→10) and 10 ml of 45% potassium hydroxide solution. Allow to stand for 5 minutes, add 0.1 g of calcon indicator mixture, titrate with disodium edetate (0.01 mol/L) VS until the colour changes from purple to blue. Perform a blank determination and make any necessary correction. Each ml of disodium edetate (0.01 mol/L) VS is equivalent to 0.5608 mg of CaO; not more than 0.50%.

Chloride Dissolve 0.10 g in 0.5 ml of nitric acid and sufficient water to produce 50 ml, mix well. Carry out the limit test for chlorides (Appendix VIII A), using 25 ml of the resulting solution. Any opalescence produced is not more pronounced than that of a reference using 7.0 ml of sodium chloride standard solution (0.14%).

Sulfate Dissolve 0.25 g in 2 ml of hydrochloric acid and sufficient water to produce 50 ml. Carry out the limit test for sulfates (Appendix VIII B), using 20 ml of the resulting solution. Any opalescence produced is not more pronounced than that of a reference using 3.0 ml of potassium sulfate standard solution (0.3%).

Carbonate Boil 0.10 g with 5 ml of water, cool, add 5 ml of acetic acid, no effervescence occurs.

Acid insoluble substances Add 75 ml of water to 2.0 g and then add hydrochloric acid in small portions with stirring until no more of the substance being examined is dissolved. Boil the solution for 5 minutes and filter. Wash the residue with water until the washing shows no reaction of chlorides. Ignite the residue to constant weight. The residue is not more than 2.0 mg (0.10%).

Loss on ignition When ignited to constant weight, loses not more than 5.0%, using 0.5 g.

Iron Dissolve 50 mg in 2 ml of dilute hydrochloric acid and 23 ml of water. Carry out the limit test for iron (Appendix VIII G). Any colour produced is not more intense than that of a reference solution using 2.5 ml of iron standard solution (0.05%).

Manganese To 1.0 g add 20 ml of water, 5 ml of nitric acid, 5 ml of sulfuric acid and 1 ml of phosphoric acid, boil for 2 minutes, cool to room temperature. Add 2.0 g of potassium periodate and boil again for 5 minutes, cool to room temperature. Transfer the solution to a 50 ml Nessler cylinder, dilute to volume with non-reducing water (add 3 ml of nitric acid and 5 g of potassium periodate to 1000 ml of water, boil for 2 minutes and cool), mix well. Any colour produced is not more intense than that of a reference solution prepared in the same manner, using 0.30 ml of manganese standard solution (dissolve 0.275 g of anhydrous manganese sulfate previously ignited to constant weight at 400–500°C in a 1000 ml volumetric flask, with water dilute to volume and mix well. Each ml of the resulting solution is equivalent to 0.10 mg of Mn) (0.003%).

Heavy metals Dissolve by heating 0.50 g with 10 ml of dilute hydrochloric acid and 5 ml of water, boil for 1 minute, allow to cool and filter. To the filtrate add 1 drop of phenolphthalein IS and add dropwise ammonia TS until the solution becomes pink. Add 2 ml of acetate BS (pH 3.5) and sufficient water to produce 25 ml, add 0.5 g of ascorbic acid and shake to dissolve. Carry out the limit test for heavy metals (Appendix VIII H, method 1), compare the colour after 5 minutes; not more than 0.004%.

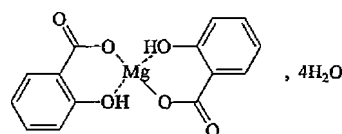
Arsenic Dissolve 0.40 g in 5 ml of hydrochloric acid and 23 ml of water. Carry out the limit test for arsenic (Appendix VIII J, method 1); not more than 0.0005%.

Assay Dissolve 0.5 g, accurately weighed, in 30 ml of sulfuric acid (0.5 mol/L) VS, accurately measured, add 1 drop of methyl orange IS. Titrate with sodium hydroxide (1 mol/L) VS. The quantity of sulfuric acid consumed by MgO is calculated by subtracting the quantity consumed by CaO from the total amount of sulfuric acid consumed. Each ml of sulfuric acid (0.5 mol/L) VS is equivalent to 20.15 mg of MgO or 28.04 mg of CaO.

Category Antiacids.

Storage Preserve in tightly closed containers.

Magnesium Salicylate



$C_{14}H_{10}MgO_6 \cdot 4H_2O$ 370.60

[18917-89-0]

Magnesium Salicylate is *bis* (2-hydroxybenzoic acid- O^1 , O^2) magnesium tetrahydrate. It contains $C_{14}H_{10}MgO_6 \cdot 4H_2O$ not less than 98.0% and not more than 103.0%, calculated on the dried basis.

Description A white crystalline powder; odourless; efflorescent; aqueous solution yields slight acid reaction. Freely soluble in ethanol, soluble in water.

Identification (1) The light absorption of a solution obtained in the Assay exhibits a maximum at 296 nm (Appendix IV A). (2) The infrared absorption spectrum (Appendix IV C) is concordant with the reference spectrum of magnesium salicylate (Appendix VI). (3) The aqueous solution yields the reactions characteristic of magnesium salts and salicylates (Appendix III).

Magnesium Weigh accurately about 0.8 g, in a 200 ml volumetric flask, add a quantity of water, shake for 15 minutes, dilute with water to volume, mix well, filter. Measure accurately 50 ml of the successive filtrate to a 250 ml conical flask, add 50 ml of water, 5 ml of ammonia-ammonium chloride BS (pH 10.0) and a small quantity of eriochrome black T indicator, titrate with disodium edetate (0.05 mol/L) VS, until the colour changes from purplish-red to pure blue. Each ml of disodium edetate (0.05 mol/L) VS is equivalent to 1.215 mg of Mg. The amount of Mg is not less than 7.9% and not more than 8.3%, calculated on the dried basis.

Loss on drying When dried to constant weight at 105°C for 4 hours, loses 17.5%–20.0% of its weight (Appendix VII L).

Heavy metals Dissolve 0.50 g in 20 ml of water, add 2 ml of acetate BS (pH 3.5) and water to 25 ml, carry out the limit test for heavy metals (Appendix VIII H, method 1); not more than 0.004%.

Assay Dissolve a quantity, accurately weighed, in water to produce a solution of about 20 µg of anhydrous magnesium salicylate per ml. Repeat the operation using magnesium salicylate CRS, treat in the same manner to produce a solution of about 20 µg per ml of anhydrous magnesium salicylate. Measure the absorbance of the two solutions at 296 nm (Appendix IV A), calculate the content of $C_{14}H_{10}MgO_6$.

Category Anti-inflammatory and analgesic non-steroids anti-inflammatory agent.

Storage Preserve in tightly closed containers.

Preparation (1) Magnesium Salicylate Capsules
(2) Magnesium Salicylate Tablets

Magnesium Salicylate Capsules

Magnesium Salicylate Capsules contain not less than 95.0% and not more than 105.0% of the labelled amount of anhydrous Magnesium Salicylate ($C_{14}H_{10}MgO_6$).

Identification A quantity of the contents of capsules complies with the tests (1) and (3) for Identification described under Magnesium Salicylate.

Loss on drying When dried for 4 hour at 105°C, loses not less than 17.5% and not more than 20.0% of its weight. (Appendix VII L)

Dissolution Comply with the dissolution test as described under Magnesium Salicylate Tablets.

Other requirements comply with the general requirements for capsules (Appendix I E).

Assay Dissolve the mixed contents obtained from the test for weight variation of contents, accurately weighed with water to produce a solution of 20 µg of anhydrous magnesium salicylate per ml. Carry out the Assay as described under Magnesium Salicylate, beginning at the words "Repeat the operation using magnesium salicylate CRS..." Calculate the content of $C_{14}H_{10}MgO_6$ in each capsule.

Category As described under Magnesium Salicylate.

Strength 0.25 g (calculated as $C_{14}H_{10}MgO_6$)

Storage Preserve in tightly closed containers.

Magnesium Salicylate Tablets

Magnesium Salicylate Tablets contain not less than 95.0% and not more than 105.0% of the labelled amount of anhydrous magnesium salicylate ($C_{14}H_{10}MgO_6$).

Description White tablets.

Identification (1) The light absorption of the solution obtained in Assay exhibits maximum at 296 nm (Appendix IV A). (2) Powdered one tablet, add water to dissolve magnesium salicylate, filter. The filtrate yields the reactions characteristic of magnesium salts and salicylates salts (Appendix III).

Dissolution Carry out the method for dissolution test (Appendix X C, method 2), using 900 ml of water as the dissolution medium, Adjust the rotation speed at 50 rpm. Withdraw 10 ml of the solution after exactly 45 minutes, filter. Measure accurately a quantity of the successive filtrate, dilute with water to produce a solution of 20 µg per ml. Proceed the Assay described under Magnesium Salicylate, beginning at the words "Repeat the operation using magnesium salicylate CRS..." Calculate the dissolution of $C_{14}H_{10}MgO_6$ from each tablet. The amount of magnesium salicylate dissolved in 45 minutes is not less than 80% of the labelled amount.

Other requirements Comply with the general requirements for tablets. (Appendix I A).

Assay Weigh and powder 20 tablets. Dissolve a quantity of the powder equivalent to about 0.5 g of anhydrous magnesium salicylate, accurately weighed, in 250 ml volumetric flask in water by shaking, dilute to volume, and mix well. Filter, and discard initial filtrate, measure accurately 2 ml of the successive filtrate to 200 ml volumetric flask, dilute with water to volume and mix well. Carry out the method described under the Assay for Magnesium Salicylate beginning at the word "Repeat the operation using magnesium salicylate CRS...". Measure the absorbances of two solutions at 296 nm, calculate the content of $C_{14}H_{10}MgO_6$.

Category As described under Magnesium Salicylate.

Strength 0.25 g (calculate as $C_{14}H_{10}MgO_6$)

Storage Preserve in tightly closed containers.

Magnesium Sulfate

$MgSO_4 \cdot 7H_2O$ 246.48

[7487-88-9]

Magnesium Sulfate contains not less than 99.5% of $MgSO_4$, calculated with reference to the substance ignited to constant weight.

Description Colourless crystals, odourless; taste, bitter

and salty; efflorescent.

Freely soluble in water; practically insoluble in ethanol.

Identification The aqueous solution yields the reactions characteristic of magnesium salts and sulfates (Appendix III).

Acidity or alkalinity Dissolve 5.0 g in 50 ml of water, add 3 drops of bromothymol blue IS. If the solution is yellow, add 0.10 ml of sodium hydroxide (0.02 mol/L) VS, the colour changes to bluish-green. If the solution is bluish-green or green, it changes to yellow on adding of 0.10 ml of hydrochloric acid (0.02 mol/L) VS.

Clarity of solution Dissolve 2.5 g in 20 ml of water by shaking, the solution is clear. Any opalescence produced is not more pronounced than that of reference suspension 1 (Appendix IX B).

Chloride Carry out the limit test for chlorides (Appendix VIII H), using 0.50 g. Any opalescence produced is not more pronounced than that of a reference solution using 5.0 ml of sodium chloride standard solution (0.01%).

Loss on ignition Weigh accurately 1.0 g, dry at 105°C for 2 hours, then ignite at 450°C ± 25°C to constant weight, loses not less than 48.0% and not more than 52.0% of its weight.

Iron Boil 2.0 g with 5 ml of nitric acid (1 → 10) for 1 minute, cool, dilute with water to produce 35 ml. Carry out the limit test for iron (Appendix VIII G). Any colour produced is not more intense than that of a reference solution prepared in the same manner using 3.0 ml of iron standard solution (0.0015%).

Heavy metals Dissolve 2.0 g in 10 ml of water, add 2 ml of acetate BS (pH 3.5) and sufficient water to produce 25 ml, then add 0.5 g of ascorbic acid. Carry out the limit test for heavy metals (Appendix VIII H, method 1), compare the colour after standing for 5 minutes; not more than 0.001%.

Arsenic Dissolve 1.0 g in 23 ml of water, add 5 ml of hydrochloric acid. Carry out the limit test for arsenic (Appendix VIII J, method 1); not more than 0.0002%.

Assay Dissolve about 0.25 g, accurately weighed, in 30 ml of water, add 10 ml of ammonia-ammonium chloride BS (pH 10.0) and a small quantity of eriochrome black T indicator, titrate with disodium edetate (0.05 mol/L) VS until the colour changes from purplish-red to pure blue. Each ml of disodium edetate (0.05 mol/L) VS is equivalent to 6.018 mg of MgSO_4 .

Category Laxative and choleric.

Storage Preserve in tightly closed containers.

Preparation Magnesium Sulfate Injection

Magnesium Sulfate Injection

Magnesium Sulfate Injection is a sterile solution of magnesium sulfate in Water for Injection. It contains not less than 95.0% and not more than 105.0% of the labelled amount of Magnesium sulfate ($\text{MgSO}_4 \cdot 7\text{H}_2\text{O}$).

Description A colourless, clear liquid.

Identification Yields the reactions characteristic of magnesium salts and sulfates (Appendix III).

pH value 5.0-7.0 (Appendix VI H).

Bacterial endotoxin Carry out the test for bacterial endotoxin (Appendix XI E); less than 0.03 EU per mg of magnesium sulfate.

Other requirements Complies with the general requirements for injections (Appendix I B).

Assay Measure accurately a quantity equivalent to 0.5 g of magnesium sulfate into a 50 ml volumetric flask, dilute with water to volume and mix well. Measure accurately 25 ml of the solution to complete the assay described under Magnesium Sulfate, beginning at the words "add 10 ml of ammonia-ammonium chloride BS (pH 10.0)...". Each ml of disodium edetate (0.05 mol/L) VS is equivalent to 12.32 mg of $\text{MgSO}_4 \cdot 7\text{H}_2\text{O}$.

Category Laxative, choleric and anticonvulsant agent.

Strength (1) 10 ml : 1 g (2) 10 ml : 2.5 g

Storage Preserve in well closed containers, protected from light.

Magnesium Trisilicate

[14987-04-3]

Magnesium Trisilicate is a hydrated magnesium silicate with varying Components. It contains not less than 20.0% of MgO and not less than 45.0% of SiO_2 . The ratio of SiO_2 to MgO is 2.1-2.3.

Description A white fine powder with no sandy feeling; odourless; tasteless; slightly hygroscopic. Insoluble in water or ethanol.

Identification (1) Prepare a bead by fusing a few crystals of sodium ammonia phosphate on a platinum loop in the non-luminous flame. Place the hot, transparent bead in contact with the substance being examined and fuse again; silica floats about in the bead and an opaque bead with a web-like structure is produced upon cooling.

(2) Mix about 0.5 g with 10 ml of dilute hydrochloric acid, filter and neutralize the filtrate with ammonia TS; the filtrate yields reactions characteristic of magnesium salts (Appendix III).

Acid-consuming capacity Weigh accurately about 0.30 g into a glass-stoppered conical flask. Add accurately 50 ml of hydrochloric acid (0.1 mol/L) VS and 50 ml of water. Heat the flask in a water bath at 37°C for 2 hours, shake the mixture occasionally but leave it undisturbed during the last 15 minutes, cool. To 50 ml of the supernatant liquid add 1 drop of methyl orange IS and titrate the excess acid with sodium hydroxide (0.1 mol/L) VS. 1 g of magnesium trisilicate, calculated on the ignited basis, consumes not less than 140 ml and not more than 170 ml of hydrochloric acid (0.1 mol/L) VS.

Free alkali Boil 2.0 g with 30 ml of water for 15 minutes and filter with 2-3 layers of filter paper. Wash the residue with water in portions, combine the washings and filtrate, dilute to 50 ml with water and mix well. Add 2 drops of phenolphthalein IS to 25 ml of the solution; if a pink colour is produced, not more than 1.0 ml of hydrochloric acid (0.1 mol/L) VS is required to discharge it.

Chloride Boil 0.50 g with 5 ml of dilute nitric acid and 30 ml of water, cool, add water to produce 50 ml, mix well. Allow it to stand for 30 minutes and filter. Carry out the limit test for chlorides (Appendix VIII A) using 10 ml of the filtrate. Any opalescence produced is not more pronounced than that of a reference solution using 5.0 ml of sodium chloride standard solution (0.05%).

Sulfate Boil 0.10 g with 5 ml of dilute hydrochloric acid and 30 ml of water, cool and filter. Carry out the limit test for

sulfates (Appendix VIII B) using the filtrate. Any opalescence produced is not more pronounced than that of a reference solution using 5.0 ml of potassium sulfate standard solution 0.5%.

Soluble salts Evaporate 25 ml of the filtrate obtained in the test for free alkali to dryness and ignite to constant weight. The weight of the residue is not more than 15 mg.

Loss on ignition Weigh accurately about 0.5 g, ignite to constant weight at 700-800°C, loses not more than 30.0% of its weight (Appendix VIII N).

Heavy metals Boil 3.0 g with 5 ml of hydrochloric acid and 40 ml of water for 20 minutes, cool, add 2 drops of phenolphthalein IS and concentrated ammonia TS until a pink colour is produced. Add 1 ml of hydrochloric acid (0.1 mol/L) VS to make it slightly acid. Filter and wash the residue with small amount of water in portions, combine the washings and filtrate. Add ammonia TS dropwise until a pink colour is produced, add 8 ml of hydrochloric acid (0.1 mol/L) VS and sufficient quantity of water to produce 75 ml, mix well. Carry out the limit test for heavy metals (Appendix VIII H, method 1) using 25 ml; not more than 0.002%.

Arsenic Dissolve 0.40 g in 23 ml of water, add 5 ml of hydrochloric acid, it complies with the limit test for arsenic (Appendix VIII J, method 1) (0.0005%).

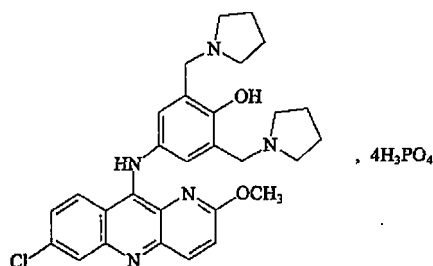
Assay Magnesium Oxide To about 1.5 g accurately weighed, add 50 ml of sulfuric acid (0.5 mol/L) VS, accurately measured, heat on a water bath for 15 minutes and allow to cool. Add 1 drop of methyl orange IS, titrate with sodium hydroxide (1 mol/L) VS. Each ml of sulfuric acid (0.5 mol/L) VS is equivalent to 20.15 mg of MgO.

Silicon Dioxide To about 0.4 g, accurately weighed, in a porcelain dish add a mixture of 3 ml of sulfuric acid and 5 ml of nitric acid, heat gently until the reaction is complete. Evaporate on a sand-bath to dryness, allow to cool. Add 10 ml of dilute sulfuric acid and 100 ml of water, boil to dissolve the magnesium salt. Decant the supernatant liquid through an ashless filter paper, wash the residue by decantation for three times with hot water and filter the washings. Finally transfer the residue to the filter paper, wash it with hot water. Transfer the filter paper and its contents to a platinum crucible, dry, incinerate, and ignite for further 30 minutes, cool and weigh accurately. Moisten the residue with water, add 3 ml of hydrofluoric acid and 3 drops of sulfuric acid. Evaporate to dryness, ignite for 5 minutes, cool, and weigh: the loss in weight represents the weight of SiO₂ in the substance being examined.

Category Antiacid.

Storage Preserve in tightly closed containers.

Malaridine Phosphate



$C_{23}H_{32}ClN_5O_2 \cdot 4H_3PO_4$ 910.04

Malaridine Phosphate is 10 [[3',5'-bis (1-pyrrolidylmethyl)-4'-hydroxyphenyl]-amino]-2-methoxy-7-chloro-benzo [b]-1,5-naphthyridine tetrphosphate. It contains not less than 98.0% and not more than 102.0% of $C_{23}H_{32}ClN_5O_2 \cdot 4H_3PO_4$, calculated on the dried basis.

Description A yellow to orange-yellow crystalline powder; odourless; taste, bitter; hygroscopic. Soluble in water; practically insoluble in ethanol or ether.

Identification (1) Dissolve about 10 mg in 1 ml of water, add a few drops of trinitrophenol TS, a yellow precipitate is produced.

(2) The light absorption of a solution of 10 µg per ml in phosphate BS (pH 7.0) exhibits two maxima at 260 nm and 276 nm (Appendix IV A).

(3) The infrared absorption spectrum (Appendix IV C) is concordant with the reference spectrum of malaridine phosphate (Appendix XVI).

(4) Dissolve about 20 mg in 5 ml of water, add ammonia TS to precipitate completely, filter. The filtrate yields the reactions characteristic of phosphates (Appendix III).

Acidity Dissolve 1.0 g in 25 ml of water, the pH value is up to 2.4 (Appendix VI H).

Water-insoluble substances Dissolve 2.0 g in 25 ml of water, shake thoroughly. Allow to stand for 30 minutes, filter with a No.4 sintered glass crucible, previously dried to constant weight at 105°C. Wash the precipitate with 15 ml of water in portions. Dry at 105°C for 4 hours, the residue obtained is not more than 4 mg (for injection) or 7 mg (for oral administration).

Chloride Dissolve 0.1 g in 4 ml of water, add 5 ml of 20% sodium carbonate solution to precipitate completely. Filter with a No.5 sintered glass crucible, wash the precipitate with 15 ml of water in portions. Combine the filtrate and washings, dilute with water to 25 ml. Carry out the limit test for chlorides (Appendix VIII A). Any opalescence produced is not more pronounced than that of a reference solution, using 3.0 ml of sodium chloride standard solution (0.03%).

Formaldehyde Dissolve 50 mg in 2 ml of water, add 4 ml of 5% sodium carbonate solution, stir and filter. add 3 ml of sulfuric acid solution (1→2) to the filtrate and allow to cool. Add 5 ml of fuchsin-sulfurous acid TS and warm at 20-30°C for 30 minutes. any colour produced is not more intense than that of 1.0 ml of a freshly prepared 0.10 mg per ml formaldehyde reference solution 0.1 mg per ml and treated in the same manner (0.2%).

Tetrahydropyrrole Dissolve 10 mg in 2 ml of water, add 2 ml of 5% sodium carbonate solution, stir and filter. Add 1 ml of freshly prepared sodium nitroprusside-acetaldehyde TS to the filtrate, mix well, no bluish-violet colour is developed within 5 minutes.

Loss on drying When dried to constant weight at 105°C, loses not more than 4.0% of its weight (Appendix VIII L).

Assay Dissolve about 0.2 g, accurately weighed, in 40 ml of glacial acetic acid by warming and then cool. Carry out the method for potentiometric titration (Appendix VII A), titrate with perchloric acid (0.1mol/L) VS. Each ml of perchloric acid (0.1 mol/L) VS is equivalent to 30.33 mg of $C_{23}H_{32}ClN_5O_2 \cdot 4H_3PO_4$.

Category Antimalarial agent.

Storage Preserve in tightly closed containers, protected from light.

Preparation (1) Malaridine Phosphate Injection

(2) Malaridine Phosphate Enteric-coated Tablets

Malaridine Phosphate Injection

Malaridine Phosphate Injection is a sterile solution of malaridine phosphate in Water for Injection. It contains not less than 94.0% and not more than 106.0% of the labelled amount of malaridine ($C_{29}H_{32}ClN_5O_2$).

Description An orange-red and clear liquid.

Identification Complies with the tests (1), (2) and (4) for Identification described under Malaridine Phosphate.

pH value 2.3-4.0 (Appendix VI H).

Pyrogens Dilute with sodium chloride injection or 5% glucose injection to produce a solution of 1.0 mg of malaridine per ml. The solution complies with the requirement of the test for pyrogens (Appendix XI D), using 10 ml per kg of the rabbit's weight, injected slowly.

Sterility Complies with the test for sterility (Appendix XI H), treated with the membrane filtration method.

Other requirements Complies with the general requirements for injections (Appendix I B).

Assay Dilute an accurately measured quantity with phosphates BS (pH 7.0) to produce a solution of 10 µg of malaridine phosphate per ml in an amber coloured flask. Carry out the Assay as described under Malaridine Phosphate Tablets.

Category As described under Malaridine phosphate.

Strength 2 ml : 80 mg (calculated on malaridine)

Storage Preserve in well closed containers, protected from light and stored in a cool and dark place.

Malaridine Phosphate Enteric-coated Tablets

Malaridine Phosphate Tablets contain not less than 90.0% and not more than 110.0% of the labelled amount of malaridine ($C_{29}H_{32}ClN_5O_2$).

Description Enteric film coated tablets with yellow core.

Identification A quantity of the powdered tablets complies with the test (1), (2) and (4) for Identification described under malaridine phosphate.

Other requirements Comply with the general requirements for tablets (Appendix I A).

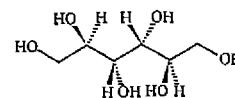
Assay Weigh accurately and powder 10 tablets with coating removed. Dissolve an accurately weighed quantity of the powdered tablets equivalent to about 10 mg of malaridine phosphate in a 100 ml amber coloured volumetric flask with phosphate BS (pH 7.0), dilute to volume and mix well. Filter quickly, discard the initial filtrate and collect the successive filtrate. Measure accurately 5 ml each of the reference preparation and test preparation to a 50 ml amber coloured volumetric flask separately, add phosphate BS (pH 7.0) to volume, mix well. Measure the light absorbance of the resulting solutions at 260 nm (Appendix IV A). Dissolve a quantity of malaridine phosphate CRS, accurately weighed, in an amber coloured volumetric flask with phosphate BS (pH 7.0) and dilute to produce a solution of 10 µg per ml. Repeat the operation. Calculate the content of

$C_{29}H_{32}ClN_5O_2 \cdot 4H_3PO_4$ and multiply the result by 0.569.

Category As described under Malaridine Phosphate.

Strength 0.1 g (calculated on malaridine)

Storage Preserve in tightly closed containers, protected from light.

Mannitol

$C_6H_{14}O_6$ 182.17

[69-65-8]

Mannitol is D-mannitol. It contains not less than 98.0% and not more than 102.0% of $C_6H_{14}O_6$, calculated on the dried basis.

Description A white crystalline powder; odourless; taste, sweetish.

Freely soluble in water; sparingly soluble in ethanol; practically insoluble in ether.

Melting range 166-170°C (Appendix VI C).

Identification (1) To about 0.5 g in a test tube add 3 ml of acetyl chloride and add dropwise 0.5 ml of pyridine with shake until the reaction is complete. Cool with ice and filter. Wash the crystals with 10 ml of ether and dissolve the crystals in another test tube with 15 ml of ether by warming in a water bath. Decant the ether solution while warm and evaporate the solvent; white crystals are obtained (if necessary, recrystallize again). After drying, the melting range of the crystals is 120-125°C (Appendix VI C).

(2) To 1 ml of the saturated aqueous solution of the substance being examined add 0.5 ml each of ferric chloride TS and sodium hydroxide TS; a brownish-yellow precipitate is produced which is unchanged on shake but dissolved in an excess of sodium hydroxide TS to form a brown solution.

(3) The infrared absorption spectrum (Appendix IV C) is concordant with the reference spectrum of mannitol (Appendix XVI).

Acidity Dissolve 5.0 g in 50 ml of freshly boiled and cooled water, add 3 drops of phenolphthalein IS and 0.30 ml of sodium hydroxide (0.02 mol/L) VS; a pink colour is produced.

Clarity and colour of solution A solution of 1.5 g in 10 ml of water is clear and colourless. Any opalescence produced is not more pronounced than that of reference suspension 1 (Appendix IX B).

Chloride Carry out the limit test for chlorides (Appendix VIII A), using 1.0 g. Any opalescence produced is not more pronounced than that of a reference solution using 3.0 ml of sodium chloride standard solution (0.003%).

Sulfate Carry out the limit test for sulfates (Appendix VIII B), using 2.0 g. Any opalescence produced is not more pronounced than that of a reference solution using 2.0 ml of potassium sulfate standard solution (0.01%).

Oxalate Dissolve 1.0 g in 6 ml of water by warming, cool, add 3 drops of ammonia TS and 1 ml of calcium chloride TS, mix well, warm in a water bath for 15 minutes and cool. Any opalescence produced is not more pronounced than that of a reference solution prepared in the same manner using 2.0 ml of sodium oxalate standard solution [Dissolve 0.1523 g of sodium oxalate with a quantity of water in a 1000 ml

volumetric flask, dilute with water to volume and mix well. Each ml is equivalent to 0.1 mg of oxalate (C_2O_4)] (0.02%).

Loss on drying When dried to constant weight at 105°C, loses not more than 0.5% of its weight (Appendix VIII L).

Residue on ignition Not more than 0.1% (Appendix VIII N).

Heavy metals Dissolve 2.0 g in 23 ml of water, add 2 ml of acetate BS (pH 3.5), carry out the limit test for heavy metals (Appendix VIII H, method 1); not more than 0.001%.

Arsenic Dissolve 1.0 g in 10 ml of water, add 5 ml of dilute sulfuric acid and 0.5 ml of potassium bromide-bromine TS, warm on a water bath for 20 minutes (if necessary, add dropwise potassium bromide-bromine TS to keep it slightly in excess) and add water to replace the water evaporated. Cool, add 5 ml of hydrochloric acid and a quantity of water to produce 28 ml, carry out the limit test for arsenic (Appendix VIII J, method 1); it complies with the requirement (0.0002%).

Assay Dissolve about 0.2 g, accurately weighed, in water in a 250 ml volumetric flask, add water to volume and mix well. Measure accurately 10 ml to an iodine flask, add accurately 50 ml of sodium (potassium) periodate solution [mix 90 ml of sulfuric acid solution (1→20) with 110 ml of sodium (potassium) periodate solution (2.3 → 1000)], warm on a water bath for 15 minutes and cool. Add 10 ml of potassium iodide TS, stopper the flask and allow to stand for 5 minutes. Titrate with sodium thiosulfate (0.05 mol/L) VS, add 1 ml of starch IS towards the end of titration until the blue colour disappears. Perform a blank determination and make any necessary correction. Each ml of sodium thiosulfate (0.05 mol/L) VS is equivalent to 0.9109 mg of $C_{20}H_{23}N$.

Category Dehydrant, diuretic.

Storage Preserve in tightly closed containers, protected from light.

Preparation Mannitol Injection

Mannitol Injection

Mannitol Injection is a sterile solution of mannitol in Water for Injection. It contains not less than 95.0% and not more than 105.0% of the labelled amount of mannitol ($C_6H_{14}O_6$).

Description A clear, colourless liquid.

Identification (1) Evaporate 2.5 ml on a water bath to dryness and then dry at 105°C, the residue complies with test (1) for Identification described under Mannitol, and has a melting range of 120-125°C.

(2) Complies with test for Identification (2) described under Mannitol, using 1 ml.

pH value 4.5-6.5 (Appendix VI H).

Bacterial Endotoxin Carry out the test for bacterial endotoxin (Appendix XI E); less than 2.5 EU per mg of mannitol.

Other requirements Complies with the general requirements for injections (Appendix I B).

Assay Measure accurately quantity (equivalent to about 2.0 g of mannitol), in a 100 ml volumetric flask, add water to volume and mix well. Transfer 10 ml, accurately measured, to a 250 ml volumetric flask, add water to volume and mix

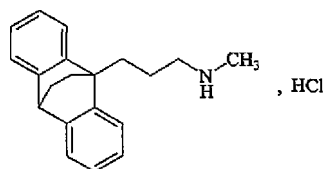
well. Carry out the Assay described under Mannitol, beginning at the words "Measure accurately 10 ml to an iodine flask, ..". Each ml of sodium thiosulfate (0.05 mol/L) VS is equivalent to 0.9109 mg of $C_6H_{14}O_6$.

Category As described under Mannitol.

Strength (1) 20 ml : 4 g (2) 50 ml : 10 g
(3) 100 ml : 20 g (4) 250 ml : 50 g
(5) 500 ml : 100 g (6) 3000 ml : 150 g

Storage Preserve in well closed containers, protected from light.

Maprotiline Hydrochloride



$C_{20}H_{23}N \cdot HCl$ 313.87

[10347-81-6]

Maprotiline Hydrochloride is N-methyl-9,10-ethanoanthracene-9 (10H)-propylamine hydrochloride. It contains not less than 99.0% of $C_{20}H_{23}N \cdot HCl$, calculated on the dried basis.

Description A white or almost white crystalline powder; odourless; taste, bitter.

Freely soluble in methanol or chloroform, slightly soluble in water, insoluble in heptane.

Identification (1) Dissolve about 5 mg in 5 ml of water, add a few drops of potassium iodobismuthate TS, an orange-yellow precipitate is produced immediately.

(2) The light absorption of a solution of 100 µg per ml in water exhibits two maxima at 264 and 271 nm (Appendix IV A).

(3) The infrared absorption spectrum (Appendix IV C) is concordant with the reference spectrum of maprotiline hydrochloride (Appendix XVI).

(4) The aqueous solution yields the reactions characteristic of chlorides (Appendix III).

Related substances Carry out the method for thin-layer chromatography (Appendix V B), using silica gel G as the coating substance (previously elute the plate with chloroform and dry at 100°C for 30 minutes) and a mixture of isobutanol-ethyl acetate-2 mol/L ammonium hydroxide solution (6 : 3 : 1) as the mobile phase (place a beaker containing 4 ml of concentrate ammonia solution on the bottom of the chamber, add the mobile phase into the chamber and allow it to equilibrate for 1 hour). Apply separately to the plate 15 µl of each of four solutions in methanol containing (1) 20 mg per ml, (2) 0.2 mg per ml, (3) 0.1 mg per ml, (4) 0.05 mg per ml of the substance being examined. After developing and removal of the plate, dry in air and expose the plate to hydrogen chloride vapour for 30 minutes, place it under the ultraviolet light at 254 nm for 10 minutes. Examine under ultraviolet light at 365 nm, any spots other than the principal spot in the chromatogram obtained with solution (1) are not more than 2 spots, and the sum of any secondary spots obtained with solution (1) is not more than 1.0% by comparing the intensity of the principal spots obtained with solution (2), (3), (4).

Loss on drying When dried to constant weight at 105°C, loses not more than 1.0% of its weight (Appendix VIII L).

Residue on ignition Not more than 0.1% (Appendix VII N); using 1.0 g.

Heavy metals Carry out the limit test for heavy metals (Appendix VIII H, method 2), using the residue obtained in the test for residue on ignition; not more than 0.001%.

Assay Dissolve about 0.25 g, accurately weighed, in 25 ml of glacial acetic acid and 5 ml of mercuric acetate TS, add 1 drop of crystal violet IS, titrate with perchloric acid (0.1 mol/L) VS until the colour changes to blue. Perform a blank determination and make any necessary correction. Each ml of perchloric acid (0.1 mol/L) is equivalent to 31.39 mg of $C_{20}H_{23}N \cdot HCl$.

Category Antidepressant.

Storage Preserve in tightly closed containers.

Preparation Maprotiline Hydrochloride Tablets

Maprotiline Hydrochloride Tablets

Maprotiline Hydrochloride Tablets contain not less than 90.0% and not more than 110.0% of the labelled amount of maprotiline hydrochloride ($C_{20}H_{23}N \cdot HCl$).

Description White or almost white tablets.

Identification (1) To a quantity of powdered tablets add a quantity of water, shake to dissolve maprotiline hydrochloride. Filter, the filtrate complies with tests (1), (2) and (4) for Identification described under Maprotiline Hydrochloride.

(2) To a quantity of powdered tablets, equivalent to about 100 mg of maprotiline hydrochloride, add 5 ml of methanol, shake to dissolve maprotiline hydrochloride, centrifuge, using the supernatant liquid as the test solution. Dissolve a quantity of maprotiline hydrochloride CRS in methanol to produce a solution of 20 mg per ml as the reference solution. Carry out the thin-layer chromatography (Appendix V B), using silica gel G as the coating substance (previously elute the plate with chloroform and dry at 100°C for 30 minutes) and a mixture of isobutanol-ethyl acetate-2 mol/L ammonium hydroxide solution (6 : 3 : 1) as the mobile phase (place a beaker containing 4 ml of concentrated ammonia solution in the bottom of the chamber, add the mobile phase into the chamber and allow it to equilibrate for 1 hour). Apply separately to the plate 5 µl of each of above two solutions, after developing and removal of the plate, dry in air and expose the plate to hydrogen chloride vapour for 30 minutes, place it under the ultra violet light at 254 nm for 10 minutes. Examine under ultra violet light at 365 nm, the position of the principal spot in the chromatogram obtained with the test solution corresponds to the principal spot obtained with the reference solution.

Content uniformity Comply with the requirements (Appendix X E). Shake 1 tablet with about 60 ml of 0.05 mol/L hydrochloric acid solution in a 100 ml volumetric flask to dissolve maprotiline hydrochloride, proceed as described under Assay, beginning at the word "shake to dissolve maprotiline hydrochloride...", calculate the content of $C_{20}H_{23}N \cdot HCl$.

Dissolution Carry out dissolution test (Appendix X C, method 1), using 500 ml of 0.01 mol/L hydrochloric acid solution as the dissolution medium, adjust the rotational speed of the basket to 100 rpm. Withdraw 10 ml of the solution after exactly 20 minutes and filter, using the successive filtrate as the test solution. Dissolve a quantity of maprotiline hydrochloride CRS, accurately weighed, in a

quantity of 0.01 mol/L hydrochloric acid solution, and dilute with 0.01 mol/L hydrochloric acid solution to volume to produce a solution of 50 µg per ml as reference solution. Measure accurately 1 ml each of the solutions to two 15 ml test tubes with stopper, to each test tube add 6 ml of phosphate BS (pH 3.5), 1 ml of bromocresol green solution, and, accurately measured, 5 ml of chloroform, shake for 2 minutes and allow to stand for 30 minutes. Measure the absorbance of the chloroform layer at 415 nm (Appendix IV A). Calculate the dissolution of $C_{20}H_{23}N \cdot HCl$ from each tablet; not less than 75% of the labelled amount is dissolved.

Assay Reference preparation Dissolve about 25 mg of maprotiline hydrochloride CRS, accurately weighed, in a 100 ml volumetric flask in a quantity of 0.05 mol/L hydrochloric acid solution and dilute with the same solvent to volume, mix well. Transfer 3 ml of the solution, accurately measured, to another 100 ml volumetric flask, dilute with phosphate BS (pH 3.5) to volume and mix well.

Test preparation Weigh accurately and powder 20 tablets. Weigh accurately a quantity of the powdered tablets, equivalent to about 25 mg of maprotiline hydrochloride, to a 100 ml volumetric flask, add 60 ml of 0.05 mol/L hydrochloric acid solution, shake to dissolve maprotiline hydrochloride, dilute with the same solvent to volume and mix well. Filter, transfer 3 ml of the successive filtrate, accurately measured, to another 100 ml volumetric flask, dilute with phosphate BS (pH 3.5) [dissolve 13.61 g of potassium dihydrogen phosphate in a quantity of water, add 50 ml of 0.1 mol/L hydrochloric acid solution, dilute with water to 2000 ml] to volume and mix well.

Procedure Transfer 5 ml each of the two solutions, accurately measured, to separate 15 ml test tubes with stopper, to each test tube add 2 ml of phosphate BS (pH 3.5), 1 ml of bromocresol green solution [tritrate 0.35 g of bromocresol green with 5 ml of 0.1 mol/L sodium hydroxide solution to dissolve it and transfer it to a 250 ml volumetric flask, dilute with water to volume, mix well and filter, the filtrate is ready for use], and 5 ml of chloroform, accurately measured, shake for 2 minutes, allow to stand for 30 minutes. Measure the absorbance of the chloroform layer at 415 nm (Appendix IV A). Perform a blank determination of the chloroform solution, treated in the same manner. Calculate the content of $C_{20}H_{23}N \cdot HCl$.

Category As described under Maprotiline Hydrochloride.

Strength 25 mg

Storage Preserve in tightly closed containers.

Mebendazole



$C_{16}H_{13}N_3O_3$ 295.30

[31431-39-7]

Mebendazole is (5-benzoyl-1H-benzimidazol-2-yl)-carbamic acid methyl ester. It contains not less than 98.0% and not more than 102.0% of $C_{16}H_{13}N_3O_3$, calculated on the dried basis.

Description A white, almost white or faintly yellow crystalline powder; odourless.

Freely soluble in formic acid; sparingly soluble in glacial acetic acid; very slightly soluble in acetone or chloroform; insoluble in water.

Specific absorbance Dissolve about 50 mg, accurately weighed, in 5 ml of formic acid. Dilute with isopropanol to produce a solution of 10 µg per ml. Measure the absorbance at 312 nm (Appendix IV A), the value of A (1%, 1 cm) is 485-505.

Identification (1) Dissolve about 50 mg, accurately weighed, in 5 ml of formic acid, dilute with isopropanol to produce a solution of 10 µg per ml. The light absorption exhibits a maximum at 312 nm (Appendix IV A).

(2) The infrared absorption spectrum (Appendix IV C) is concordant with the reference spectrum of mebendazole (Appendix XVI).

Polymorph A Weigh accurately about 25 mg each of the substance being examined and mebendazole CRS which contains about 10% of polymorph A. Triturate with 0.3 ml of liquid paraffin separately to form smooth creamy pastes. Mount the mull of about 0.15 mm in thickness between rock salt plates, using a blank liquid paraffin mull as reference. Carry out the method for infrared spectrophotometry (Appendix IV C). Record the infrared spectra over the range 620-803 cm^{-1} under the condition that the transmission of the substance being examined and mebendazole CRS at 803 cm^{-1} is 90%-95%. Draw a baseline between the minimum absorption occurring at 620 cm^{-1} and 803 cm^{-1} and lines from peaks at 640 cm^{-1} and 662 cm^{-1} perpendicular to the base line. Measure the corrected peak heights of the maxima at about 640 cm^{-1} and 662 cm^{-1} . Calculate the ratio of the peak heights of the maximum at about 640 cm^{-1} to that of the maximum at about 662 cm^{-1} . The peak height ratio of the substance being examined is not greater than that of mebendazole CRS containing 10% of polymorph A.

Related substances Dissolve about 50 mg, accurately weighed, in 2 ml of formic acid in a 10 ml volumetric flask, dilute with acetone to volume [solution (1)]. Transfer 1 ml, accurately measured, to a 200 ml volumetric flask, dilute with acetone to volume [solution (2)]. Carry out the method for thin-layer chromatography (Appendix V B), using silica gel GF₂₅₄ as the coating substances and a mixture of chloroform-methanol-formic acid (90 : 5 : 5) as the mobile phase. Apply separately to the plate 10 µl each of the two solutions. After developing and removal of the plate, dry and examine under ultraviolet light at 254 nm. Any spot other than the principal spot in the chromatogram obtained with solution (1) is not more intense than the principal spot obtained with solution (2).

Loss on drying When dried at 105°C to constant weight, loses not more than 0.5% of its weight (Appendix VIII L).

Residue on ignition Not more than 0.1% (Appendix VIII N), using 1.0 g.

Heavy metals Carry out the limit test for heavy metals (Appendix VIII H, method 2), using the residue obtained in the test for residue on ignition: not more than 0.002%.

Assay Dissolve about 0.25 g, accurately weighed, in 8 ml of formic acid, add 40 ml of glacial acetic acid and 5 ml of acetic anhydride. Carry out the method for potentiometric titration (Appendix VII A), titrate with perchloric acid VS (0.1 mol/L). Perform a blank determination and make any necessary correction. Each ml of perchloric acid VS (0.1 mol/L) is equivalent to 29.58 mg of $\text{C}_{16}\text{H}_{13}\text{N}_3\text{O}_3$.

Category Anthelmintic.

Storage Preserve in tightly closed containers.

Preparation (1) Mebendazole Tablets
(2) Compound Mebendazole Tablets

Mebendazole Tablets

Mebendazole Tablets contain not less than 90.0% and not more than 110.0% of the labelled amount of Mebendazole ($\text{C}_{16}\text{H}_{13}\text{N}_3\text{O}_3$).

Description White or almost white tablets, or colouring tablets.

Identification (1) To a quantity of the powdered tablets equivalent to about 20 mg of mebendazole add 2 ml of formic acid, shake thoroughly. Add 18 ml of acetone, mix well and filter [solution (1)]. Dissolve about 20 mg of mebendazole CRS in 2 ml of formic acid, add 18 ml of acetone, mix well [solution (2)]. Carry out the method for thin-layer chromatography (Appendix V B), using silica gel GF₂₅₄ as the coating substance and a mixture of chloroform-methanol-formic acid (90 : 5 : 5) as the mobile phase. Apply separately to the plate 10 µl each of the two solutions. After developing and removal of the plate, dry and examine under ultraviolet light at 254 nm. The principal spot in the chromatogram obtained with solution (1) is identical in position to that obtained with solution (2).

(2) The light absorption of the solution obtained in Assay exhibits a maximum at 312 nm (Appendix IV A).

Dissolution Carry out the dissolution test (Appendix X C, method 2), using 900 ml of 1% sodium laurylsulfate in 0.1 mol/L hydrochloric acid solution as the dissolution medium, adjust the rotational speed of the paddle to 75 rpm. Withdraw 10 ml of the solution after exactly 120 minutes and filter. Take the successive filtrate as the test solution. Dissolve 25 mg of mebendazole CRS, accurately weighed, with 10 ml formic acid and dilute to 50 ml with methanol, mix well. Transfer 5 ml, accurately measured, to a 25 ml volumetric flask, dilute to volume with the dissolution medium as the reference solution. Carry out the method for high performance liquid chromatograph (Appendix V D), using a column packed with aminopropyl bonded silica gel and a mixture of acetonitrile-0.15% sodium laurylsulfate solution (dissolve 3.0 g sodium laurylsulfate and 8 g sodium hydroxide with water and dilute to 2000 ml, add 20 ml of phosphoric acid, adjust the pH to 2.5) (30 : 70) as the mobile phase. Detection wavelength is 254 nm. Inject separately 10 µl of above two solutions, and record the chromatogram, calculate the dissolution of $\text{C}_{16}\text{H}_{13}\text{N}_3\text{O}_3$ from each tablet by the external standard method, not less than 75% of the labeled amount is dissolved.

Other requirements Comply with the general requirements for tablets (Appendix I A).

Assay Weigh accurately and powder finely 20 tablets. Transfer an accurately weighed quantity of the powdered tablets, equivalent to about 50 mg mebendazole to a 100 ml volumetric flask. Add 5 ml of formic acid, warm in a water bath (60°C) for 15 minutes. Cool, dilute with isopropanol to volume, mix well. Filter, discard the initial filtrate. Transfer 2 ml of the successive filtrate, accurately measured, to another 100 ml volumetric flask, dilute with isopropanol to volume, mix well. Measure the absorbance of the resulting solution at 312 nm (Appendix IV A), calculate the content of $\text{C}_{16}\text{H}_{13}\text{N}_3\text{O}_3$, taking 495 as the value of A (1%, 1 cm).

Category As described under Mebendazole.

Strength (1) 0.1g (2) 0.2 g

Storage Preserve in tightly closed containers.

Compound Mebendazole Tablets

Compound Mebendazole Tablets contain not less than 90.0% and not more than 110.0% of the labelled amounts of Mebendazole ($C_{16}H_{13}N_3O_3$) and Levamisole Hydrochloride ($C_{11}H_{12}N_2S \cdot HCl$).

Formula	Mebendazole	100 g
	Levamisole hydrochloride	25 g
	Excipient	a quantity

To make 1000 tablets

Description Pink tablets.

Identification (1) To a quantity of the powdered tablets equivalent to about 0.15 g of levamisole hydrochloride add 50 ml of water, shake thoroughly and filter. Add 2 ml of sodium hydroxide TS to 20 ml of the filtrate, boil for 10 minutes and cool, add a few drops of sodium nitroprusside TS; a red colour is produced, which fades on standing.

(2) To a quantity of the powdered tablets equivalent to about 20 mg of mebendazole add 2 ml of formic acid, shake thoroughly. Add 18 ml of acetone, mix well and filter [solution (1)]. Dissolve about 20 mg of mebendazole CRS in 2 ml of formic acid, add 18 ml of acetone, mix well [solution (2)]. Carry out the method for thin-layer chromatography (Appendix V B), using silica gel GF₂₅₄ as the coating substance and a mixture of chloroform-methanol-formic acid (90 : 5 : 5) as the mobile phase. Apply separately to the plate 10 μ l each of the two solutions. After developing and removal of the plate, dry and examine under ultraviolet light (254 nm). The principal spot in the chromatogram obtained with solution (1) is identical in position to that obtained with solution (2).

(3) The filtrate obtained under Identification (1) yields the reactions characteristic of chlorides (Appendix III).

Other requirements Comply with the general requirements for tablets (Appendix I A).

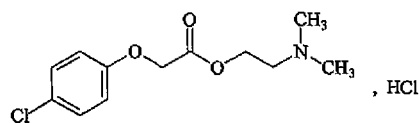
Assay Levamisole Hydrochloride Weigh accurately and powder finely 40 tablets. Transfer an accurately weighed quantity of the powdered tablets equivalent to about 0.4 g of levamisole hydrochloride to a 250 ml conical flask with stopper. Add 100 ml of water, shake for 25 minutes and filter. Discard the initial filtrate, transfer 50 ml of the successive filtrate, accurately measured, to a separator, add 5 ml of sodium hydroxide TS and mix well. Extract with 50 ml of chloroform, accurately measured, allow to stand, separate the chloroform layer and filter with a dry filter paper. Add 15 ml of glacial acetic acid and 1 drop of crystal violet IS to 25 ml of successive filtrate. Titrate with perchloric acid (0.1 mol/L) VS until the colour changes to blue. Perform a blank determination and make any necessary correction. Each ml of perchloric acid (0.1 mol/L) VS is equivalent to 24.08 mg of $C_{11}H_{12}N_2S \cdot HCl$.

Mebendazole Transfer an accurately weighed quantity of the powdered tablets equivalent to about 50 mg of mebendazole to a 100 ml volumetric flask. Add 5 ml of 98% formic acid, warm on a water bath for 15 minutes. Cool, dilute with isopropanol to volume and mix well. Filter, discard the initial filtrate, transfer 2 ml of the successive filtrate, accurately, measured, to another 100 ml volumetric flask, dilute with isopropanol to volume, mix well. Measure the absorbance of the resulting solution at 312 nm (Appendix IV A), calculate the content of $C_{16}H_{13}N_3O_3$, taking 495 as the value of A (1%, 1 cm).

Category Anthelmintic.

Storage Preserve in tightly closed containers.

Meclofenoxate Hydrochloride



$C_{12}H_{16}ClNO_3 \cdot HCl$ 294.18

[3685-84-5]

Meclofenoxate Hydrochloride is 2-(dimethylamino) ethyl *p*-chlorophenoxy acetate hydrochloride. It contains not less than 98.5% of $C_{12}H_{16}ClNO_3 \cdot HCl$, calculated on the dried basis.

Description A white crystalline powder; odour slightly characteristic; taste, sour and bitter.

Very soluble in water; freely soluble in ether; soluble in chloroform.

Melting range 137-142°C (Appendix VI C).

Identification (1) To about 10 mg, add 1 ml of acetic anhydride saturated with citric acid and heat gently; a deep purple colour is produced gradually.

(2) Dissolve about 10 mg in 1 ml of water, add several drops of bromine TS; A pale yellow precipitate or opalescence is produced.

(3) The infrared absorption spectrum (Appendix IV C) is concordant with the reference spectrum of meclofenoxate Hydrochloride (Appendix XVI).

(4) The aqueous solution yields the reactions characteristic of chlorides (Appendix III).

Acidity Dissolve 0.20 g in 20 ml of water, pH 3.5-4.5 (Appendix VI H).

Clarity of solution Dissolve 1.0 g in 10 ml of water, the solution is clear (used for injection).

Loss on drying When dried to constant weight at 105°C, loses not more than 1.0% (used for oral) or 0.5% (used for injection) (Appendix VIII L).

Residue on ignition Not more than 0.1% (Appendix VIII N).

Heavy metals Dissolve 1.0 g with 23 ml of water, add 2 ml of actate BS (pH 3.5), carry out the limit test for heavy metals (Appendix VIII H, method 1); not more than 0.001%.

Sterility Complies with the test for sterility (Appendix XI H). To each portion add water to produce a solution of about 25 mg per ml (used for injection).

Assay Dissolve about 0.2 g, accurately weighed, in 15 ml of glacial acetic acid, add 5 ml of mercury actate TS and 1 drop of crystal violet IS. Titrate with perchloric acid (0.1 mol/L) VS until the solution becomes green. Perform a blank determination and make any necessary correction. Each ml of perchloric acid (0.1 mol/L) VS is equivalent to 29.42 mg of $C_{12}H_{16}ClNO_3 \cdot HCl$.

Category Cerebral stimulant.

Storage Preserve in tightly closed containers, protected from light.

Preparation (1) Meclofenoxate Hydrochloride Capsules
(2) Meclofenoxate Hydrochloride for Injection

Meclofenoxate Hydrochloride Capsules

Meclofenoxate Hydrochloride Capsules contain not less than 93.0% and not more than 107.0% of the labelled amount of meclofenoxate hydrochloride ($C_{12}H_{16}ClNO_3 \cdot HCl$).

Identification (1) A quantity of the contents complies with the test (1) for Identification described under Meclofenoxate Hydrochloride.

(2) To a quantity of the content equivalent to about 20 mg of meclofenoxate hydrochloride add 20 ml of water, shake and filter. The filtrate complies with the tests (2) and (4) for Identification described under Meclofenoxate Hydrochloride.

(3) The retention time of principal peaks of the substance being examined in the chromatogram obtained in the Assay is identical with that of meclofenoxate hydrochloride CRS.

Other requirements Comply with the general requirements for capsules (Appendix I E).

Assay Carry out the method for high performance liquid chromatograph (Appendix V D), using a column packed with octadecylsilane bonded silica gel and a mixture of 0.02 mol/L sodium heptanesulfonate solution-methanol (37 : 63) as the mobile phase previously adjusted to pH 2.0 with phosphoric acid. Detection wavelength is 225 nm and the number of the theoretical plates of the column is not less than 2000, calculated with reference to the peak of meclofenoxate hydrochloride.

Procedure Transfer an accurately weighed quantity of the mixed contents obtained in the test for weight variation of contents equivalent to about 50 mg of meclofenoxate hydrochloride to a 50 ml volumetric flask, add a quantity of dehydrated ethanol to dissolve meclofenoxate hydrochloride, mix well and filter. Measure accurately 5 ml of successive filtrate in a 50 ml volumetric flask, dilute with dehydrated ethanol to volume and mix well. Inject 20 μ l of the solution into the column within 2 hours and record the chromatogram. Dissolve a quantity of meclofenoxate hydrochloride, accurately weighed, in dehydrated ethanol and dilute to produce a solution of 0.1 mg per ml. Repeat the operation, using the resulting solution instead of the substance being examined, calculate the content of $C_{12}H_{16}ClNO_3 \cdot HCl$ with respect to the peak area obtained in the chromatogram by the external standard method.

Category As described under Meclofenoxate hydrochloride.

Strength 0.1 g

Storage Preserve in tightly closed containers, protected from light.

Meclofenoxate Hydrochloride for Injection

Meclofenoxate Hydrochloride for Injection is a sterile powder or crystalline powder of meclofenoxate hydrochloride. Each container contains not less than 93.0% and not more than 107.0% of the labelled amount of Meclofenoxate Hydrochloride ($C_{12}H_{16}ClNO_3 \cdot HCl$), calculated with reference to the average weight of contents.

Description white crystals or a crystalline powder; odour slightly; taste, sour and bitter.

Identification Complies with the tests (1), (2) and (4) for Identification described under Meclofenoxate Hydrochloride.

Clarity of solution Dissolve the contents in each container with 5 ml of water, the solution is clear. Any opalescent produced is not more pronounced than that of reference suspension I (Appendix IX B).

Loss on drying When dried to constant weight at 105°C, loses not more than 1.0% of its weight (Appendix VIII L).

Sterility Complies with the test for sterility described under Meclofenoxate Hydrochloride.

Other requirements Complies with the general requirements for injections (Appendix I B).

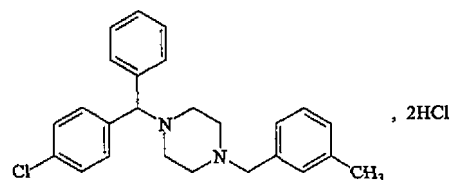
Assay Weigh accurately about 0.2 g, carry out the Assay described under Meclofenoxate Hydrochloride. Each ml of perchloric acid (0.1 mol/L) VS is equivalent to 29.42 mg of $C_{12}H_{16}ClNO_3 \cdot HCl$.

Category As described under Meclofenoxate Hydrochloride.

Strength (1) 0.06 g (2) 0.1 g (3) 0.25 g

Storage Preserve in well closed containers, protected from light.

Meclozine Hydrochloride



$C_{25}H_{27}ClN_2 \cdot 2HCl$ 463.88 [1104-22-9]

Meclozine Hydrochloride is (R, S)-1-(4-chlorobenzhydryl)-4-(3-methylbenzyl) piperazine dihydrochloride. It contains not less than 97.0% of $C_{25}H_{27}ClN_2 \cdot 2HCl$, calculated on the dried basis.

Description A pale yellow to yellow crystalline powder; odour, slightly characteristic; tasteless. Freely soluble in chloroform; soluble in ethanol; very slightly soluble in water; practically insoluble in ether.

Specific absorbance Measure the absorbance of a solution of 15 μ g per ml in 0.1 mol/L hydrochloric acid solution at 232 nm (Appendix IV A), the value of A (1%, 1 cm) is 345-380.

Identification (1) The infrared absorption spectrum (Appendix IV C) is concordant with the reference spectrum of meclozine hydrochloride CRS (Appendix XVI).

(2) The ethanolic solution yields the reactions characteristic of chlorides (Appendix III).

Clarity and colour of ethanol solution A solution of 0.20 g in 10 ml of ethanol is clear and colourless; any colour produced is not more intense than that of reference solution Y₂ (Appendix IX A, method 1).

Related substances Carry out the method for thin-layer chromatography (Appendix V B), using silica gel G as the coating substance and a mixture of dichloromethane-toluene-methanol-concentrated ammonia solution (60 : 30 : 5 : 0.5) as the mobile phase. Apply separately to the plate 10 μ l each

of two solutions of the substance being examined in a mixture of equal volumes of dichloromethane and methanol containing (1) 50 mg per ml, (2) 0.25 mg per ml. After developing and removal of the plate, dry in air and spray with dilute potassium iodobismuthate TS. Any spot, other than the principal spot in the chromatogram, obtained with solution (1) is not more intense than the principal spot obtained with solution (2).

Water Not more than 5.0% (Appendix VIII M, method 1).

Residue on ignition Not more than 0.1% (Appendix VIII N).

Assay Dissolve about 0.2 g, accurately weighed, in 50 ml of chloroform, add 50 ml of glacial acetic acid, 5 ml of acetic anhydride and 10 ml of mercuric acetate TS. Carry out the method for potentiometric titration (Appendix VII A), titrate with perchloric acid (0.1 mol/L) VS. Perform a blank determination and make any necessary correction. Each ml of perchloric acid (0.1 mol/L) VS is equivalent to 23.19 mg of $C_{25}H_{27}ClN_2 \cdot 2HCl$.

Category Antihistaminic.

Storage Preserve in tightly closed containers, protected from light.

Preparation Meclozine Hydrochloride Tablets

Meclozine Hydrochloride Tablets

Meclozine Hydrochloride Tablets contain not less than 90.0% and not more than 110.0% of the labelled amount of meclozine hydrochloride ($C_{25}H_{27}ClN_2 \cdot 2HCl$).

Description Pale yellow tablets with colouring agent.

Identification Triturate and extract 15 tablets with chloroform for 3 times, filter, evaporate the filtrate on a water bath to dryness, dry the residue at 105°C for 1 hour and use it for the tests (1) and (2).

(1) Dissolve about 0.2 g in 25 ml of ethanol, filter. To the filtrate add 25 ml of a saturated solution of trinitrophenol in ethanol, stir and filter, wash the precipitate with several portions of ethanol and followed by water, dry it at 105°C for 4 hours. The melting range of the precipitate is 213–219°C, with decomposition (Appendix VI C).

(2) Dissolve a quantity of the powdered tablets equivalent to about 20 mg of meclozine hydrochloride in ethanol to produce a solution of about 0.01 mg per ml, filter. The light absorption of the filtrate exhibits a maximum at 230 nm (Appendix IV A).

(3) Dissolve about 25 mg in water and the solution yields the reactions characteristic of chlorides (Appendix III).

Other requirements Comply with the general requirements for tablets (Appendix I A).

Assay Weigh accurately and powder 20 tablets. Transfer an accurately weighed quantity of the powder equivalent to about 0.2 g of meclozine hydrochloride to a separator, add 50 ml of water, shake thoroughly, and then extract with chloroform for 3 times (50, 20 and 20 ml). Evaporate the combined chloroform extracts on a water bath to 10–15 ml, allow to cool. Add 15 ml of glacial acetic acid, 5 ml of acetic anhydride, 5 ml of mercuric acetate TS and 2 drops of quinaldine red IS, titrate with perchloric acid (0.1 mol/L) VS until the red colour disappears. Perform a blank determination and make any necessary correction. Each ml of perchloric acid (0.1 mol/L) VS is equivalent to 23.19 mg of $C_{25}H_{27}ClN_2 \cdot 2HCl$.

Category As described under Meclozine Hydrochloride.

Strength 25 mg

Storage Preserve in tightly closed containers, protected from light.

Medicinal Charcoal

Description A black powder; odourless; tasteless; free from grittiness.

Acidity or alkalinity Boil 2.5 g in 50 ml of water for 5 minutes, cool and filter, wash the residue with water. Combine the filtrate and washings to produce 50 ml. The solution is clear and neutral to litmus paper.

Chloride Dilute 10 ml of the filtrate obtained in the test for acidity or alkalinity with water to produce 200 ml, mix well. Carry out the limit test for chloride (Appendix VII A), using 20 ml of the resulting solution. Any opalescence produced is not more pronounced than that of a reference using 5.0 ml of sodium chloride standard solution (0.10%).

Sulfate Carry out the limit test for sulfate (Appendix VII B), using 20 ml of the filtrate obtained in the test for acidity or alkalinity. Any opalescence produced is not more pronounced than that of a reference solution using 5.0 ml of potassium sulfate standard solution (0.05%).

Uncarbonized substances Boil 0.25 g in 10 ml of sodium hydroxide TS, filter. Any colour produced is not more intense than that of a reference solution prepared by mixing 0.3 ml of standard cobaltous chloride CS with 0.2 ml of standard potassium dichromate CS and 9.5 ml of water.

Acid-soluble substances Boil 1.0 g in 20 ml of water and 5 ml of hydrochloric acid for 5 minutes and filter. Wash the residue with 10 ml of hot water, combine the filtrate and the washings. Add 1 ml of sulfuric acid to the solution, evaporate to dryness and ignite the residue to constant weight; not more than 10 mg.

Loss on drying When dried to constant weight at 120°C, loses not more than 10.0% of its weight (Appendix VII L).

Residue on ignition Moisten about 0.5 g with 2–3 drops of ethanol. Carry out the test for residue on ignition (Appendix VIII N); not more than 3.0%.

Iron Boil 1.0 g in 25 ml of 1 mol/L hydrochloric acid VS for 5 minutes, cool and filter. Wash the residue with 30 ml of hot water in portions, combine the filtrate and the washings, add a quantity of water to produce 100 ml and mix well. Measure accurately 5 ml to a 50 ml Nessler cylinder, carry out the limit test for iron (Appendix VIII G). Any colour produced is not more intense than that of a reference solution using 2.5 ml of iron standard solution (0.05%).

Zinc Boil 1.0 g in 25 ml of water for 5 minutes, cool and filter. Wash the residue with 30 ml of hot water in portions, combine the filtrate and washings, add a quantity of water to produce 100 ml and mix well. Measure accurately 10 ml, add 0.5 g of ascorbic acid. Complete the test described under Primidone, beginning at the words "transfer to a 50 ml Nessler cylinder..." (0.02%).

Heavy metals Boil 1.0 g in 10 ml of dilute hydrochloric acid and 5 ml of bromine TS for 5 minutes and filter. Wash the residue with 35 ml of hot water, combine the filtrate and washing, add a quantity of water to produce 50 ml and mix well. To 20 ml add 1 drop of phenolphthalein IS and add ammonia TS dropwise until the solution becomes pink, then add 2 ml of acetate BS (pH 3.5) and a quantity of water to

produce 25 ml, add 0.5 g of ascorbic acid. Carry out the limit test for heavy metals (Appendix VIII H, method 1), compare the colour of the solution with that of the reference solution immediately after 5 minutes; not more than 0.003%.

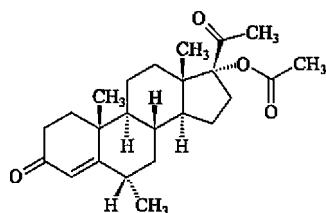
Adsorptive power (1) To 1.0 g, dried to constant weight previously, add 100 ml of 0.12% quinine sulfate solution, shake vigorously for 5 minutes at a temperature not lower than 20°C. Filter through a dry medium rate filter paper immediately and discard the initial filtrate. To 10 ml of the successive filtrate add 1 drop of hydrochloric acid and 5 drops of potassium mercuric iodide TS; no opalescence is produced.

(2) Transfer 50 ml of 0.1% methylene blue solution, accurately measured, to each of two 100 ml cylinders with stoppers. To one cylinder add 0.25 g of the substance being examined (dried to constant weight previously), stopper, shake vigorously for 5 minutes at a temperature not lower than 20°C. Filter the two solutions through dry medium rate filter papers separately and discard the initial filtrates. Transfer 25 ml each of the successive filtrates, accurately measured, to two 250 ml volumetric flasks, add to each flask 50 ml of 10% sodium acetate solution and mix well. Add accurately 35 ml of iodine (0.1 mol/L) VS while swirling, stopper the flask, mix well and allow to stand with vigorous shake every 10 minutes. Dilute with water to volume after 50 minutes, mix well and allow to stand for 10 minutes. Filter through dry filter papers separately, discard the initial filtrates. Measure accurately 100 ml each of the successive filtrates and titrate with sodium thiosulfate (0.1 mol/L) VS separately. The difference between the volumes of iodine (0.1 mol/L) VS consumed is not less than 1.2 ml.

Category Adsorbent.

Storage Preserve in tightly closed containers.

Medroxyprogesterone Acetate



$C_{24}H_{34}O_4$ 386.53

[71-58-9]

Medroxyprogesterone Acetate is 17-(acetyloxy)-6 α -methyl-pregn-4-ene-3,20-dione. It contains not less than 97.0% and not more than 103.0% of $C_{24}H_{34}O_4$, calculated on the dried basis.

Description A white or almost white crystalline powder; odourless.

Very soluble in chloroform; soluble in acetone; sparingly soluble in ethyl acetate; slightly soluble in dehydrated ethanol; insoluble in water.

Melting range 202-208°C (Appendix VI C).

Specific optical rotation +53° to +59°, in a solution of 10 mg per ml in chloroform (Appendix VI E).

Identification (1) Dissolve 5 mg in 5 ml of sulfuric acid in a test tube, add slowly along the wall of the test tube 5 ml of ethanol; a bluish-violet colour is produced at the interface of the two layers.

(2) The retention time of principal peak of the substance being examined is identical with that of principal peak of the

reference solution in the chromatogram obtained in Assay.

(3) The infrared absorption spectrum (Appendix IV C) is concordant with the reference spectrum of medroxyprogesterone acetate (Appendix XVI).

Related substances Carry out the method as described under Assay. Dissolve a quantity of the substance being examined, in methanol to produce a solution of about 0.8 mg per ml as the test solution (1). Measure accurately 1 ml of solution (1) into a 50 ml volumetric flask and dilute with methanol to volume, mix well as the reference solution (2). Inject 10 μ l of solution (2) into the column, adjust the attenuation so that the peak height of principal peak in the chromatogram is about 25% of full scale of the chart. Inject separately accurately 10 μ l each of the solution (1) and (2) into the column and record the chromatogram for 1.5 times the retention time of the principal peak. No more than four secondary peaks in the chromatogram obtained with solution (1), each secondary peak and the sum of the areas of all secondary peak are not greater than 1/2 and 3/4 of the area of the principal peak of solution (2) respectively.

Loss on drying When dried to constant weight at 105°C, loses not more than 0.5% of its weight (Appendix VIII L).

Assay Carry out the method for high performance liquid chromatograph (Appendix V D), with an octadecylsilane bonded silica gel column, using methanol-water (70 : 30) as the mobile phase and the wavelength of the detector is 254 nm. The number of the theoretical plates of the column is not less than 2000, calculated with reference to the peak of Medroxyprogesterone Acetate. The resolution factor between the peaks of medroxyprogesterone acetate and internal standard is not less than 3.0%, the resolution factor of the secondary peak closed to medroxyprogesterone acetate and medroxyprogesterone acetate complies with the related requirements.

Internal Standard Solution Dissolve a quantity of norethisterone, accurately weighed, in methanol to produce a solution of about 0.8 mg per ml.

Procedure Dissolve a quantity of medroxyprogesterone acetate CRS, accurately weighed, in methanol to produce a solution of about 0.8 mg per ml. Transfer 2 ml each of the test solution and the internal standard solution, both measured accurately, in a 10 ml volumetric flask, dilute with methanol to volume, mix well. Inject 10 μ l of the resulting solution into the column. Repeat the operation, using the substance being examined instead of medroxyprogesterone acetate CRS, calculate the content of $C_{24}H_{34}O_4$.

Category Progestoid.

Storage Preserve in tightly closed containers, protected from light.

Preparation Medroxyprogesterone Acetate Tablets

Medroxyprogesterone Acetate Tablets

Medroxyprogesterone Acetate Tablets contain not less than 90.0% and not more than 110.0% of the labelled amount of medroxyprogesterone acetate ($C_{24}H_{34}O_4$).

Description White tablets.

Identification (1) Dissolve an amount of the finely powdered tablets equivalent to 60 mg of medroxyprogesterone acetate in 30 ml of chloroform with stirring, filter, evaporate the filtrate to dryness on a water bath, the residue complies with tests (1) for Identification described under Medroxyprogesterone

Acetate.

(2) Extract a quantity of the finely powdered tablet equivalent to 10 mg of medroxyprogesterone acetate with 20 ml of chloroform and filter, use the filtrate as test preparation. Prepare a solution containing 5 mg of medroxyprogesterone acetate CRS in 1 ml chloroform as reference preparation. Carry out the method for thin-layer chromatography (Appendix V B), using silica gel G as the coating substance and chloroform-ethyl acetate (10 : 1) as the mobile phase. Apply separately to the plate 10 μ l each of the two solutions. After developing and removal of the plate, allow it to dry in air, heat at 120°C for half an hour, cool, spray with sulfuric acid-dehydrated ethanol (1 : 1), heat at 120°C for 10 minutes, cool, examine under ultraviolet light at 365 nm. The principal spots in the chromatogram obtained with the two solutions are identical in colour and position.

Content uniformity Comply with the requirements (Appendix X E).

Triturate 1 tablet with dehydrated ethanol in a mortar and transfer with the same solvent in several portions into a 100 ml volumetric flask. Gently heat for 15 minutes with shake, cool, dilute with dehydrated ethanol to volume, shake thoroughly, filter, discard the initial filtrate, dilute an accurately measured quantity of the successive filtrate with dehydrated ethanol to produce a solution of about 8 μ g per ml. Determine the content of medroxyprogesterone acetate as described under Assay.

Other requirements Comply with the general requirements for tablets (Appendix I A).

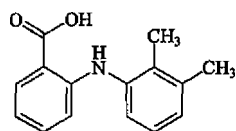
Assay Weigh accurately and powder 10 tablets (for strength 10 mg), 15 tablets (for strength 4 mg) or 25 tablets (for strength 2 mg). To an amount of the powder equivalent to 20 mg of medroxyprogesterone acetate, accurately weighed, in a 100 ml volumetric flask add 60 ml of dehydrated ethanol and shake for 15 minutes, add dehydrated ethanol to volume and mix well. Filter, discard the initial filtrate, transfer 5 ml of the successive filtrate, accurately measured, to another 100 ml volumetric flask, dilute with dehydrated ethanol to volume and mix well. Measure the absorbance of the resulting solution at 240 nm (Appendix IV A), calculate the content of $C_{24}H_{34}O_4$, taking 408 as the value of A (1%, 1 cm).

Category As described under Medroxyprogesterone acetate.

Strength (1) 2 mg (2) 4 mg (3) 10 mg (4) 250 mg

Storage Preserve in tightly closed containers, protected from light.

Mefenamic Acid



$C_{15}H_{15}NO_2$ 241.29

[61-68-7]

Mefenamic Acid is *N*-(2,3-dimethylphenyl) amino]-benzoic acid. It contains $C_{15}H_{15}NO_2$ not less than 99.0%, calculated on the dried basis.

Description A white or almost white fine crystalline powder; odourless.

Sparingly soluble in ether; slightly soluble in ethanol or chloroform; insoluble in water.

Identification (1) Dissolve about 25 mg in 15 ml of chloroform, examine under an ultraviolet light at 254 nm; exhibits a strong green fluorescence.

(2) Dissolve about 5 mg in 2 ml of sulfuric acid, add 0.05 ml of 0.5% potassium dichromate solution; a deep blue colour is produced, the colour fades immediately to brownish-green.

(3) The light absorption of a solution of 20 μ g per ml in a mixture of 1 mol/L hydrochloric acid and methanol (1 : 99), exhibits two maxima at 279 nm and 350 nm; the absorbance is about 0.69-0.74 and 0.56-0.60, respectively (Appendix IV A).

(4) The infrared absorption spectrum (Appendix IV C) is concordant with the spectrum of mefenamic acid (Appendix XVI).

Copper Moisten 1.0 g with sulfuric acid in a silica crucible. Ignite until all the carbon is burned off and dissolve the residue in 0.1 mol/L nitric acid solution. Transfer it into 25 ml volumetric flask, dilute with the same solution to the volume, mix well, as the test solution. Transfer 1.0 ml of standard copper solution [Weigh accurately 0.393 g of copper sulfate to a 1000 ml volumetric flask, dissolve in 0.1 mol/L nitric acid solution and dilute to the volume, mix well. Measure accurately 10 ml into a 100 ml volumetric flask, add 0.1 mol/L nitric acid to volume, mix well], accurately measured, to 25 ml volumetric flask, dilute with 0.1 mol/L nitric acid to the volume, mix well, as the reference solution. Carry out the method for atomic absorption spectrophotometry (Appendix IV D test for impurities), measure the absorbance of the solutions at 324.8 nm, complies with the requirement. The absorbance of the test solution is not more than the absorbance obtained in reference solution (0.001%).

Related substances Carry out the method for high performance liquid chromatography (Appendix V D), using a column packed with octadecylsilane bonded silica gel and a mixture of 0.05 mol/L ammonium dihydrogen phosphate solution (adjust with ammonia TS to pH 5.0)-acetonitrile-tetrahydrofuran (40 : 46 : 14) as the mobile phase. Detection wavelength is at 254 nm, and the number of theoretical plates of the column is not less than 5000, calculated with reference to the peak of mefenamic acid. Dissolve a quantity in the mobile phase to produce the test solution of 1 mg per ml. Measure accurately a quantity of the test solution and dilute with the mobile phase to produce the reference solution of 5 μ g per ml. Inject 10 μ l of the reference solution into the column, accurately measured, adjust the attenuation so that the principal peak height in the chromatogram is 15% of the full scale of the chart. Inject separately 10 μ l each of the test and reference solution, both accurately measured, into the column and record the chromatogram for 2.5 times the retention time of the principal peak. The single peak area due to impurities is not greater than 20% of the principal peak area of the reference solution. The sum of peak areas due to impurities is not greater than twice the principal peak area of the reference solution.

Loss on drying When dried to constant weight at 105°C, loses not more than 0.5% of its weight (Appendix VIII L).

Residue on ignition Not more than 0.1% (Appendix VIII N), using 1.0 g.

Heavy metals Carry out the limit test for heavy metals (Appendix VIII H, method 2), using the residue obtained in the test for Residue on ignition; not more than 0.002%.

Assay Dissolve about 0.5 g accurately weighed, in 100 ml of warm dehydrated neutral ethanol (neutral to phenolsulfonphthalein IS) by shaking, add 3 drops of phenolsulfonphthalein IS, titrate with sodium hydroxide

(0.1 mol/L) VS. Each ml of sodium hydroxide (0.1 mol/L) VS is equivalent to 24.13 mg of $C_{15}H_{15}NO_2$.

Category Antipyretic and analgesic non-steroids anti-inflammatory agent.

Storage Preserve in tightly closed containers, stored in a dry place.

Preparation (1) Mefenamic Acid Capsules
(2) Mefenamic Acid Tablets

Mefenamic Acid Capsules

Mefenamic Acid Capsules contain not less than 90.0% and not more than 110.0% of the labelled amount of mefenamic acid ($C_{15}H_{15}NO_2$).

Identification (1) The powdered contents of capsules comply with the tests (1) and (2) for Identification described under Mefenamic acid.

(2) Dissolve a quantity of the powdered contents of capsules, equivalent to 0.25 g mefenamic acid in a mixture of 10 ml of 0.1 mol/L hydrochloric acid solution-methanol (1 : 99), shake and filter. To a quantity of the successive filtrate, dilute with above mixed solution to produce a solution of 20 μ g per ml. The light absorption of the solution exhibits maxima at 279 nm and 350 nm (Appendix IV A).

Dissolution Carry out the method for dissolution test (Appendix X C, method 2), using 40 ml of ethanol and adding phosphate BS (pH 8.0) to 800 ml as the dissolution medium, adjust the rotation speed at 75 rpm. Withdraw a quantity of the solution exactly after 45 minutes, filter. Measure accurately 3 ml of the successive filtrate to a 100 ml volumetric flask, dilute with phosphate BS (pH 8.0) to volume, mix well; then dissolve about 20 mg of mefenamic acid CRS in 5 ml of ethanol, dilute with phosphate BS (pH 8.0) appropriately to produce a solution of 10 μ g per ml. Measure the absorbances of two solutions at 286 nm (Appendix IV A) and calculate the dissolution of ($C_{15}H_{15}NO_2$) in each capsule. The dissolution of each capsule is not less than 50% of the labelled amount.

Other requirements Comply with the general requirements for Capsules (Appendix I E).

Assay Weigh accurately a quantity of the mixed powdered contents obtained in test for weight variation of contents equivalent to about 0.5 g of mefenamic acid, carry out the Assay as described under Mefenamic Acid, beginning at the words "add 100 ml of anhydrous neutral ethanol. Shake to dissolve". Each ml of sodium hydroxide (0.1 mol/L) VS is equivalent to 24.13 mg of $C_{15}H_{15}NO_2$.

Category As described under Mefenamic Acid.

Strength 0.25 g

Storage Preserve in tightly closed containers, stored in a dry place.

Mefenamic Acid Tablets

Mefenamic Acid Tablets contain not less than 93.0% and not more than 107.0% of the labelled amount of mefenamic acid ($C_{15}H_{15}NO_2$).

Description White or almost white tablets.

Identification (1) Dissolve a quantity of powdered tablets

equivalent to about 25 mg of mefenamic acid in 15 ml of chloroform on shake, it complies with the test (1) for Identification described under Mefenamic Acid.

(2) Dissolve a quantity of powdered Tablets equivalent to about 5 mg of mefenamic acid in 2 ml of sulfuric acid, it complies with the test (2) for Identification described under Mefenamic Acid.

(3) Dissolve a quantity of powdered tablets equivalent to 0.25 g of mefenamic acid in 10 ml of a mixture of 1 mol/L hydrochloric acid solution-methanol (1 : 99) on shake, filter. Measure a quantity of the successive filtrate, dilute with a solvent mixture described above to produce a solution of 20 μ g per ml. The light absorption of the solution exhibits two maxima at 279 nm and 350 nm, respectively (Appendix IV A).

Dissolution Comply with the dissolution test (Appendix X C method 2), using 40 ml of ethanol and adding phosphate BS (pH 8.0) to 800 ml as the dissolution medium. Adjust the rotational speed of the paddle to 75 rpm. Withdraw a quantity of the solution exactly after 45 minutes, filter, measure accurately 3 ml of the successive filtrate to a 100 ml volumetric flask, dilute with phosphate BS (pH 8.0) to volume, mix well. Dissolve 20 mg of mefenamic acid CRS, accurately weighed with 5 ml of ethanol in a 100 ml volumetric flask, dilute with phosphate BS (pH 8.0) to volume, mix well. Measure accurately a quantity, dilute with phosphate BS (pH 8.0) to produce a solution of 10 μ g per ml. Measure the absorbances of the two solutions at 286 nm (Appendix IV A), calculate the dissolution of $C_{15}H_{15}NO_2$ from each tablet, not less than 60% of the labelled amount is dissolved.

Other requirements Comply with the general requirements for tablets (Appendix I A).

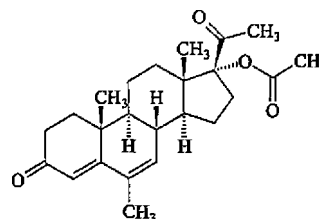
Assay Weigh accurately and powder 20 tablets. Weigh accurately a quantity, equivalent to about 0.5 g of mefenamic acid, carry out the Assay as described under Mefenamic Acid, beginning at the words "add 100 ml of warm dehydrated neutral ethanol (neutral to phenolsulfonphthalein IS), shake to dissolve". Each ml of sodium hydroxide (0.1 mol/L) VS is equivalent to 24.13 mg of $C_{15}H_{15}NO_2$.

Category As described under Mefenamic Acid.

Strength 0.25 g

Storage Preserve in tightly closed containers, stored in a dry place.

Megestrol Acetate



$C_{24}H_{32}O_4$ 384.52

[595-33-5]

Megestrol Acetate is 17 α -hydroxy-6-methylpregna-4,6-diene-3,20-dione-17-acetate. It contains not less than 97.0% and not more than 103.0% of $C_{24}H_{32}O_4$, calculated on the dried basis.

Description A white or almost white crystalline powder; odourless; tasteless.

Freely soluble in chloroform; soluble in acetone or ethyl acetate; sparingly soluble in ethanol; slightly soluble in ether; insoluble in water.

Melting range 213-220°C (Appendix VI C).

Specific optical rotation +9° to +12° in a solution of about 50 mg per ml in chloroform (Appendix VI E).

Identification (1) The retention time of principal peak of the substance being examined is identical with that of principal peak of the reference solution in the chromatogram obtained in Assay.

(2) The infrared absorption spectrum (Appendix IV C) is concordant with the reference spectrum of megestrol acetate (Appendix XVI).

Light absorption The light absorption of the solution obtained in the Assay (Appendix IV A), exhibits a maximum at 287 nm only, the ratio of absorbance at 240 nm to that at 287 nm is not more than 0.17.

Related substances Carry out the method as described under Assay. Dissolve a quantity of the substance being examined, in absolute ethanol to produce a solution of about 2 mg per ml as the test solution (1). Measure accurately 1 ml of solution (1) into a 50 ml volumetric flask and dilute with absolute ethanol to volume, mix well as the reference solution (2). Inject 10 µl of solution (2) into the column, adjust the attenuation so that the peak height of principal peak in the chromatogram is about 25% of full scale of the chart. Inject separately accurately 10 µl each of the solution (1) and (2) into the column and record the chromatogram for twice the retention time of the principal peak. No more than four secondary peaks in the chromatogram obtained with solution (1), each secondary peak and the sum of the areas of all secondary peak are not greater than 1/2 and 3/4 of the area of the principal peak of solution (2) respectively.

Loss on drying When dried to constant weight at 105°C, loses not more than 0.5% of its weight (Appendix VIII L).

Assay Carry out the method for high performance liquid chromatography (Appendix V D), using a column packed with octadecylsilane bonded silica gel and a mixture of methanol-water (70 : 30) as the mobile phase. Detection wavelength is 288 nm. The number of the theoretical plates of the column is not less than 2000, calculated with reference to the peak of megestrol acetate.

Procedure Dissolve about 20 mg of the substance being examined, weighed accurately, in methanol into a 100 ml volumetric flask and dilute with methanol to volume, mix well. Measure accurately 2 ml of the above solution into a 10 ml volumetric flask and dilute with methanol to volume, mix well as the test solution (1). Inject 10 µl of solution (1) into the column and record the chromatogram. Repeat the operation using megestrol acetate CRS instead of the substance being examined, calculate the content of $C_{24}H_{32}O_4$ with respect to the peak area obtained in the chromatogram by the external standard method.

Category Progesteroïd.

Storage Preserve in tightly closed containers, protected from light.

Preparation Megestrol Acetate Tablets

Megestrol Acetate Tablets

Megestrol Acetate Tablets contain not less than 90.0% and not more than 110.0% of the labelled

amount of megestrol acetate ($C_{24}H_{32}O_4$).

Description Sugar coated or film coated tablets with white or almost white core.

Identification The retention time of principal peak of the substance being examined is identical with that of principal peak of the reference solution in the chromatogram obtained in Assay.

Related substances Add absolute ethanol to a quantity of fine powdered tablets, shake well and dilute to prepare a solution of 2 mg per ml. Filter, use the successive filtrate as solution (1), and dilute it with absolute ethanol to produce a solution containing 0.04 mg per ml as solution (2). Carry out the test as described under Megestrol Acetate, the individual secondary peak area in the chromatogram of solution (1) and the sum of peak areas is not greater than 1/2 and 3/4 of the principal peak area in that of solution (2), respectively.

Content uniformity Comply with the requirements (Appendix X E). Take 1 tablet into a 50 ml (for strength 1 mg) or 200 ml (for strength 4 mg) volumetric flask, add 2 ml of water to make the tablet disintegrate, then add quantities of methanol, ultrasonic to make megestrol acetate dissolved and dilute with methanol to volume, shake well and centrifugate, take the supernate as the test solution. Carry out the method as described under Assay, calculate the content of $C_{24}H_{32}O_4$.

Dissolution Carry out the dissolution test (Appendix X C, method 3), using 200 ml of 0.8% lauryl sodium sulfate solution as the dissolution medium, adjust the rotational speed of the paddle to 75 rpm, Withdraw a quantity of the solution after exactly 60 minutes and filter. Take the successive filtrate (for strength 1 mg) or measure accurately 5 ml of the successive filtrate into a 20 ml volumetric flask and dilute with the dissolution medium to volume, mix well (for strength 4 mg) as the test solution. Dissolve about 25 mg of megestrol acetate CRS, weighed accurately, in methanol into a 50 ml volumetric flask and dilute with methanol to volume, mix well. Measure a quantity of the solution and dilute with 1% lauryl sodium sulfate solution to produce a solution of about 5 µg per ml as the reference solution. Carry out the method as described under Assay. Inject separately 20 µl of the test solution and the reference solution and record the chromatogram. Calculate the dissolution of $C_{24}H_{32}O_4$ from each tablet with respect to the peak area obtained in the chromatogram by the external standard method. Not less than 75% of the labelled amount.

Other requirements Comply with the general requirements for tablets (Appendix I A).

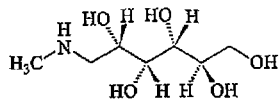
Assay Weigh accurately and powder 20 tablets. To a quantity, weighed accurately, equivalent to about 1 mg of megestrol acetate, to a 50 ml volumetric flask, add a quantity of methanol and ultrasonic to make megestrol acetate dissolved, then dilute with methanol to volume, mix well and centrifugate, take the supernate as the test solution. Dissolve a quantity of megestrol acetate CRS, accurately weighed, in methanol to produce a solution of about 20 µg per ml as the reference solution. Carry out the method in Assay as described under Megestrol Acetate, calculate the content of $C_{24}H_{32}O_4$ with respect to the peak area obtained in the chromatogram by the external standard method.

Category As described under Megestrol Acetate.

Strength (1) 1 mg (2) 4 mg

Storage Preserve in tightly closed containers, protected from light.

Meglumine



$C_7H_{17}NO_5$ 195.22

[6284-40-8]

Meglumine is 1-deoxy-1-(methylamino)-D-glucitol. It contains not less than 99.0% of $C_7H_{17}NO_5$, calculated on the dried basis.

Description A white crystalline powder; almost odourless; taste, slightly sweet salty and astringent. Freely soluble in water; sparingly soluble in ethanol, practically insoluble in chloroform.

Melting point 128-132°C (Appendix VI C).

Specific optical rotation -15.5° to -17.5° , measured at 25°C, in a solution of about 0.10 g per ml in water (Appendix VI E).

Identification (1) To about 20 mg in a clean test tube add 2 ml of water and 1 ml of ammoniacal silver nitrate TS, shake thoroughly, and heat in a water bath; silver mirror is deposited on the inner wall of the tube.

(2) To 10 mg add 1 ml of ferric chloride TS and 2 ml of 20% sodium hydroxide solution dropwise; a brownish-red precipitate is produced and subsequently dissolved to form a brownish-red solution.

(3) Dissolve 50 mg in 1 ml of saturated aqueous solution of carbon disulfide, add a few drops of 4% nickel sulfate solution; a yellowish-green colour is produced with yellowish-green precipitate.

(4) The infrared absorption spectrum (Appendix IV C) is concordant with the reference spectrum of meglumine (Appendix XVI).

Clarity and colour of solution A solution of 1.0 g in 10 ml of water is clear and colourless.

Readily carbonizable substance Carry out the limit test for readily carbonizable substances (Appendix VIII O) using 0.25 g; any colour produced is not more intense than that of a reference solution OR_2 .

Loss on drying When dried to constant weight at 105°C, loses not more than 0.5% of its weight (Appendix VIII L).

Nickel Ignite 1.0 g, to the residue add 0.5 ml of nitric acid, evaporate to remove nitrous oxide completely. Allow to cool, add 2 ml of hydrochloric acid, and evaporate to dryness on a water bath. Dissolve the residue in 5 ml of water and transfer to a Nessler cylinder, add 1 drop of bromine TS, shake for 1 minute, then make alkaline with ammonia TS, add 1 ml of dimethylglyoxime TS, mix well and allow to stand for 5 minutes. Any colour produced is not more intense than that of a reference solution using 5 ml of nickel sulfate standard solution (dissolve a quantity of hydrated nickel sulfate in water to produce a solution of 1.0 μ g Ni per ml), proceed as directed above, beginning at the words "add 1 drop of bromine TS...", (0.0005%).

Residue on ignition Not more than 0.1% (Appendix VIII N); using 1.0 g.

Heavy metals Carry out the limit test for heavy metals (Appendix VIII H, method 2), using the residue obtained in the test for residue on ignition; not more than 0.001%.

Pyrogens Complies with the test for pyrogens (Appendix

XI D), using 600 mg per kg of the rabbit's weight dissolved in 5 ml of Water for Injection.

Assay Dissolve 0.4 g, accurately weighed, in 20 ml of water, add 2 drops of methyl red IS, titrate with hydrochloric acid (0.1 mol/L) VS. Each ml of hydrochloric acid (0.1 mol/L) VS is equivalent to 19.52 mg of $C_7H_{17}NO_5$.

Category Diagnostic agent.

Storage Preserve in tightly closed containers, protected from light.

Preparation (1) Meglumine Adipiodone Injection
(2) Meglumine Diatrizoate Injection

Meglumine Adipiodone Injection

Meglumine Adipiodone Injection is a sterile solution of Adipiodone and Meglumine in Water for Injection. It contains not less than 95.0% and not more than 105.0% of the labelled amount of meglumine adipiodone ($C_{20}H_{14}I_6N_2O_6 \cdot 2C_7H_{17}NO_5$).

Description A clear, white or pale yellow to yellow liquid.

Identification (1) Evaporate about 1 ml to dryness and heat gently, purple iodine vapour is evolved.

(2) To 0.1 ml add 1 ml of ferric chloride TS and add dropwise 2 ml of 20% sodium hydroxide solution, a brownish-red precipitate is formed, which dissolves subsequently to produce a brownish-red solution.

(3) Complies with test (3) for Identification described under Meglumine Diatrizoate Injection, using adipiodone CRS instead of diatrizoic acid CRS.

pH value 6.5-8.0 (Appendix VI H).

Colour The injection with a strength of 20 ml : 10 g is not more intensely coloured than reference solution Y_8 ; with a strength of 1 ml : 0.3 g or 20 ml : 6 g is not more intensely coloured than reference solution Y_6 (Appendix IX A, method 1).

Free iodine To a quantity equivalent to about 1 g of meglumine adipiodone add water to produce 10 ml, carry out the test for Free iodine described under Diatrizoic Acid, the result complies with the requirement.

Iodide Dilute a quantity equivalent to about 0.8 g of adipiodone meglumine with water to produce 10 ml, add dropwise 3 ml of dilute nitric acid, stir for a few minutes to form a precipitate, filter and wash the residue with 5 ml of water. Filter the combined filtrate and washings. Add 1 ml of chloroform and 1 ml of concentrate hydrogen peroxide solution, shake and allow to separate. The chloroform layer is not more intensely coloured than a reference solution prepared similarly using 6 ml of 0.0013% potassium iodide solution (equivalent to 10 μ g of I per ml).

Pyrogens Complies with test for pyrogens (Appendix XI D), using 3 ml per kg of the rabbit's weight, inject slowly.

Other requirements Complies with the general requirements for injections (Appendix I B).

Assay To a quantity equivalent to about 5 g, accurately measured, of meglumine adipiodone in a 100 ml volumetric flask add water to volume and mix well. Measure accurately 10 ml of the solution, carry out the Assay described under Diatrizoic Acid, beginning at the words "add 30 ml of sodium hydroxide TS...". Each ml of silver nitrate (0.1 mol/L) VS is equivalent to 25.50 mg of $C_{20}H_{14}I_6N_2O_6 \cdot 2C_7H_{17}NO_5$.

Category Diagnostic agent.

Strength (1) 1 ml : 0.3 g (2) 20 ml : 6 g
(3) 20 ml : 10 g

Storage Preserve in well closed containers, protected from light.

Meglumine Diatrizoate Injection

Meglumine Diatrizoate Injection is a sterile solution of Diatrizoic acid and Meglumine (1 : 1) in Water for Injection. It contains not less than 95.0% and not more than 105.0% of the labelled amount of meglumine diatrizoate ($C_{11}H_9I_3N_2O_4 \cdot C_7H_{17}NO_5$).

Description A clear, colourless to pale yellow liquid.

Identification (1) Evaporate about 1 ml to dryness, heat the residue gently; violet iodine vapor is evolved.

(2) To about 0.1 ml add 1 ml of ferric chloride TS and add dropwise 2 ml of 20% sodium hydroxide solution; a brownish-red precipitate is produced which dissolves immediately to form a brownish-red solution.

(3) Carry out the method for thin-layer chromatography (Appendix V B), using silica gel HF₂₅₄ as the coating substance and a mixture of *n*-butanol-glacial acetic acid-water (4 : 1 : 5) as the mobile phase. Apply separately to the plate 10 μ l each of (1) an aqueous dilution of the injection equivalent to 3 mg of meglumine diatrizoate per ml; (2) a 2 mg per ml solution of diatrizoic acid CRS in water containing 0.04% of sodium hydroxide. After developing and removal of the plate, examine under an ultraviolet light at 254 nm. The principal spots obtained with the two solutions are identical in position.

pH value 6.0-7.6 (Appendix VI H).

Colour Not more intense than reference solution Y₆ (Appendix IX A, method 1).

Free iodine To a quantity equivalent to 1.0 g of meglumine diatrizoate add water to produce 10 ml, the resulting solution complies with the test for Free iodine described under Diatrizoic Acid.

Iodide Complies with the test for Iodide described under Sodium Diatrizoate Injection, using a quantity equivalent to 1.0 g of meglumine diatrizoate.

Pyrogens Complies with the test for pyrogens (Appendix XI D), inject 3 ml per kg of the rabbit's weight slowly.

Other requirements Complies with the general requirements for injections (Appendix I B).

Assay Transfer accurately a quantity equivalent to about 6 g of meglumine diatrizoate to a 100 ml volumetric flask, add water to volume, mix well. Measure accurately 10 ml, carry out the Assay described under Diatrizoic Acid, beginning at the words "add 30 ml of sodium hydroxide TS and 1.0 g of powdered zinc...". Each ml of silver nitrate (0.1 mol/L) VS is equivalent to 26.97 mg of $C_{11}H_9I_3N_2O_4 \cdot C_7H_{17}NO_5$.

Category Diagnostic agent.

Strength (1) 1 ml : 0.3 g (2) 20 ml : 12 g
(3) 20 ml : 15.2 g (4) 50 ml : 32.5 g
(5) 100 ml : 60 g (6) 100 ml : 65 g
(7) 200 ml : 130 g

Storage Preserve in well closed containers, protected from light.

Compound Meglumine Diatrizoate Injection

Compound Meglumine Diatrizoate Injection is a sterile solution of 1 part of sodium diatrizoate and 6.6 parts of Meglumine Diatrizoate containing suitable amount of sodium hydroxide in Water for Injection. It contains not less than 90.0% and not more than 110.0% of the labelled total amount of sodium diatrizoate ($C_{11}H_9I_3N_2NaO_4$) and meglumine diatrizoate ($C_{11}H_9I_3N_2O_4 \cdot C_7H_{17}NO_5$).

Description A colourless or pale yellow, clear liquid.

Identification (1) Evaporate 1 ml to dryness, heat gently, a violet vapour of iodine is produced on decomposition.

(2) To 0.1 ml add 1 ml of ferric chloride TS and 2 ml of 20% sodium hydroxide solution, a brownish-red precipitate is produced, which is dissolved to form a brownish-red solution.

(3) Dissolve a quantity in water to make a solution of 2 mg of sodium diatrizoate and meglumine diatrizoate per ml. Dissolve 20 mg of diatrizoic acid CRS in 10 ml of 0.04% sodium hydroxide solution. Carry out the method for thin-layer chromatography (Appendix V B), using silica gel HF₂₅₄ as the coating substance and a mixture of *n*-butanol-glacial acetic acid-water (4 : 1 : 5) as the mobile phase. Apply separately to the plate 10 μ l of each of the above two solutions. After developing and removal of the plate, examine under ultraviolet light at 254 nm. The principal spot in the chromatogram obtained with the test solution corresponds in position to the principal spot in the chromatogram obtained with the reference solution.

pH value 6.0-7.6 (Appendix VI H).

Colour Not more intense than that of reference solution Y₆ (Appendix IX A, method 1).

Free iodine Shake a quantity equivalent to 1.0 g of sodium diatrizoate and meglumine diatrizoate with 1 g of potassium iodide in 10 ml of water. Add a few drops of starch IS to the solution and shake well, no blue colour is produced immediately.

Iodide Dilute a quantity equivalent to 1.0 g of sodium diatrizoate and meglumine diatrizoate with water to 10 ml. Add dilute nitric acid dropwise until the precipitation is complete and then add 3 ml of dilute nitric acid in excess. Stir and filter, wash the precipitate with 5 ml of water. Combine the filtrate and the washings, add 1 ml of concentrated hydrogen peroxide solution and 1 ml of chloroform, mix well. Allow to stand until separation takes place, any colour produced in chloroform layer is not more intense than that of a reference solution prepared in the same manner, using 4.0 ml of 0.0013% potassium iodide solution (equivalent to 10 μ g of I per ml).

Pyrogens Complies with the test for pyrogens (Appendix XI D), using 3 ml per kg of the rabbit's weight and inject slowly.

Other requirements Complies with the general requirements for injections (Appendix I B).

Assay Place a quantity equivalent to about 5 g of sodium diatrizoate and meglumine diatrizoate in 100 ml volumetric flask. Carry out the Assay described under Diatrizoic Acid, Beginning at the word "Add 30 ml of sodium hydroxide TS and 1.0 g of zinc powder". Each ml of silver nitrate (0.1 mol/L) VS is equivalent to 26.04 mg of sodium diatrizoate

and meglumine diatrizoate.

Category Diagnostic agent.

Strength (1) 1 ml : 0.3 g (2) 20 ml : 12 g
(3) 20 ml : 15.2 g

Storage Preserve in well closed containers, protected from light.

Meleumycin

Meleumycin is a mixture mainly containing Midecamycin A₁ and Kitasamycin A₆. It contains not less than 35% of Midecamycin A₁. It has a potency of not less than 850 Meleumycin Units per mg, calculated on the dried basis.

Description A white or almost yellow powder or crystalline powder; slightly bitter, taste. Very soluble in methanol, free soluble in ethanol, acetone, ethyl acetate or chloroform; very slightly soluble in water; insoluble in petroleum ether.

Identification (1) The retention times of the two principal peaks of meleumycin in the substance being examined in the chromatogram obtained in the test for Midecamycin A₁ components are identical with those of the two principal peaks of meleumycin CRS in the chromatogram of the reference solution.

(2) The light absorption of a solution of 16 µg per ml in absolute ethanol solution exhibits a maximum at 232 nm (Appendix IV A).

Loss on drying When dried to constant weight at 105°C, loses not more than 2.0% of its weight (Appendix VII L).

Residue on ignition Not more than 0.5% (Appendix VII N).

Midecamycin A₁ components Carry out the method for high performance liquid chromatography (Appendix VD), using a column packed with octadecylsilane bonded silica gel and a mixture of 0.2 mol/L ammonium formate (adjust to pH 7.3 with triethylamine)-acetonitrile (62 : 38) as the mobile phase. The Column temperature is about 30°C. Detection wavelength is 232 nm. Dissolve an accurately weighed quantity in mobile phase to produce a solution containing 3 mg Midecamycin CRS per ml. Inject 10 µl of the successive filtrate into the column and record the chromatogram. Detection wavelength is 254 nm. The resolution factor between Midecamycin A₁ and the adjacent peaks is more than 1.5.

Procedure Dissolve an accurately weighed quantity in mobile phase to produce a solution of 2 mg per ml, mix well and filter. Inject 10 µl of the successive filtrate into the column and record the chromatogram. Repeat the operation, using meleumycin CRS instead of the substance being examined, calculate the content of midecamycin A₁ (C₄₁H₆₇NO₁₅).

Assay Dissolve an accurately weighed quantity in ethanol (using 1 ml of ethanol for 4 mg of the substance being examined), dilute with sterile water to produce a solution of 1000 Units per ml. Carry out the microbiological assay of antibiotics (Appendix XI A). 1000 Meleumycin Units are equivalent to 1 mg of Meleumycin.

Category Macrolide antibiotic.

Storage Preserve in tightly closed containers, stored in a dry place.

Preparation Meleumycin Tablet

Meleumycin Tablets

Meleumycin Tablets contain not less than 90.0% and not more than 110.0% of the labeled amount of meleumycin. It contains not less than 35% of Midecamycin A₁, calculated on the labeled amount.

Description Sugar coated or film coated tablets with white or almost white core.

Identification Dissolve a quantity of powdered and coating-removed tablets in ethanol and filter. The successive filtrate complies with the test for Identification described under Meleumycin.

Dissolution Carry out the dissolution test (Appendix X C, method 1), using hydrochloric acid solution (24 ml of dilute hydrochloric acid solution → 1000 ml) 900 ml as the dissolution medium, adjust the rotational speed of the paddle to 100 rpm. Withdraw the solution after exact 30 minutes and filter. Dilute an accurately measured quantity of the successive filtrate with the same solvent to produce a solution of 16 µg per ml. Triturate 10 tablets, weigh an accurately weighed quantity equivalent to about the average weight of one tablet, dilute with the dissolution medium to produce a solution of 16 µg per ml and filter. Measure the absorbance of the resulting solutions at 232 nm (Appendix IV A), calculate the dissolution of meleumycin from each tablet. Not less than 80% is dissolved.

Midecamycin A₁ Weigh accurately and triturate 10 tablets, weigh a quantity of powdered tablets equivalent to 20 mg of meleumycin in 10 ml volumetric flasks, dilute with mobile phase, mix well and filter. Inject 10 µl of the successive filtrate and carry out the test for Midecamycin A₁ described under Meleumycin.

Other requirements Comply with the general requirements for tablets (Appendix I A)

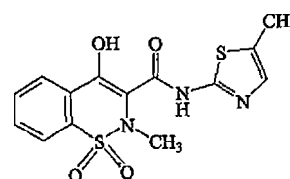
Assay Weigh accurately and triturate 10 tablets, dissolve quantity of powdered tablets equivalent to 0.1 g of meleumycin in 25 ml of ethanol (triturate 5 tablets for the sugar coated tablets in 125 ml of ethanol) in portions to dissolve meleumycin, dilute with sterile water to produce a solution of 1000 Units per ml, mix well and allow to stand. carry out the Assay described under Meleumycin (Appendix VI A). 1000 Meleumycin Units are equivalent to 1 mg of Meleumycin.

Category As described under Meleumycin.

Strength 0.1 g (100000 units)

Storage Preserve in tightly closed containers, stored in a dry place.

Meloxicam



C₁₄H₁₃N₃O₄S₂ 351.42

Meloxicam is 4-hydroxy-2-methyl-N-(5-methyl-

1,3-thiazol-2-yl)-2H-1,2-benzothiazine-3-carboxamide-1,1-dioxide. It contains not less than 98.5% of $C_{14}H_{13}N_3O_4S_2$, calculated on the dried basis.

Description A slightly yellow to pale yellow, or slightly yellowish green to pale yellowish green crystalline powder, odourless; tasteless.

Soluble in dimethylformamide; slightly soluble in acetone; very slightly soluble in methanol or ethanol; practically insoluble in water.

Identification (1) Ignite about 30 mg in a test tube, the vapour produced turns moistened lead acetate TP to black.

(2) Dissolve 10 mg in 5 ml of chloroform, add 1 drop of Ferric chloride TS, shake and allow to stand, a pale violet red colour is produced in the chloroform layer.

(3) The light absorption of a solution of 7 μ g per ml in 0.1 mol/L sodium hydroxide solution exhibits maxima at 270 nm and 362 nm (Appendix IV A).

(4) The infrared absorption spectrum (Appendix IV C) is concordant with the reference spectrum of meloxicam (Appendix XXIII).

Related substances Carry out the method for performance liquid chromatography (Appendix V D), using a column packed with octadecylsilane bonded silica gel and a mixture of 0.1 mol/L ammonium acetate solution-methanol (1 : 1) as the mobile phase. The detection wavelength is 270 nm. The number of the theoretical plate of the column is not less than 2000, calculated with reference to the peak of meloxicam. Dissolve a quantity in mobile phase to produce a solution of 1 mg per ml as test solution. Dilute an accurately measured volume of the test solution with mobile phase to produce a solution of 10 μ g per ml as reference solution. Inject 20 μ l of the reference solution into the column, adjust the attenuation so that the principal peak height in the chromatogram is 20%-25% full scale of the chart. Inject each 20 μ l of the test solution and the reference solution into the column respectively, and record the chromatogram for twice the retention time of the principal peak. The sum of the secondary peak is not greater than the area of the principal peak in the chromatogram obtained with the reference solution.

Chloride Spread 2 g of anhydrous sodium carbonate on the bottom and the wall of a crucible, place 1.0 g of the substance being examined upon the anhydrous sodium carbonate, moisten with a few quantity of water, after dryness, ignite gently until thoroughly incinerated. Dissolve the cooled residue in a quantity of water, filter. Wash the crucible with water and filter, combine the filtrate and washings, dilute to 20 ml with water, mix well. To 1 ml of the filtrate add nitric acid dropwise to make the solution neutral, then add 1 drop of nitric acid, mix well, heat at 75-85°C on a water bath until hydrogen sulfide fumes are no longer evolved, cool, neutralize with 1% sodium carbonate solution, dilute to 25 ml with water. Carry out the limit test for chloride (Appendix VIII A), any opalescence produced is not more pronounced than that of a reference solution using 5.0 ml of sodium chloride standard solution (0.1%).

Loss on drying When dried to constant weight at 105°C, loses not more than 0.5% of its weight (Appendix VIII L).

Residue on ignition Not more than 0.1% (Appendix VIII N), using 1.0 g.

Heavy metals Carry out the limit test for heavy metals (Appendix VIII H, method 2), using the residue obtained in the test for Residue on ignition; not more than 0.001%.

Arsenic Mix 1.0 g with 1 g of calcium hydroxide, dropwise 2 ml of water and mix well. After dryness, heat gently until it is thoroughly charred, then ignite at 500-600°C until the incineration is completed. Dissolve the cooled residue in a

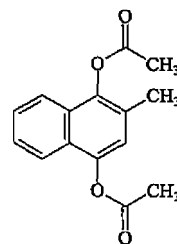
mixture of 5 ml of hydrochloric acid and 23 ml of water. Carry out the limit test for arsenic (Appendix VIII J, method 1); not more than 0.0002%.

Assay Dissolve about 0.4 g, accurately weighed, in 100 ml of neutralized ethanol (neutral to bromothymol blue IS) and 25 ml of sodium hydroxide (0.1 mol/L) VS, accurately measured. Add 3 drops of bromothymol blue IS, titrate with hydrochloric acid (0.1 mol/L) VS. Perform a blank determination and make any necessary correction. Each ml of sodium hydroxide (0.1 mol/L) VS is equivalent to 35.14 mg of $C_{14}H_{13}N_3O_4S_2$.

Category Antipyretic and analgesic non-steroid anti-inflammatory drug.

Storage Preserve in tightly closed containers, protected from light.

Menadiol Diacetate



$C_{15}H_{14}O_4$ 258.27

Menadiol Diacetate is 2-methyl-1,4-naphthalenediol diacetate. It contains not less than 99.0% of $C_{15}H_{14}O_4$, calculated on the dried basis.

Description A white or almost white crystalline powder; odourless or with a faint acetic acid odour.

Freely soluble in boiling ethanol; slightly soluble in ethanol; practically insoluble in water.

Melting point 112-115°C (Appendix VI C).

Specific absorbance Measure the absorbance of a solution of 0.003%, calculated on the dried basis, in dehydrated ethanol at 285 nm (Appendix IV A), the value of A (1%, 1 cm) is 230-260.

Identification (1) Heat gently 50 mg with 5 ml of 0.1 mol/L sodium hydroxide solution for a few minutes, cool, add a few drops of hydrogen peroxide solution, neutralize with dilute hydrochloric acid. Filter, wash the precipitate with water and allow to dry. Dissolve 0.5 mg of the residue in 5 ml of ethanol, add 2 ml of concentrated ammonia TS and a few drops of ethyl cyanoacetate, a bluish-violet colour is produced; add 5 ml of 20% sodium hydroxide solution, a brownish-yellow colour is produced; add acid or expose to light, the bluish-violet colour disappears.

(2) The light absorption of the solution obtained in Specific absorbance exhibits two maxima at 285 nm and 322 nm (Appendix IV A).

(3) The infrared absorption (Appendix IV C) is concordant with the reference spectrum of menadiol diacetate (Appendix XVI).

Loss on drying When dried to constant weight at 80°C, loses not more than 1.0% of its weight (Appendix VIII L).

Zinc Heat 1.0 g with 10 ml of dilute hydrochloric acid, filter, wash the residue with a quantity of hot water. Combine the filtrate and the washings, add water to produce 50 ml, add 1 ml of 5% potassium ferrocyanide solution.

Any opalescence produced is not more pronounced than that of a reference solution prepared in the same manner, using 0.20 mg of zinc sulfate in place of the substance being examined.

Residue on ignition Not more than 0.1% (Appendix VIII N).

Assay To about 0.2 g, accurately weighed, add 15 ml of glacial acetic acid and 15 ml of dilute hydrochloric acid and heat under reflux for 15 minutes. Allow to cool, protected from oxidation, add 0.1 ml of *o*-phenanthroline IS, titrate with ceric sulfate (0.1 mol/L) VS. Perform a blank determination and make any necessary correction. Each ml of ceric sulfate (0.1 mol/L) VS is equivalent to 12.92 mg of $C_{15}H_{14}O_4$.

Category Vitamin.

Storage Preserve in tightly closed container, protected from light.

Preparation Menadiol Diacetate Tablets

Menadiol Diacetate Tablets

Menadiol Diacetate Tablets contain not less than 92.5% and not more than 107.5% of the labeled amount of menadiol diacetate ($C_{15}H_{14}O_4$).

Description Sugar coated tablets with white to pale yellow core.

Identification (1) The light absorption of the solution obtained in Assay exhibits two maxima at 285 nm and 322 nm (Appendix IV A).

(2) To a quantity of the powdered tablets equivalent to about 50 mg of menadiol diacetate, add a quantity of ethanol, boil and filter. Evaporate the filtrate to dryness on a water bath, add 5 ml of sodium hydroxide solution (4→1000), heat gently for a few minutes, cool, add a few drops of hydrogen peroxide solution, neutralize with dilute hydrochloric acid. Filter, wash the precipitate with water and allow to dry. Dissolve about 0.5 mg of the residue with 5 ml of ethanol, add 2 ml of concentrated ammonia TS and a few drops of ethyl cyanoacetate, a bluish-violet colour is produced; add 5 ml of 20% sodium hydroxide solution, a brownish-yellow colour is produced; add acid or on exposure to light, the bluish-violet colour disappears.

(3) The filtrate obtained under test (2) for Identification yields the reactions characteristic of diacetates (Appendix III).

Content uniformity Comply with the requirements (Appendix X E).

Triturate 1 tablet moisten with 5 drops of absolute ethanol with a quantity of absolute ethanol, transfer to a 250 ml (for strength 5 mg) or 200 ml (for strength 4 mg) or 100 ml (for strength 2 mg) volumetric flask with 40 ml of absolute ethanol in divided portions, shake thoroughly to dissolve menadiol diacetate, dilute with dehydrated ethanol to volume and mix well, filter. Measure the absorbance of the successive filtrate at 285 nm (Appendix IV A). Dissolve about 40 mg of menadiol diacetate CRS, accurately weighed, in absolute ethanol, dilute with absolute ethanol to produce a solution of 0.02 mg per ml. Measure the absorbance in the same manner, calculate the content of $C_{15}H_{14}O_4$ in each tablet.

Other requirements Comply with the general requirements for tablets (Appendix I A).

Assay Weigh accurately and powder 40 tablets with coating removed. To an accurately weighed quantity of the powder, equivalent to about 20 mg of menadiol acetate, in a 100 ml volumetric flask add a quantity of absolute ethanol and shake

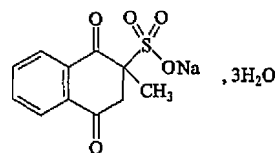
to dissolve menadiol acetate, dilute to volume and mix well. Filter, measure accurately 10 ml of the successive filtrate to another 100 ml volumetric flask, dilute with absolute ethanol to volume and mix well. Measure the absorbance of the resulting solution at 285 nm (Appendix IV A); dissolve about 20 mg of menadiol diacetate CRS, accurately weighed, in absolute ethanol, and dilute to produce a solution of 0.02 mg per ml. Measure the absorbance in the same manner. Calculate the content of $C_{15}H_{14}O_4$.

Category As described under Menadiol Diacetate.

Strength (1) 2 mg (2) 4 mg (3) 5 mg

Storage Preserve in tightly closed containers, protected from light.

Menadione Sodium Bisulfite



$C_{11}H_9NaO_5S \cdot 3H_2O$ 330.30

[6147-37-1]

Menadione Sodium Bisulfite is a mixture of menadione sodium bisulfite and sodium bisulfite. It contains not less than 63.0% and not more than 75.0% of $C_{11}H_9NaO_5S \cdot 3H_2O$; and not less than 30.0% and not more than 38.0% of $NaHSO_3$, calculated on the dried basis.

Description A white crystalline powder; odourless or slightly characteristic; hygroscopic; decomposed easily on exposure to light.

Freely soluble in water; practically insoluble in ethanol, ether or benzol.

Identification (1) Dissolve about 50 mg in 5 ml of water, add dropwise 0.1 mol/L sodium hydroxide solution, a freshly yellow precipitate of menadione sodium bisulfite is produced.

(2) Dissolve about 80 mg in 2 ml of water, add a few drops of dilute hydrochloric acid, warm, the sulfur dioxide odour is perceptible.

(3) The infrared absorption spectrum (Appendix IV C) is concordant with reference spectrum of menadione sodium bisulfite (Appendix XVI).

Sulfonic acid menadione sodium bisulfite Dissolve 0.1 g in 5 ml of water, add 2 drops of ortho-phenanthroline TS, no precipitate is produced.

Water 9.0%-13.0% (Appendix VIII M, method 1 A).

Assay Sodium bisulfite Dissolve about 1.5 g, accurately weighed, in a 100 ml volumetric flask, in water and shake, dilute to volume and mix well. Accurately measure 15 ml to a conical flask with stopper, add accurately 25 ml of iodine (0.05 mol/L) VS, stopper and mix well, allow to stand for 5 minutes. Add slowly 1 ml of hydrochloric acid, titrate with sodium thiosulfate (0.1 mol/L) VS, add 3 ml of starch IS towards the end of the titration, continue the titration until blue colour disappears. Perform a blank determination and make any necessary correction. Each ml of iodine (0.05 mol/L) VS is equivalent to 5.203 mg of $NaHSO_3$.

Menadione sodium bisulfite Protect from light in the procedure.

Reference solution To 50 mg of menadione CRS, accurately weighed, in a 250 ml volumetric flask, add chloroform to volume and shake thoroughly. Measure accurately 2 ml of the solution to a 100 ml volumetric flask, dilute with dehydrated ethanol to volume, mix well.

Test solution Dissolve about 1.0 g, accurately weighed, in a 200 ml volumetric flask, in water and dilute to volume, mix well. Measure accurately 20 ml to a separator, add 40 ml of chloroform and 5 ml of sodium carbonate TS, shake vigorously for 30 seconds. Allow to stand, separate the chloroform layer and filter through the cotton moistened by chloroform. Transfer the filtrate to a 200 ml volumetric flask, wash the filter with 40 ml of chloroform immediately, combine the washings in the same volumetric flask. Extract twice the water layer with 20 ml each of chloroform, filter the extracts, wash the filter with 20 ml of chloroform. Combine the extracts and washings to the volumetric flask, add chloroform to volume and mix well. Measure accurately 2 ml in another 100 ml volumetric flask, dilute with absolute ethanol to volume, mix well.

Procedure Measure the absorbances of the solutions at 250 nm and make necessary correction using 2% chloroform absolute ethanol solution (Appendix IV A). Calculate the content of $C_{11}H_9NaO_5S \cdot 3H_2O$, multiply the result by 1.918.

Category Vitamin.

Storage Preserve in tightly closed containers, protected from light.

Preparation Menadione Sodium Bisulfite Injection

Menadione Sodium Bisulfite Injection

Menadione Sodium Bisulfite Injection is a sterile solution of Menadione Sodium Bisulfite in Water for Injection. It contains not less than 90.0% and not more than 110.0% of the labelled amount of menadione sodium bisulfite ($C_{11}H_9NaO_5S \cdot 3H_2O$).

Description A clear, colourless liquid; decomposes easily on exposure to light.

Identification Complies with test (1) and (2) for Identification described under Menadione Sodium Bisulfite, using a quantity of the injection.

pH value 2.0-4.0 (Appendix VI H).

Other requirements Complies with the general requirements for injections (Appendix I B).

Assay Protect from light in the procedure. Weigh accurately a quantity equivalent to about 20 mg of menadione to a separator. Add 40 ml of chloroform and 2.5 ml of sodium carbonate TS, shake vigorously for 30 seconds, allow to stand, separate the chloroform layers and filter with the cotton moistened by chloroform. Transfer the filtrate into a 100 ml volumetric flask, wash the filter with 20 ml of chloroform immediately, combine the washing in the same volumetric flask. Extract the water layer with 10 ml each of chloroform twice, filter the extracts, wash the filter with 20 ml of chloroform. Combine the extracts and washing to the volumetric flask, add chloroform to volume and mix well. Measure accurately 2 ml in another 100 ml volumetric flask, dilute with absolute ethanol to volume, mix well. Measure the absorbances of the solutions at 250 nm and make any necessary correction using 2% chloroform absolute ethanol solution as blank (Appendix IV A). Weigh accurately about

20 mg of menadione CRS in a 100 ml volumetric flask add chloroform to volume and shake thoroughly. Measure accurately 2 ml of the solution to a 100 ml volumetric flask, dilute with absolute ethanol to volume, mix well. Calculate the content of $C_{11}H_9NaO_5S \cdot 3H_2O$ (multiply the result by 1.918).

Category As described under Menadione Sodium Bisulfite.

Strength (1) 1 ml : 2 mg (2) 1 ml : 4 mg

Storage Preserve in tightly closed containers, protected from light.

Menotropins

Menotropins is gonads-stimulating hormone obtained from the urine of postmenopausal women, mainly containing follicle-stimulating hormone (FSH) and luteinising hormone (LH). It contains not less than 40 Units of follicle-stimulating hormone activity per mg. The ratio of Units of LH activity to Units of FSH activity is approximately 1.

The manufacturing process must have been shown to reduce any viral contamination such as hepatitis virus or HIV by appropriate validated methods.

Description An almost white or pale yellow powder. Soluble in water.

Identification The results of the Assay indicates the ovaries of immature female rats increase and the weight of the seminal vesicles and prostate gland of immature male rats also increase.

Loss on drying When dried in vacuum over phosphorous pentoxide for 4 hours, loses not more than 5.0% of its weight (Appendix VIII L).

Undue toxicity Complies with the test for undue toxicity (Appendix XI C), using a solution of 100 Units of FSH activity per ml in Sodium Chloride Injection, injected intravenously.

Bacterial endotoxin Carry out the test for bacterial endotoxin (Appendix XI E); less than 1 EU per units of menotropins.

Assay FSH Carry out the method for biological assay of FSH (Appendix XIII M), the result is not less than 80% and not more than 125% of the labelled potency.

LH Carry out the method for biological assay of LH (Appendix XIII N), the result is not less than 80% and not more than 125% of the labelled potency.

Category Gonads-stimulant.

Storage Preserve in tightly closed containers, stored in a cool place and protected from light.

Preparation Menotropins for Injection

Menotropins for Injection

Menotropins for Injection is a sterile, lyophilized mixture of menotropins and suitable excipients. It has a potency of not less than 76% and not more than 135% of the labelled potency of follicle-stimulating hormone (FSH) and luteotropic

hormone (LH).

Description A white, or almost white lyophilized mass or powder.

Identification The result of the assay indicates the ovaries of the immature female rats increase, and vesicula seminalis and prostate of the immature male rats gain weight.

Acidity or alkalinity Dissolve the content each of 3 vials in 3 ml of water respectively, combine the solutions, pH 6.0–8.0 (Appendix VI H).

Sterility Complies with the test for sterility (Appendix XI H), dissolving the content of each container in 2 ml of sterile water.

Loss on drying, Undue toxicity, Bacterial endotoxin Complies with the corresponding test described under Menotropins.

Other requirements Complies with the general requirements for injections (Appendix I B).

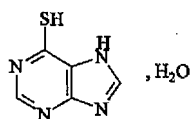
Assay Carry out the Assay described under Menotropins.

Category As described under Menotropins.

Strength (1) 75 Units (2) 150 Units

Storage Preserve in well closed containers, stored in a cool place, protected from light.

Mercaptopurine



$C_5H_4N_4S \cdot H_2O$ 170.19

[50-44-2]

Mercaptopurine is 6-mercaptopurine monohydrate. It contains not less than 97.0% and not more than 103.0% of $C_5H_4N_4S$, calculated on the dried basis.

Description A yellow crystalline powder; odourless; taste, slightly sweet. Very slightly soluble in water or ethanol, practically insoluble in ether.

Identification (1) To about 20 mg add 20 ml of ethanol, warm to dissolve. Add 1 ml of 1% ethanolic lead acetate solution; a yellow precipitate is produced.

(2) To 20 mg add a few drops of nitric acid, evaporate to dryness on a water bath. The residue is yellow in colour. Cool and add 1–2 drops of sodium hydroxide TS; the colour changes to yellowish-brown.

(3) Dissolve 10 mg in 10 ml of ammonia TS, a clear solution is produced; add 1 ml of silver nitrate TS, a white, curdy precipitate is produced; the precipitate is not dissolved on heating with nitric acid.

(4) The infrared absorption spectrum (Appendix IV C) is concordant with the reference spectrum of mercaptopurine (Appendix XVI).

Sulfate Shake 0.25 g with 25 ml of water for 5 minutes, filter. To the filtrate add 1 ml of dilute hydrochloric acid, 2 ml of barium chloride TS and mix, no opalescence is produced.

6-Hydroxypurine Carry out the method for spectrophotometry (Appendix IV A), using the solution obtained in the Assay,

the ratio of the absorbance at 255 nm to that at 325 nm is not greater than 0.06.

Loss on drying When dried to constant weight at $140^\circ C$, loses not more than 11.0% of its weight (Appendix VIII L).

Heavy metals Carry out the limit test for heavy metals (Appendix VIII H, method 2), using 1.0 g; not more than 0.001%.

Assay Dissolve an accurately weighed quantity in hydrochloric acid solution (9→1000) to produce a solution of 5 μg per ml, measure the absorbance at 325 nm (Appendix IV A). Calculate the content of $C_5H_4N_4S$, taking 1265 as the value of A (1%, 1 cm).

Category Antineoplastic.

Storage Preserve in tightly closed containers, protected from light.

Preparation Mercaptopurine Tablets

Mercaptopurine Tablets

Mercaptopurine Tablets contain not less than 90.0% and not more than 110.0% of the labelled amount of mercaptopurine ($C_5H_4N_4S \cdot H_2O$).

Description Pale yellow tablets.

Identification (1) To a quantity of finely powdered tablets equivalent to about 30 mg of mercaptopurine add 30 ml of ethanol, heat on a water bath to dissolve mercaptopurine, cool and filter. The filtrate complies with the tests (1) and (2) for Identification described under Mercaptopurine.

(2) Extract a quantity of finely powdered tablets equivalent to about 10 mg of mercaptopurine with 10 ml of ammonia TS and filter. The filtrate complies with the test (3) for Identification described under Mercaptopurine.

Dissolution Carry out dissolution test (Appendix X C, method 2), using 900 ml of hydrochloric acid solution (9→1000) as the dissolution medium, adjust the rotational speed of the paddle to 100 rpm. Withdraw 10 ml of the solution after exactly 45 minutes and filter. Dilute a quantity of successive filtrate with hydrochloric acid solution (9→1000) to produce a solution of 5 μg per ml. Measure the absorbance of the resulting solution at 325 nm (Appendix IV A). Calculate the dissolution of $C_5H_4N_4S \cdot H_2O$ from each tablet, taking 1131 as the value of A (1%, 1 cm). Not less than 70% of the labelled amount is dissolved.

Other requirements Comply with the general requirements for tablets (Appendix I A).

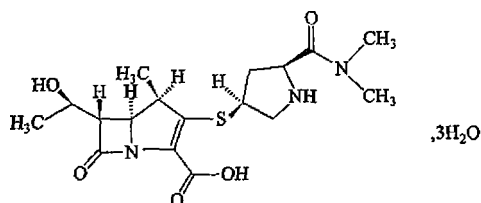
Assay Weigh accurately and powder 10 tablets. Dissolve a portion of the powder, equivalent to about 50 mg of mercaptopurine, in a 100 ml volumetric flask with 50 ml of hydrochloric acid solution (9→1000) by heating in a water bath. Cool and dilute with hydrochloric acid solution (9→100) to volume, mix and filter. Dilute an accurately measured portion of the successive filtrate with hydrochloric acid solution (9→100) to produce a solution of 5 μg per ml, measure the absorbance at 325 nm (Appendix IV A). Calculate the content of $C_5H_4N_4S \cdot H_2O$, taking 1131 as the value of A (1%, 1 cm).

Category As described under Mercaptopurine.

Strength (1) 25 mg (2) 50 mg (3) 100 mg

Storage Preserve in tightly closed containers, protected from light.

Meropenem



$C_{17}H_{25}N_3O_5S \cdot 3H_2O$ 437.51

Meropenem is trihydrate (–)-(4R,5S,6S)-3-[(3S,5S)-5-(Dimethylamino) Carbonyl-3-pyrrolidiny] thio-6-[(1R)-1-hydroxyethyl]-4-methyl-7-oxo-1-azabicyclo[3,2,0]hept-2-ene-2-carboxylic acid. It contains not less than 92.0% of $C_{16}H_{16}N_4O_8S$, calculated on the anhydrous basis.

Description A white to slightly yellow crystalline powder; odourless, bitter odor.

Soluble in methanol; sparingly soluble in water, insoluble in acetone, ethanol and ether, soluble in 0.1 mol/L sodium hydroxide, soluble in 0.1 mol/L hydrochloric acid.

Specific optical rotation -17° to -21° in a solution of 10 mg per ml in water (Appendix VI E).

Identification (1) The retention time of principal peak of the substance being examined is identical with that of principal peak of the reference solution in the chromatogram obtained in Assay. (2) The infrared absorption spectrum (Appendix IV C) is concordant with the reference spectrum of meropenem (Appendix XVI).

Crystallinity Complies with the test for crystallinity (Appendix IX D).

Acidity An aqueous solution of 10 mg per ml, pH 4.0-6.0 (Appendix VI).

Clarity and colour of solution To each of 5 portions add suitable amount (the amount is 0.2 times of that of meropenem) sodium carbonate (for Injection) and water to produce solutions of 0.11 g per ml according to the labelled amount respectively, the solution are clear and colourless; any opalescence produced is not more pronounced than that of reference suspension I (Appendix IX B); any colour produced is not more intense than that of reference solution Y₅ or YG₅ (Appendix IX A, method 1).

Related substance Dissolve an accurately weighed quantity in mobile phase solution to produce a solution of 5 mg per ml as test solution. Dissolve an accurately weighed quantity of meropenem CSR in mobile phase solution to produce a solution of 25 µg per ml as reference solution. Carry out the method for Assay. Inject 20 µl of the reference solution into the column. Adjust the attenuation so that the principal peak height in the chromatogram is 20%-25% of the full scale of the chart. Inject 20 µl of the test solution and the reference solution into the column and record the chromatograms for 3.5 times the retention time of the principal peak. The sum of the areas of all peaks other than the principle peak is not greater than 1.5% of the area of the principle peak in the reference solution. The area of single peak is not more than 0.5% of the area of the principle peak in the reference solution.

Dichloromethane and Acetone Carry out the method for determination of residual solvents (Appendix VIII P), using a capillary column coated with 5% phenyl-95% methylpolysiloxane

(or with the similar polarity stationary phase). Maintaining the temperature at 50°C, use flame ionization detector (FID) with temperature at 250°C, the injector temperature is 140°C. The incubation temperature of headspace oven is 90°C, the incubation time of headspace vial is 20 minutes, the volume of injection is 1.0 ml. Dissolve 0.2 g, accurately weighed, in headspace vial, and a quantity of sodium carbonate equivalent to 20% weight of the substance being examined in 5 ml of water, accurately measured, well closed, as the test solution. Measure accurately a quantity of acetone and methylene chloride with water to produce a solution containing 0.2 mg of acetone and 24 µg of methylene chloride per ml, measure accurately 5 ml in headspace vial, tightly closed, as the reference solution.

Inject the reference solution, record the chromatogram. The order of elution of the peaks is acetone and methylene chloride, the resolution factor between the peaks is not less than 1.5.

Inject the test solution and the reference solution separately, record the chromatogram. Calculate the content of acetone and methylene chloride respectively with respect to the peak area obtained in the chromatogram by the external standard method, the result complies with the related requirements.

Water 11.4%-13.4% (Appendix VIII M, method 1 A).

Residue on ignition Not more than 0.2% (Appendix VIII N), using 1.0 g.

Heavy metals Carry out the limit test for heavy metals (Appendix VIII H, method 2), using the residue obtained in the test for residue on ignition: not more than 0.001%.

Bacterial endotoxin Carry out the test for bacterial endotoxin (Appendix XI E): not more than 0.12 EU per mg of meropenem.

Sterility Complies with test for Sterility (Appendix XI H, membrane filtration method), to each portion add 0.1 g of sterile sodium carbonate solution (dissolve anhydrous sodium carbonate in water and dilute to 100 ml) and not more than 500 ml of 0.9% sterile sodium chloride solution.

Assay Carry out the method for high performance liquid chromatography (Appendix V D), using a column packed with octadecylsilane bonded silica gel and a mixture of 0.3% triethylamine solution [measure 3.0 ml of triethylamine in 900 ml water, adjust pH to 5.0 with phosphate acid solution (1 → 10), dilute with water to 1000 ml] -acetonitrile (100 : 7), detection wavelength is 220 nm. Measure a quantity of reference solution and heat the reference solution in a water bath for one hour. Inject 20 µl of the solution into the column, and record the chromatogram. The number of the theoretical plate of the column is not less than 3000, calculated with reference to the peak of meropenem. The resolution factor between the peak of meropenem and the open-cycle of meropenem complies with the related requirements. The order of the peaks in the chromatogram is meropenem and the open-cycle of meropenem.

Procedure Dissolve an accurately weighed quantity in mobile phase solution to produce a solution of 0.5 mg per ml as the test solution. Inject 20 µl of the test solution into the column and record the chromatogram. Dissolve an accurately weighed quantity of meropenem CSR in mobile phase solution as the reference solution and repeat the operation. Calculate the content of $C_{17}H_{25}N_3O_5S$ with respect to the peak area obtained in the chromatogram by the external standard method.

Category β-lactam antibiotic.

Storage Preserve in tightly closed containers in cool, dark and dry place.

Preparation Meropenem for Injection

Meropenem for Injection

Meropenem for Injection is a sterile mixture of meropenem and suitable amount of anhydrous sodium carbonate. Each container contains not less than 75.0% of meropenem ($C_{17}H_{25}N_3O_5S$), calculated on the anhydrous basis. Each container contains not less than 90.0% and not more than 110.0% of the labelled amount of meropenem ($C_{17}H_{25}N_3O_5S$), calculated with reference to the average weight of contents.

Description A white or slightly yellow powder.

Identification (1) The retention time of principal peak of the substance being examined in the chromatogram obtained in the Assay is identical with that of principal peak of CRS.

(2) To a quantity add dilute acid, effervescence is produced with carbon dioxide, when which is passed into calcium hydroxide TS, a white precipitate is produced immediately.

Alkalinity An aqueous solution of 5 mg per ml, pH 7.0-8.5 (Appendix VI H).

Clarity and colour of solution To each of 5 containers add water to produce solutions of 0.1 g per ml according to the labelled amount respectively, the solutions are clear and colourless; any opalescence produced is not more pronounced than that of reference suspension I (Appendix IX B); any colour produced is not more intense than that of reference solution Y₆ or YG₅ (Appendix IX A, method 1).

Loss on drying When dried to constant weight in vacuum over phosphorous pentoxide at 60°C, loses not less than 9.0% and not more than 12.0% (Appendix VIII L).

Related substances and bacterial endotoxin Comply with the corresponding requirements described under meropenem.

Sterility Complies with test for Sterility (Appendix XI H, membrane filtration method), to each portion add not less than 500 ml of 0.9% sterile sodium chloride solution.

Other requirements Comply with the general requirements for Injection (Appendix I B).

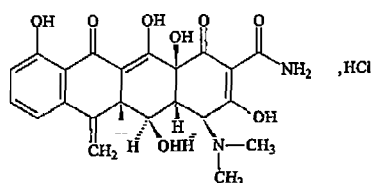
Assay Carry out the Assay described under Meropenem, using an accurately weighed quantity of the mixed contents obtained from the test for Weight variation of contents.

Category As described under Meropenem.

Strength Calculated as $C_{17}H_{25}N_3O_5S$
(1) 0.25 g (2) 0.5 g

Storage preserve in well closed containers in cool, dark and dry place.

Metacycline Hydrochloride



$C_{22}H_{22}N_2O_8 \cdot HCl$ 478.89

[3963-95-9]

Metacycline Hydrochloride is [4S-(4 α , 4a α , 5 α , 5a α , 12a α)]-6-methylene-4-(dimethylamino)-3,5,10,12,12a-pentahydroxy-1,11-dioxo-2-naphthacene carboxamide monohydrochloride. It contains not less than 87.0% of metacycline ($C_{22}H_{22}N_2O_8$), calculated on the dried basis.

Description A yellow crystalline powder; odourless; taste, bitter.

Sparingly soluble in water or methanol; insoluble in chloroform.

Identification (1) The light absorption of a solution of 10 μ g per ml in a mixture of hydrochloric acid (1 mol/L)-methanol (1:99) exhibits a maximum at 345 nm. The absorbance at 345 nm is 0.31 to 0.33 (Appendix IV A).

(2) The retention time of the principal peak of the substance being examined in the chromatogram obtained in the Assay is identical with that of the principal peak of metacycline RS.

(3) The infrared absorption spectrum (Appendix IV C) is concordant with the reference spectrum of metacycline hydrochloride (Appendix XVI).

(4) The aqueous solution yields the reactions characteristic of chlorides (Appendix III).

Acidity Dissolve 0.1 g in 10 ml of water, pH 2.0-3.0 (Appendix VI H).

Light absorbing impurities The absorbance of a solution of 10 mg per ml in a mixture of hydrochloric acid (1 mol/L)-methanol (1:100) at 490 nm, is not greater than 0.20 (Appendix IV A).

Loss on drying When dried to constant weight at 105°C, loses not more than 1.5% (Appendix VIII L), using 0.2 g to 0.3 g.

Residue on ignition Not more than 0.2% (Appendix VIII N).

Related substances Carry out the method as described under Assay. Dissolve a quantity of the substance being examined in 0.01 mol/L hydrochloric acid solution to produce solutions of 0.2 mg per ml (solution 1) and 2 μ g per ml (solution 2). Inject 20 μ l of solution 2 into the column. Adjust the attenuation so that the principal peak height in the chromatogram is 20% full scale of the chart. And then inject 20 μ l each of solution 1 and 2 into the column, and record the chromatogram for twice the retention time of the principal peak.

The peak area of oxytetracycline in the chromatogram of solution 1 is not more than the area of the principal peak of solution 2.

Assay Carry out the method for high performance liquid chromatogram (Appendix V D), using a column packed with octadecylsilane bonded silica gel and a mixture of 0.05 mol/L ammonium oxalate solution-dimethylformamide-0.2 mol/L diammonium hydrogen phosphate solution (65:27:7) adjusting pH to 7.6 ± 0.2 with phosphoric acid as the mobile phase. The flow rate is 1.0 ml per minute, and the temperature of the column is 35°C, detection wavelength is 280 nm. Dissolve a quantity of oxytetracycline RS and metacycline RS in 0.01 mol/L hydrochloric acid solution to produce a solution each of 0.08 mg per ml. Inject the above solution into the column. The resolution factor between the peaks of oxytetracycline and metacycline is greater than 4.0.

Procedure Dissolve 20 mg of the substance being examined, accurately weighed, with 0.01 mol/L hydrochloric acid solution in a 25 ml volumetric flask and dilute to volume, mix well. Transfer a portion of the solution into a 10 ml volumetric flask and dilute to volume with 0.01 mol/L hydrochloric acid solution, mix well. Inject 20 μ l of the resulting solution into the column. Repeat the operation, using metacycline RS instead of the substance being

examined, calculate the content of $C_{22}H_{22}N_2O_8$.

Category Tetracycline antibiotic.

Storage Preserve in tightly closed containers, protected from light.

Preparation (1) Metacycline hydrochloride capsules
(2) Metacycline hydrochloride tablets

Metacycline Hydrochloride Capsules

Metacycline Hydrochloride Capsules contain not less than 90.0% and not more than 110.0% of the labelled amount of metacycline ($C_{22}H_{22}N_2O_8$).

Identification The contents of capsules comply with the tests for Identification described under Metacycline hydrochloride tablets.

Related substances Dissolve a quantity of mixed contents obtained in the test for Weight variation, accurately weighed, in 0.01 mol/L hydrochloric acid solution to produce a solution of about 0.2 mg per ml, and filter. Use the successive filtrate as the solution 1. Dilute a quantity of solution 1, accurately measured, with 0.01 mol/L hydrochloric acid solution to produce a solution of 2 μ g per ml as solution 2. Carry out the method described under metacycline hydrochloride.

Dissolution Carry out the dissolution test (Appendix X C, method 2), using 900 ml of water as the dissolution medium, adjust the rotational speed of the paddle to 60 rpm. Withdraw a quantity of the solution after exactly 45 minutes and filter. Dilute 5 ml of the successive filtrate, accurately measured, with water to 50 ml. Dissolve a quantity of metacycline hydrochloride CRS in water to produce a solution of about 10 μ g per ml. Measure the absorbances of the resulting solutions at 345 nm (Appendix IV A). Calculate the dissolution of $C_{22}H_{22}N_2O_8$ from each capsule. Not less than 75% of the labelled amount is dissolved.

Loss on drying When dried to constant weight at 105°C, the contents of the capsules lose not more than 2.0% of their weights (Appendix VIII L).

Other requirements Comply with the general requirements for capsules (Appendix I E).

Assay Dissolve an accurately weighted quantity (equivalent to about 80 mg of metacycline) of mixed contents obtained in the test for weight variation with 0.01 mol/L hydrochloric acid solution in a 100 ml volumetric flask and dilute to volume, mix well, filter. Transfer 5 ml of successive filtrate into a 50 ml of volumetric flask, dilute with 0.01 mol/L hydrochloric acid solution to volume. Inject 20 μ l of the resulting solution into the column, carry out the Assay as described under metacycline hydrochloride.

Category As described under Metacycline Hydrochloride.

Strength Calculated on $C_{22}H_{22}N_2O_8$ (1) 0.1 g (2) 0.2 g

Storage Preserve in tightly closed containers, stored in a cool and dry place.

Metacycline Hydrochloride Tablets

Metacycline Hydrochloride Tablets contain not less than 90.0% and not more than 110.0% of the labelled amount of metacycline ($C_{22}H_{22}N_2O_8$).

Description Sugar coated or film coated with yellow or yellowish brown core.

Identification A quantity of powdered tablets with coating removed complies with tests (1), (2), and (4) for Identification described under Metacycline Hydrochloride.

Related substances Dissolve a quantity of powdered tablets in 0.01 mol/L hydrochloric acid solution to produce a solution of about 0.2 mg per ml, and filter. Use the successive filtrate as the solution 1. Dilute a quantity of solution 1, accurately measured, with 0.01 mol/L hydrochloric acid to produce a solution of 2 μ g per ml as solution 2. Carry out the method described under metacycline hydrochloride.

Dissolution Carry out the dissolution test (Appendix X C, method 2), using 900 ml of water as the dissolution medium, the rotational speed of the paddle is adjusted to 60 rpm. Withdraw a quantity of the solution after exactly 45 minutes and filter. Dilute 5 ml of the successive filtrate, accurately measured, with water to 50 ml. Dissolve a quantity of metacycline hydrochloride CRS in water to produce a solution of about 10 μ g per ml. Measure the absorbance of the resulting solutions at 345 nm (Appendix IV A). Calculate the dissolution of $C_{22}H_{22}N_2O_8$ from each tablet. Not less than 75% of the labelled amount is dissolved.

Other requirements Comply with the general requirements for tablets (Appendix I A).

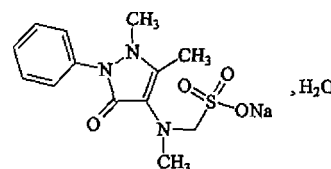
Assay Weigh accurately and powder 10 tablets. Dissolve an accurately weighed quantity (equivalent to about 80 mg of metacycline) in 0.01 mol/L hydrochloric acid solution in a 100 ml volumetric flask and dilute to volume, mix well, filter. Transfer 5 ml of successive filtrate into a 50 ml volumetric flask, dilute with 0.01 mol/L hydrochloric acid solution to volume. Inject 20 μ l of the resulting solution into the column, carry out the Assay as described under metacycline hydrochloride.

Category As described under Metacycline Hydrochloride.

Strength 0.1 g calculated as $C_{22}H_{22}N_2O_8$.

Storage Preserve in tightly closed containers, stored in a cool and dry place.

Metamizole Sodium



$C_{13}H_{16}N_3NaO_4S \cdot H_2O$ 351.36

Metamizole Sodium is [(1, 5-dimethyl-2-phenyl-3-oxo-2,3-dihydro-1H-pyrazol-4-yl) methylamino] methanesulfonic acid sodium salt, monohydrate. It contains not less than 99.0% of $C_{13}H_{16}N_3NaO_4S$ (for parenteral administration) or 98.5% (for oral administration), calculated on the dried basis.

Description White (for parenteral administration) or slightly yellow (for oral administration) crystals or a crystalline powder; odourless; taste, slightly bitter. The aqueous solution turns gradually to yellow on standing. Freely soluble in water; sparingly soluble in ethanol; practically insoluble in ether.

Identification (1) Dissolve about 20 mg in 1 ml of dilute hydrochloric acid, add 2 drops of sodium hypochlorite TS, a

transient blue colour is produced, which turns to yellow on boiling.

(2) Dissolve about 0.2 g in 8 ml of dilute hydrochloric acid, the odour of sulfur dioxide is evolved on heating, then the odour of formaldehyde is produced.

(3) The infrared absorption spectrum (Appendix IV C) is concordant with the reference spectrum of Metamizole Sodium (Appendix XVI).

(4) Yields the flame reaction of sodium salts (Appendix III)

Acidity Dissolve 0.50 g in 50 ml of water, pH 6.0-7.0 (Appendix VI H).

Clarity and colour of solution Dissolve 2.5 g (for parenteral administration) or 1.0 g (for oral administration) in 10 ml of water, when the bubbles disappear, examine immediately, the solution is clear and colourless. Any colour produced is not more intense than that of a reference solution (to 1.2 ml of standard potassium dichromate CS, 0.10 ml of standard copper sulfate CS and 0.10 ml of standard cobaltous chloride CS add water to 50 ml and mix well), compared immediately.

Clarity of methanol solution Shake 0.50 g with 10 ml of methanol to dissolve. Any opalescence produced is not more pronounced than that of the reference solution [to 0.50 ml of potassium sulfate standard solution, 1 ml of hydrochloric acid solution (1 mol/L) VS and 3 ml of freshly prepared barium chloride solution (1→20) add water to 10 ml, mix well and allow to stand for 10 minutes] (for parenteral administration).

Sulfate Carry out the limit test for sulfates (Appendix VIII B), using 0.20 g. Any opalescence produced is not more pronounced than that of a reference solution, using 2.0 ml of potassium sulfate standard solution (0.1%).

4-N-nor Metamizole Sodium To 0.50 g in a 50 ml volumetric flask add water to dissolve and dilute to volume, mix well. Measure 1.0 ml to a 25 ml Nessler cylinder, add water to 10 ml, add 5 ml of hydrochloric acid solution (1→2), heat on a water bath for 5 minutes. Cool, add 7 ml of water, mix well, add 2.0 ml of 10% ethanolic solution of vanilin, add water to volume and mix well. Any colour produced is not more intense than that of reference solution prepared by mixing 1.0 ml of a solution containing 10 mg of metamizole sodium CRS with 2.0 ml (for parenteral administration) or 7.0 ml (for oral administration) of a solution containing 10 µg of anhydrous 4-N-nor metamizole sodium CRS per ml treated in similar manner (0.2% for parenteral administration or 0.7% for oral administration).

Loss on drying When dried to constant weight at 105°C, loses not more than 5.5% of its weight (Appendix VIII L).

Heavy metals Moisten 1.0 g in quartz crucible or hard glass evaporating dish with 1 ml of sulfuric acid, heat gently until white fumes are no longer evolved. Cool, add 0.5 ml of nitric acid, continue to ignite until nitrous oxide fumes are no longer evolved, then ignite at 500-600°C until the incineration is complete. Cool, add 2 ml of hydrochloric acid, evaporate to dryness on a water bath. Dissolve the residue in 15 ml of water, add ammonia TS dropwise until the solution is neutral to phenolphthalein IS, then add 2 ml of acetate BS (pH 3.5) and a quantity of water to produce 25 ml. Carry out the limit test for heavy metals (Appendix VIII H, method 1); not more than 0.001% (for parenteral administration) or 0.002% (for oral administration).

Assay Dissolve about 0.3 g, accurately weighed, in 10 ml of ethanol and 10 ml of hydrochloric acid (0.01 mol/L) VS. Titrate immediately with iodine (0.05 mol/L) VS at a rate of 3-5 ml per minutes until a pale yellow colour persists for 30 seconds. Each ml of iodine (0.05 mol/L) VS is equivalent to 16.67 mg of $C_{13}H_{16}N_3NaO_4S$.

Category Antipyretic and analgesic agent.

Storage Preserve in tightly closed containers, protected from light.

Preparation (1) Metamizole Sodium Drops
(2) Metamizole Sodium Injection
(3) Metamizole Sodium Nasal Drops
(4) Metamizole Sodium Tablets

Metamizole Sodium Drops

Metamizole Sodium drops contain not less than 95.0% and not more than 105.0% of the labelled amount of Metamizole Sodium ($C_{13}H_{16}N_3NaO_4S \cdot H_2O$).

Description A clear to slightly yellow liquid.

Identification Comply with tests (1) and (2) for Identification as described under Metamizole Sodium.

pH value 5.0-7.0 (Appendix VI H).

Colour Not more intense than the reference solution of Y₄ (Appendix IX A, method 1).

Other requirements Comply with the general requirements for oral solutions (Appendix I O).

Assay To 5 ml of Metamizole Sodium, accurately measured, add 40 ml of ethanol and dilute to 50 ml with water, mix well. Remove 10 ml of the resulting solution, accurately measured, to a conical flask and add 2 ml of ethanol, 6.5 ml of water and 0.5 ml of formaldehyde solution, stand for 1 minute. And then add 1 ml of hydrochloric acid solution (9→1000), mix well. Titrate with iodine (0.05 mol/L) VS (the titration speed is 3-5 ml per minute) until a pale yellow colour persists for 30 seconds. Each ml of iodine (0.05 mol/L) VS is equivalent to 17.57 mg of $C_{13}H_{16}N_3NaO_4S \cdot H_2O$.

Category As described under Metamizole Sodium.

Strength 1 ml : 0.2 g

Storage Preserve in tightly closed containers, protected from light.

Metamizole Sodium Injection

Metamizole Sodium Injection is a sterile solution of Metamizole Sodium in Water for Injection. It contains not less than 95.0% and not more than 105.0% of the labelled amount of Metamizole Sodium ($C_{13}H_{16}N_3NaO_4S \cdot H_2O$).

Description A clear, colourless or slightly yellow liquid.

Identification Complies with tests (1) and (2) for Identification described under Metamizole Sodium.

Colour Not more intense than reference solution Y₃ (Appendix IX A, method 1).

pH value 5.0-7.0 (Appendix VI H).

Other requirements Complies with the general requirements for injections (Appendix I B).

Assay To 10 ml, accurately measured, in a 100 ml volumetric flask add 80 ml of ethanol, dilute with water to volume and mix well. To 10 ml, accurately measured, in a conical flask add 2 ml of ethanol, 6.5 ml of water and 0.5 ml

of formaldehyde solution, allow to stand for 1 minute, add 1.0 ml of hydrochloric acid solution (9 → 1000) and mix well. Titrate with iodine (0.05 mol/L) VS at a rate of 3-5 ml per minutes until a pale yellow colour persists for 30 seconds. Each ml of iodine (0.05 mol/L) VS is equivalent to 17.57 mg of $C_{13}H_{16}N_3NaO_4S \cdot H_2O$.

Category As described under Metamizole Sodium.

Strength (1) 1 ml : 0.25 g (2) 2 ml : 0.5 g

Storage Preserve in well closed containers, protected from light.

Metamizole Sodium Nasal Drops

Metamizole Sodium Nasal Drops contain not less than 90.0% and not more than 110.0% of the labelled amount of metamizole sodium ($C_{13}H_{16}NaO_4S \cdot H_2O$).

Description A clear, colourless to slightly yellow liquid.

Identification Comply with tests (1) and (2) for Identification as described under Metamizole Sodium.

p value 7.5 - 8.5 (open text)

Colour Not more intense than the reference solution of YG₄ (Appendix IX A, method 1).

Other requirements Comply with the general requirements for Nasal preparations (Appendix I R).

Assay Carry out the method for high performance liquid chromatography (Appendix V D), using a column packed with octadecylsilane bonded silica gel and a mixture of phosphate BS (dissolve 6.8 g of potassium dihydrogen phosphate with 1000 ml of water, adjust pH to 4.5 ± 0.5 with phosphoric acid) - methanol (7 : 3) as the mobile phase. Maintain the column at a temperature of 30°C. Detection wavelength is 265 nm and the number of theoretical plates of the column is not less than 1500, calculated with reference to the peak of metamizole sodium.

Procedure Dilute a quantity of the nasal drops, accurately measured, with a mixture of methanol-water (7 : 3) to produce a solution of 0.4 mg of metamizole sodium per ml. Inject 20 µl of the resulting solution into the column, record the chromatogram. Repeat the operation mentioned above, using metamizole sodium CRS instead of the nasal drops being examined, calculated the content of $C_{13}H_{16}NaO_4S \cdot H_2O$ with respect of the peak area obtained in the chromatogram by the external standard method.

Category As described under Metamizole Sodium.

Strength (1) 1 ml : 0.2 g (2) 3 ml : 0.6 g

Storage Preserve in tightly closed containers, protected from light.

Metamizole Sodium Tablets

Metamizole Sodium Tablets contain not less than 95.0% and not more than 105.0% of the labelled amount of Metamizole Sodium ($C_{13}H_{16}N_3NaO_4S \cdot H_2O$).

Description White or almost white tablets.

Identification Comply with tests (1) and (2) for Identification described under Metamizole Sodium.

Other requirements Comply with the general requirements for tablets (Appendix I A).

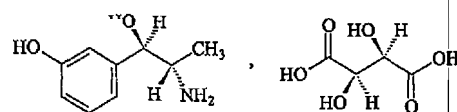
Assay Weigh and powder 10 tablets. Dissolve a quantity of the powder equivalent to about 0.3 g of Metamizole Sodium, accurately weighed, in 10 ml of ethanol and 10 ml of 0.01 mol/L hydrochloric acid solution, titrate immediately with iodine (0.05 mol/L) VS at a rate of 3-5 ml per minute until the colour persists for 30 seconds. Each ml of iodine (0.05 mol/L) VS is equivalent to 17.57 mg of $C_{13}H_{16}N_3NaO_4S \cdot H_2O$.

Category As described under Metamizole Sodium.

Strength (1) 0.25 g (2) 0.5 g

Storage Preserve in tightly closed containers, protected from light.

Metaraminol Bitartrate



$C_9H_{13}NO_2 \cdot C_4H_6O_6$ 317.29

[33402-03-08]

Metaraminol Bitartrate is α -(1-aminoethyl)-3-hydroxy-[R-(R*, S*)]-benzenemethanol and [R-(R*, R*)]-2,3-dihydrobutane-dioate (1 : 1) salt. It contains not less than 98.5% of $C_9H_{13}NO_2 \cdot C_4H_6O_6$, calculated on the dried basis.

Description A white, crystalline powder; almost odourless. Freely soluble in water; slightly soluble in ethanol; insoluble in chloroform or ether.

Melting range 171-176°C (Appendix VI C).

Identification (1) Mix about 5 mg with 2 ml of a saturated solution of ammonium molybdate in sulfuric acid, a blue colour is produced.

(2) Dissolve about 5 mg in 0.5 ml of water, add 2 drops of sodium nitroprusside TS, 2 drops of acetone and 0.2 g of sodium bicarbonate, heat at 60°C in a water bath for 1 minute, a reddish-purple colour is produced.

(3) The light absorption of a solution of 0.10 mg per ml in water exhibits a maximum at 272 nm (Appendix IV A).

(4) The infrared absorption spectrum (Appendix IV C) is concordant with the reference spectrum of metaraminol bitartrate (Appendix XVI).

Acidity Dissolve 1.0 g in 20 ml of water, pH 3.2-3.5 (Appendix VI H).

Loss on drying When dried to constant weight at 105°C, loses not more than 0.5% of its weight (Appendix VIII L).

Residue on ignition Not more than 0.1% (Appendix VIII N).

Assay Dissolve about 0.1 g, accurately weighed, in an iodine flask in 40 ml of water. Add 40 ml of bromine (0.05 mol/L) VS, accurately measured, and 8 ml of hydrochloric acid, insert the stopper tightly and allow to stand for 15 minutes. Slightly remove the stopper, add quickly 8 ml of potassium iodide TS and insert the stopper immediately, shake. Rinse the stopper and the neck of the flask with a small amount of water, add 1 ml of chloroform and shake. Titrate with sodium thiosulfate (0.1 mol/L) VS, adding starch IS towards the end of the titration, until the blue colour

disappear. Perform a blank determination and make any necessary correction. Each ml of bromine (0.05 mol/L) VS is equivalent to 5.288 mg of $C_9H_{13}NO_2 \cdot C_4H_6O_8$.

Category α -Adrenergic receptor stimulant

Storage Preserve in tightly closed containers, protected from light.

Preparation Metaraminol Bitartrate Injection

Metaraminol Bitartrate Injection

Metaraminol Bitartrate Injection is a sterile solution of Metaraminol Bitartrate in Water for Injection. It contains not less than 93.0% and not more than 107.0% of the labelled amount of metaraminol ($C_9H_{13}NO_2$).

Description A clear, colourless liquid.

Identification To 1 ml add 2 drops of sodium nitroprusside TS, 2 drops of acetone and 0.2 g of sodium bicarbonate, heat at 60°C in a water bath for 1 minutes, a reddish-purple colour is produced.

pH value 3.0-4.0 (Appendix VI H).

Other requirements Complies with the general requirements for injections (Appendix I B).

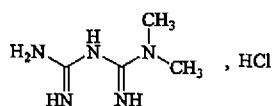
Assay To 5 ml equivalent to about 50 mg of metaraminol, accurately measured, in a 50 ml volumetric flask add water to volume and mix well. Measure accurately 5 ml of this solution to a 100 ml volumetric flask, add water to volume and mix well. Measure the absorbance at 272 nm (Appendix IV A). Calculate the content of $C_9H_{13}NO_2$, taking 111 as the value of A (1%, 1 cm).

Category As described under Metaraminol Bitartrate.

Strength (1) 1 ml : 10 mg of Metaraminol (equivalent to 19 mg of Metaraminol Bitartrate)
(2) 5 ml : 50 mg of Metaraminol (equivalent to 95 mg of Metaraminol Bitartrate)

Storage Preserve in well closed containers, protected from light.

Metformin Hydrochloride



$C_4H_{11}N_5 \cdot HCl$ 165.63

[1115-70-4]

Metformin Hydrochloride is 1, 1-dimethyl-biguanide hydrochloride. It contains not less than 98.5% of $C_4H_{11}N_5 \cdot HCl$, calculated on the dried basis.

Description White crystals or a crystalline powder; odourless. Freely soluble in water; soluble in methanol; slightly soluble in ethanol; insoluble in chloroform or ether.

Melting range 220-225°C (Appendix VI C).

Specific absorbance Measure the absorbance of a solution of about 5 μ g per ml in water at 233 nm (Appendix IV A), the value of A (1%, 1 cm) is 778-818.

Identification (1) Dissolve 10 mg in 10 ml of water and add

10 ml of a mixture of 10% sodium nitroprusside solution-potassium ferrocyanide TS-10% sodium hydroxide solution (prepared by mixing equal volumes of each of the solutions and allowing to stand for 20 minutes). A red colour is produced within 3 minutes.

(2) The infrared absorption spectrum (Appendix IV C) is concordant with the reference spectrum of metformin hydrochloride (Appendix XVI).

(3) The aqueous solution yields reactions characteristic of chlorides (Appendix III).

Related substances Carry out the method for high performance liquid chromatography (Appendix V D), using a column packed with sulfonic acid groups cation-exchange bonded silica gel and 1.7% ammonium dihydrogen phosphate (adjust the pH to 3.0 by phosphoric acid) as the mobile phase. Detection Wavelength is 218 nm. The number of the theoretical plates of the column is not less than 5000, calculated with reference to the peak of dicyandiamide and the resolution factor between the peaks of metformin hydrochloride and dicyandiamide should comply with the requirement. Dissolve a quantity of the substance being examined, weighed accurately, in mobile phase to produce a solution of about 0.5 mg per ml as the test solution (1). Dissolve a quantity of dicyandiamide CRS, weighed accurately, in water to produce a solution of about 0.1 mg per ml as the reference solution (2). Separately measure accurately 0.5 ml each of solution (1) and solution (2) into a 100 ml volumetric flask, dilute with mobile phase to volume, mix well as the reference solution (3). Inject 20 μ l of solution (3) into the column, adjust the attenuation so that the peak height of dicyandiamide in the chromatogram is about 10% of full scale of the chart. Inject separately 10 μ l each of the solution (1) and (3) into the column and record the chromatogram for twice the retention time of the peak of metformin hydrochloride. If there is any peak corresponding to the peak of dicyandiamide in the chromatogram of solution (1), its content is no more than 0.02%. The area of any other secondary peak is not greater than 1/5 of the area of the peak of metformin hydrochloride in the chromatogram of solution (3), the sum of the areas of all secondary peaks is not greater than the area of the peak of metformin hydrochloride of solution (3).

Loss on drying When dried to constant weight at 105°C, loses not more than 0.5% of its weight (Appendix VII L).

Residue on ignition Not more than 0.1% (Appendix VIII N).

Heavy metals Carry out the limit test for heavy metals (Appendix VIII H, method 1), using 1.0 g: not more than 0.002%.

Assay Dissolve about 70 mg, accurately weighed, in 10 ml of glacial acetic acid and 5 ml of mercuric acetate TS, add 2 drops of naphtholbenzein IS, titrate with perchloric acid (0.1 mol/L) VS until the colour changes to yellowish-green. Perform a blank determination and make any necessary correction. Each ml of perchloric acid (0.1 mol/L) VS is equivalent to 8.282 mg of $C_4H_{11}N_5 \cdot HCl$.

Category Hypoglycemic agent.

Storage Preserve in tightly closed containers.

Preparation Metformin Hydrochloride Tablets

Metformin Hydrochloride Tablets

Metformin Hydrochloride Tablets contain not less than 95.0% and not more than 105.0% of the

labelled amount of metformin hydrochloride ($C_4H_{11}N_5 \cdot HCl$).

Description Sugar or film coated tablets with white core.

Identification (1) To a quantity of powdered tablets, equivalent to about 50 mg of metformin hydrochloride, add 10 ml of water to dissolve metformin hydrochloride and filter, the filtrate complies with the tests (1) and (3) for Identification described under Metformin Hydrochloride. (2) The light absorption of the solution obtained in the Assay exhibits a maximum at 233 nm (Appendix IV A).

Dissolution Carry out dissolution test (Appendix X C, method 1), using 1000 ml of water as the dissolution medium, adjust the rotational speed of the basket to 100 rpm. Withdraw 10 ml of the solution after exactly 45 minutes and filter. Transfer 2 ml of the filtrate, accurately measured, to a 100 ml volumetric flask and dilute with water to volume. Measure the absorbance of the resulting solution at 233 nm (Appendix IV A). Calculate the dissolution of $C_4H_{11}N_5 \cdot HCl$ from each tablet, taking 798 as the value of A (1%, 1 cm); not less than 70% of the labelled amount is dissolved.

Related substances Carry out the method as described under Related substances in Metformin Hydrochloride. Transfer a quantity of the powdered tablet equivalent to about 50 mg of metformin hydrochloride, to a 100 ml volumetric flask, add a quantity of mobile phase and make metformin hydrochloride dissolved by ultrasonical treatment, dilute with mobile phase to volume, mix well and filter, take the successive filtrate as the test solution (1). Dissolve a quantity of dicyandiamide CRS, weighed accurately, in water to produce a solution of about 0.1 mg per ml as the reference solution (2). Separately measure accurately 0.5 ml each of solution (1) and solution (2) into a 100 ml volumetric flask, dilute with mobile phase to volume, mix well as the reference solution (3). If there is any peak corresponding to the peak of dicyandiamide in the chromatogram of solution (1), its content is no more than 0.10%. The area of any other secondary peak is not greater than the area of the peak of metformin hydrochloride in the chromatogram of solution (3), the sum of the areas of all secondary peaks is not greater than three times of the area of the peak of metformin hydrochloride of solution (3).

Other requirements Comply with the general requirements for tablets (Appendix I A).

Assay Weigh accurately and powder 20 tablets. To a quantity of the powdered tablets, equivalent to about 10 mg of metformin hydrochloride, accurately weighed, in a 100 ml volumetric flask add 75 ml of water, shake thoroughly for 15 minutes to dissolve metformin hydrochloride, dilute with water to volume and mix well. Filter, transfer 5 ml of the successive filtrate, accurately measured, to another 100 ml volumetric flask, dilute with water to volume and mix well. Measure the absorbance of the resulting solution at 233 nm (Appendix IV A). Calculate the content of $C_4H_{11}N_5 \cdot HCl$, taking 798 as the value of A (1%, 1 cm).

Category As described under Metformin Hydrochloride.

Strength 0.25 g

Storage Preserve in tightly closed containers.

Methacrylic Acid Copolymer I

Methacrylic acid copolymer I is a copolymer of methyl methacrylate, ethyl acrylate and trimethyl

ammonium chloride ethyl methacrylate in a ratio of 60 : 30 : 10.

Description Slightly white, translucent or transparent solid with different shape and size. Soluble in boiling water or acetone; practically insoluble in isopropanol.

Refractive index Dissolve 1.25 g in 10 ml of isopropanol-acetone (6 : 4), the refractive index is 1.380-1.385 (Appendix VI F).

Viscosity Dissolve 6.0 g in 100 ml of 75% ethanol solution, the kinematic viscosity at 20°C is not more than 0.015 Pa · s, using a rotating viscosimeter with a No. 0 rotator (Appendix VI G) at the speed of 30 rpm.

Alkaline value Dissolve 1 g, previously dried to constant weight at 110°C (for about 5 hours) and accurately weighed, in 25 ml of dichloromethane, add 50 ml of glacial acetic acid and 5 ml of mercuric acetate TS, mix well and add 3 drops of quinidine red IS, titrate with perchloric acid (0.1 mol/L) VS until the colour of the solution changes from red to colourless. Perform a blank determination and make any necessary correction. Each ml of perchloric acid (0.1 mol/L) VS is equivalent to 5.61 mg of KOH. The value is 23.9-32.3 mg/g, calculated on the dried basis.

Identification The infrared absorption spectrum (Appendix IV C) is concordant with the spectrum of methacrylic acid copolymer I (Appendix XVI).

Related substances Dissolve a quantity of the substance being examined, accurately weighed, in methanol to produce a solution of 1 mg per ml as test solution; Dissolve an accurately weighed quantity of methacrylic acid CRS, ethyl acrylate CRS and methyl methacrylate CRS in methanol to produce a reference solution of each 3 µg per ml. Carry out the method for high performance liquid chromatography (Appendix V D), using a column packed with octadecylsilane bonded silica gel and a mixture of methanol-phosphate buffer [dissolve 3.55 g of disodium hydrogen phosphate (Na_2HPO_4) and 3.40 g of potassium dihydrogen phosphate (KH_2PO_4) in 1000 ml of water, and adjust the pH to 2.0 with phosphoric acid] (2 : 8) as the mobile phase. Detection wavelength is 202 nm and the number of the theoretical plates of the column is not less than 1000, calculated with reference to the peak of methacrylic acid and the resolution factor between the peaks of ethyl acrylate and methyl methacrylate complies with the related requirements. Inject separately 20 µl each of the test solution and the reference solution into the column, and record the chromatograms. Calculate the content of each monomer impurity separately with respect to the peak area obtained in the chromatogram by the external standard method. The sum of contents is not more than 0.3%.

Loss on drying When dried at 110°C for 6 hours, loses not more than 5.0% of its weight (Appendix VIII L).

Residue on ignition Not more than 0.3% (Appendix VIII N), using 1.0 g.

Heavy metals Carry out the limit test for heavy metals (Appendix VIII H, method 2), using the residue obtained in the test for residue on ignition; not more than 0.003%.

Arsenic Transfer 1.0 g to a 150 ml conical flask, add 5 ml of sulfuric acid, heat until the substance is thoroughly charred, add concentrated hydrogen peroxide solution dropwise (if a lot of foam is involved, stop heating and rotate the conical flask to prevent the unreacted substance conglomerating at the bottom) until the solution is colourless. Allow to cool, add cautiously 10 ml of water, heat again until sulfur trioxide is evolved, cool and add

slowly 5 ml of hydrochloride acid and a quantity of water to produce 28 ml. Carry out the limit test for arsenic (Appendix VIII J, method 1); not more than 0.0002%.

Category Pharmaceutical aid.

Storage Preserve in tightly closed containers, and stored at a cool place.

Methacrylic Acid Copolymer II

Methacrylic acid copolymer II is a copolymer of methyl methacrylate, ethyl acrylate and trimethyl ammonium chloride ethyl methacrylate in a ratio of 65 : 30 : 5.

Description Slightly white, translucent or transparent solid with different shape and size. Sparingly soluble in acetone; practically insoluble in boiling water or isopropanol.

Refractive index Dissolve 1.25 g in 10 ml of isopropanol-acetone (6 : 4), the refractive index is 1.380-1.385 (Appendix VI F).

Viscosity Dissolve 6.0 g in 100 ml of 75% ethanol solution, the kinematic viscosity at 20°C is not more than 0.015 Pa. s, using a rotating viscosimeter with a No. 0 rotator (Appendix VI G, method 2) at the speed of 30 rpm.

Alkaline value Dissolve 1 g, previously dried to constant weight at 110°C (for about 5 hours) and accurately weighed, in 25 ml of dichloromethane, add 50 ml of glacial acetic acid, 5 ml of mercuric acetate TS, mix and add 3 drops of quinaldine red IS, titrate with perchloric acid (0.1 mol/L) VS until the colour of the solution changes from red to colourless. Perform a blank determination and make any necessary correction. Each ml of perchloric acid (0.1 mol/L) VS is equivalent to 5.61 mg of KOH. The value is 12.1-18.3 mg/g, calculated on the dried basis.

Identification The infrared absorption spectrum (Appendix IV C) is concordant with the spectrum of methacrylic acid copolymer (Appendix XVI).

Related substances Dissolve a quantity of the substance being examined, accurately weighed, in methanol to produce a solution of 1 mg per ml as test solution; Dissolve an accurately weighed quantity of methacrylic acid CRS, ethyl acrylate CRS and methyl methacrylate CRS in methanol to produce a reference solution of each 3 µg per ml. Carry out the method for high performance liquid chromatography (Appendix V D), using a column packed with octadecylsilane bonded silica gel and a mixture of methanol-phosphate buffer [dissolve 3.55 g of disodium hydrogen phosphate (Na_2HPO_4) and 3.40 g of potassium dihydrogen phosphate (KH_2PO_4) in 1000 ml of water, and adjust the pH to 2.0 with phosphoric acid] (2 : 8) as the mobile phase. Detection wavelength is 202 nm and the number of the theoretical plates of the column is not less than 1000, calculated with reference to the peak of methacrylic acid and the resolution factor between the peaks of ethyl acrylate and methyl methacrylate complies with the related requirements. Inject separately 20 µl each of the test solution and the reference solution into the column, and record the chromatograms. Calculate the content of each monomer impurity separately with respect to the peak area obtained in the chromatogram by the external standard method. The sum of contents is not more than 0.3%.

Loss on drying When dried at 110°C for 6 hours, loses not more than 5.0% of its weight (Appendix VIII L).

Residue on ignition Not more than 0.3% (Appendix VIII

N), using 1.0 g.

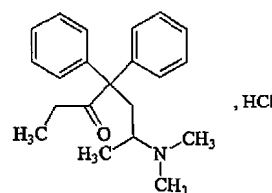
Heavy metals Carry out the limit test for heavy metals (Appendix VIII H, method 2), using the residue obtained in the test for residue on ignition; not more than 0.003%.

Arsonic Transfer 1.0 g to a 150 ml conical flask, add 5 ml of sulfuric acid, heat until the substance is thoroughly charred, add concentrated hydrogen peroxide solution dropwise (if a lot of foam is involved, stop heating and rotate the conical flask to prevent the unreacted substance conglomerating at the bottom) until the solution is colourless. Allow to cool, add cautiously 10 ml of water, heat again until sulfur trioxide is evolved, cool and add slowly 5 ml of hydrochloride acid and a quantity of water to produce 28 ml. Carry out the limit test for arsenic (Appendix VIII J, method 1); not more than 0.0002%.

Category Pharmaceutical aid.

Storage Preserve in tightly closed containers, and stored at a cool place.

Methadone Hydrochloride



$\text{C}_{21}\text{H}_{27}\text{NO} \cdot \text{HCl}$ 345.91

[1095-90-5]

Methadone Hydrochloride is 6-(dimethylamino)-4,4-diphenyl-3-heptanone hydrochloride. It contains not less than 98.5% of $\text{C}_{21}\text{H}_{27}\text{NO} \cdot \text{HCl}$, calculated on the dried basis.

Description A colourless crystal or white crystalline powder; odourless.

Freely soluble in ethanol or chloroform; soluble in water; practically insoluble in ether.

Melting range 230-234°C (Appendix VI C).

Identification (1) Dissolve 50 mg in 5 ml of water, add sodium hydroxide TS to make alkaline; a precipitate is produced. Filter, wash with water for several times and dry it in vacuum over sulfuric acid, the melting point is about 76°C (Appendix VI C).

(2) Dissolve 10 mg in 2 ml of water, add 2 ml of methyl orange IS; a yellow precipitate is produced.

(3) The aqueous solution yields the reactions characteristic of chlorides (Appendix III).

Acidity Dissolve 0.20 g in 20 ml of water, pH 4.5-6.5 (Appendix VI H).

Loss on drying When dried to constant weight at 105°C, loses not more than 0.5% of its weight (Appendix VIII L).

Residue on ignition Not more than 0.1% (Appendix VIII N).

Heavy metals Dissolve 0.50 g in 15 ml of water add 2 ml of acetate buffer (pH 3.5) and sufficient water to produce 25 ml. Carry out the limit test for heavy metals (Appendix VIII H, method 1); not more than 0.002%.

Assay To about 0.15 g, accurately weighed, in a separator add 50 ml of water and 5 ml of sodium hydroxide TS, then extract with ether for 4 times (40 ml, 20 ml, 15 ml and 15 ml). Combine the ether extracts, wash twice with water.

each of 5 ml. Combine the washings, extract with 10 ml of ether. Combine all the ether extracts, add accurately 30 ml of sulfuric acid (0.01 mol/L) VS, mix well. Evaporate ether at a low temperature, allow it to cool to room temperature, add 2 drops of methyl red IS and titrate with sodium hydroxide (0.02 mol/L) VS. Each ml of sulfuric acid (0.01 mol/L) VS is equivalent to 6.918 mg of $C_{21}H_{27}NO \cdot HCl$.

Category Analgesic.

Storage Preserve in tightly closed containers.

Preparation (1) Methadone Hydrochloride Injection
(2) Methadone Hydrochloride Tablets

Methadone Hydrochloride Injection

Methadone Hydrochloride Injection is a sterile solution of Methadone Hydrochloride in Water for Injection. It contains not less than 95.0% and not more than 105.0% of the labelled amount of methadone hydrochloride ($C_{21}H_{27}NO \cdot HCl$).

Description A clear, colourless liquid.

Identification Complies with tests (1) and (2) for Identification described under Methadone hydrochloride.

pH value 4.5-6.5 (Appendix VI H).

Other requirements Complies with the general requirements for injections (Appendix I B).

Assay Measure accurately a quantity equivalent to 50 mg of methadone hydrochloride in a separator. Carry out the Assay described under Methadone Hydrochloride beginning at the words "add 5 ml of sodium hydroxide TS...". Each ml of sulfuric acid (0.01 mol/L) VS is equivalent to 6.918 mg of $C_{21}H_{27}NO \cdot HCl$.

Category As described under Methadone Hydrochloride.

Strength 1 ml : 5 mg

Storage Preserve in well closed containers.

Methadone Hydrochloride Tablets

Methadone Hydrochloride Tablets contain not less than 90.0% and not more than 110.0% of labelled amount of methadone hydrochloride ($C_{21}H_{27}NO \cdot HCl$).

Description White tablets.

Identification Triturate a quantity of the powdered tablets equivalent to about 60 mg of methadone hydrochloride with 10 ml of warm ethanol, filter and evaporate the filtrate on a water bath to dryness. The residue complies with the tests for identification (1) and (2) described under Methadone Hydrochloride.

Other requirements Comply with the general requirements for tablets (Appendix I A).

Assay Weigh and powder 50 tablets. To a quantity of the powdered tablets equivalent to 50 mg of methadone hydrochloride, accurately weighed, in a separator add 20 ml of water. Carry out the Assay described under Methadone Hydrochloride, beginning at the words "add 5 ml of sodium hydroxide TS...". Each ml of sulfuric acid (0.01 mol/L) VS is equivalent to

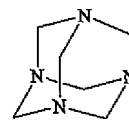
6.918 mg of $C_{21}H_{27}NO \cdot HCl$.

Category As described under Methadone Hydrochloride.

Strength 2.5 mg

Storage Preserve in tightly closed containers.

Methenamine



$C_6H_{12}N_4$ 140.19

Methenamine is hexamethylenetetramine. It contains not less than 99.0% of $C_6H_{12}N_4$, calculated on the dried basis.

Description Colourless lustrous crystals or a white crystalline powder; almost odourless; taste, sweet then bitter. When brought into contact with fire, it burns with a smokeless flame; its aqueous solution exhibits alkaline reaction. Freely soluble in water; soluble in ethanol or chloroform; slightly soluble in ether.

Identification (1) Dissolve 0.5 g in 5 ml of dilute sulfuric acid and heat, a formaldehyde odour is perceptible which darkens paper moistened with silver nitrate TS. Add an excess of sodium hydroxide TS, ammonia is produced which changes moist red litmus paper to blue.
(2) The infrared absorption spectrum (Appendix IV C) is concordant with the reference spectrum of methenamine (Appendix XVI).

Chloride Carry out the limit test for chlorides (Appendix VII A), using 2.5 g. Any opalescence produced is not more pronounced than that of a reference solution using 5.0 ml of sodium chloride standard solution (0.002%).

Ammonium salts and paraformaldehyde Dissolve 0.50 g in 10 ml of ammonia-free distilled water, add 1.0 ml of alkaline mercuric potassium iodide TS immediately, mix well and allow to stand for 2 minutes at 20-25°C. Any colour produced is not more intense than that of a reference solution prepared by mixing 1.0 ml of alkaline mercuric potassium iodide TS with 10 ml of ammonia-free distilled water; any opalescence produced is not more pronounced than that of a reference suspension prepared by mixing well (0.60 ml of potassium sulfate standard solution and 7 ml of water with 1 ml of dilute hydrochloric acid, and 2 ml of 25% barium chloride solution and allow to stand for 10 minutes).

Loss on drying When dried over sulfuric acid to constant weight, loses not more than 1.5% of its weight (Appendix VIII L).

Heavy metals Dissolve 4.0 g in 20 ml of water, filter if necessary, add a few drops of ammonia TS to the filtrate and dilute to 25 ml with water. Carry out the limit test for heavy metals (Appendix VIII H, method 3); not more than 0.0005%.

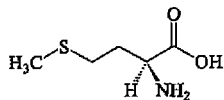
Assay Dissolve 0.5 g, accurately weighed, in 10 ml of water, add 50 ml of sulfuric acid (0.25 mol/L) VS accurately measured, and mix well. Heat to boiling until formaldehyde odour is expelled with adding water from time to time to compensate the evaporated water. Cool the resulting solution to room temperature, add 2 drops of methyl red IS, titrate with sodium hydroxide (0.5 mol/L)

VS. Perform a blank determination and make any necessary correction. Each ml of sulfuric acid (0.25 mol/L) VS is equivalent to 17.52 mg of $C_6H_{12}N_4$.

Category Antiseptic, Disinfectant.

Storage Preserve in tightly closed containers.

Methionine



$C_5H_{11}NO_2S$ 149.21

Methionine is (S)-2-amino-4-(methylthio) butanoic acid. It contains not less than 98.5% of $C_5H_{11}NO_2S$, calculated on the dried basis.

Description White crystals or crystalline powder; odour, characteristic.

Soluble in water, very slightly soluble in ethanol, insoluble in ether, freely soluble in dilute hydrochloric acid or sodium hydroxide solutions.

Specific optical rotation +21.0° to +25.0°, in a solution of 20 mg per ml in 6 mol/L hydrochloric acid solution (Appendix VI E).

Identification The infrared absorption spectrum (Appendix IV C) is concordant with the reference spectrum of Methionine (Appendix XVI).

Acidity Dissolve 0.5 g in 50 ml of water, pH 5.6-6.1 (Appendix VI H).

Transmittance of solution Dissolve 0.5 g in 20 ml of water, the transmittance at 430 nm is not less than 98.0% (Appendix IV A).

Chloride Carry out the limit test for chloride (Appendix VIII A), using 0.30 g. Any opalescence produced is not more pronounced than that of a reference solution using 6.0 ml of sodium chloride standard solution (0.02%).

Sulfate Carry out the limit test for sulfate (Appendix VIII B), using 1.0 g. Any opalescence produced is not more pronounced than that of a reference solution using 2.0 ml of potassium sulfate standard solution (0.02%).

Ammonium Carry out the limit test for ammonium (Appendix VIII K), using 0.10 g. Any colour produced is not more intense than that of a reference solution using 2.0 ml of ammonium chloride standard solution (0.02%).

Other amino acids Carry out the method for thin-layer chromatography (Appendix V B), using silica gel G as the coating substance and *n*-butanol-glacial acetic acid-water (4 : 1 : 5) as the mobile phase. Apply to the plate 5 µl of a solution of the substance being examined in water containing 10 mg per ml. After developing and removal of the plate, dry it in air, spray with ninhydrin solution (dissolve 1 g ninhydrin in 50 ml of acetone), heat at 90°C until the colour is produced and examine immediately. There is only one purple spot in the chromatogram.

Loss on drying When dried at 105°C for 3 hours, loses not more than 0.2% of its weight (Appendix VIII L).

Residue on ignition Not more than 0.1% (Appendix VIII N).

Iron Carry out the limit test for iron (Appendix VIII G), using 1.0 g. Any colour produced is not more intense than

that of a reference solution using 1.5 ml of iron standard solution (0.0015%).

Heavy metals Dissolve 0.50 g in 23 ml of water, add 2 ml of acetate BS (pH 3.5). Carry out the limit test for heavy metals (Appendix VIII H, method 1); not more than 0.001%.

Arsenic Dissolve 2.0 g in 23 ml of water, add 5 ml of hydrochloric acid, carry out the limit test for arsenic (Appendix VIII J, method 1); not more than 0.0001%.

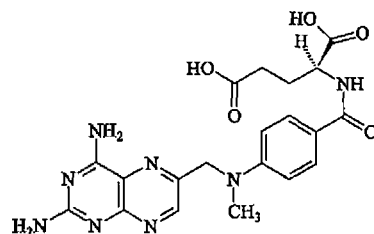
Bacterial endotoxin Carry out the test for bacterial endotoxin (Appendix XI E); less than 0.025 EU per mg of methionine (for parenteral administration).

Assay Dissolve about 0.13 g, accurately weighed, in 3 ml of dehydrated formic acid, and 50 ml of glacial acetic acid. Carry out the method for potentiometric titration (Appendix VII A), titrate with perchloric acid (0.1 mol/L) VS. Perform a blank determination and make any necessary correction. Each ml of perchloric acid (0.1 mol/L) VS is equivalent to 14.92 mg of $C_5H_{11}NO_2S$.

Category Amino acid.

Storage Preserve in tightly closed containers.

Methotrexate



$C_{20}H_{22}N_8O_5$ 454.45

[59-05-2]

Methotrexate is a mixture of 4-amino-10-methylfolate acid and closely related compounds, consists chiefly of *N*-[4-[[[(2,4-diamino-6-pteridinyl) methyl] methylamino] benzoyl]-L-glutamate. It contains not less than 90.0% of $C_{20}H_{22}N_8O_5$, calculated on the dried basis.

Description An orange-yellow crystalline powder. Practically insoluble in water, ethanol, chloroform or ether; freely soluble in dilute alkali hydroxides solutions; soluble in dilute hydrochloric acid.

Identification (1) Dissolve 5 mg in 1 ml of 0.5% ammonium carbonate solution, dilute with hydrochloric acid solution (9→1000) to produce a solution of 10 µg per ml. The light absorption of the solution exhibits two maxima at 244 nm and 306 nm, and two minima at 234 nm and 262 nm (Appendix IV A).

(2) The infrared absorption spectrum (Appendix IV C) is concordant with the reference spectrum of methotrexate (Appendix XVI).

Loss on drying When dried in vacuum, over phosphorus pentoxide to constant weight at 100°C, loses not more than 12.0% of its weight (Appendix VIII L).

Assay Carry out the method of high performance liquid chromatography (Appendix V B) with an octadecylsilane bonded silica gel column, using a mixture of acetonitrile-7.0% citric acid solution-2.0% disodium hydrogen phosphate (anhydrous) solution (10 : 10 : 80) as the mobile phase.

The wavelength of the detector is 302 nm. The number of theoretical plates of the column is not less than 1000, calculated with reference to the peak of methotrexate; the resolution factor between the peaks of methotrexate and folic acid is not less than 8.0.

Dissolve an accurately weighed quantity of the substance being examined and methotrexate CRS separately in the mobile phase to produce solutions of 0.1 mg per ml. Inject 10 μ l each of the solutions into the column. Calculate the content of $C_{20}H_{22}N_8O_5$ with respect to the peak area obtained in the chromatogram by the external standard method.

Category Antineoplastic.

Storage Preserve in tightly closed containers, protected from light and stored in a cool place.

Preparation (1) Methotrexate for Injection
(2) Methotrexate Tablets

Methotrexate for Injection

Methotrexate for Injection is a sterile, lyophilized preparation of the sodium salt of Methotrexate and a quantity of sodium chloride. It contains not less than 85.0% and not more than 110.0% of the labelled amount of Methotrexate ($C_{20}H_{22}N_8O_5$).

Description A yellow or brownish yellow, friable mass or powder.

Identification Complies with test (1) for Identification described under Methotrexate.

Alkalinity Dissolve the contents of 5 containers separately in 2 ml portions of water, combine the solutions and mix well, pH 7.0-9.0 (Appendix VI H).

Loss on drying When dried in vacuum over phosphorous pentoxide to constant weight at 100°C, loses not more than 5.0% of its weight (Appendix VIII L).

Content uniformity Dissolve the contents of 10 containers individually in 1 ml of water and dilute with hydrochloric acid solution (9→1000) to produce a solution of about 10 μ g per ml. Measure the absorbances of the resulting solutions at 306 nm (Appendix IV A). Compare the absorbance of the content of each container with the average absorbance of the contents of 10 containers. Not more than 1 individual absorbance deviates from the average absorbance by a value greater than $\pm 15\%$; and none of the deviation is greater than $\pm 25\%$ (for strength 5 mg).

Sterility Dissolve the contents individually in sterile water to produce a solution of 2.5 mg per ml, the solution complies with the test for sterility (Appendix XI H).

Other requirements Complies with the general requirements for injections (Appendix I B).

Assay Dissolve an accurately weighed quantity of the contents obtained in the test for weight variation of contents in mobile phase to produce a solution of about 0.1 mg per ml (for strength 100 mg) or dissolve the contents of 5 containers in mobile phase in a 250 ml volumetric flask, dilute to volume and mix well (for strength 5 mg). Carry out the Assay described under Methotrexate, using the resulting solution.

Category As described under Methotrexate.

Strength (1) 5 mg (2) 100 mg

Storage Preserve in well closed containers, protected from light and stored in a cool place.

Methotrexate Tablets

Methotrexate Tablets contain not less than 85.0% and not more than 110.0% of the labelled amount of methotrexate ($C_{20}H_{22}N_8O_5$).

Description Slightly orange-yellow tablets.

Identification Comply with test (1) for Identification described under Methotrexate.

Content uniformity Triturate 10 tablets individually with 2.5 ml of dilute ammonia solution (to 10 ml of water add 2 drops of concentrated ammonia solution) for 5 minutes (protect from strong light); transfer to a 50 ml volumetric flask with a quantity of water and add water to volume, mix well and filter. Measure accurately 5 ml of the successive filtrate to a 25 ml volumetric flask, add 5 ml of (0.5 mol/L) hydrochloric acid solution and then add water to volume, mix well. Measure the absorbance of the resulting solution at 306 nm (Appendix IV A). Compare the absorbance of each tablet with the average absorbance of 10 tablets. Not more than 1 individual absorbance deviates from the average absorbance by a value greater than $\pm 15\%$; and none of the deviation is greater than $\pm 25\%$.

Dissolution Carry out the dissolution test (Appendix X C, method 2), using 900 ml of hydrochloric acid solution (9→1000) as the dissolution medium. Adjust the rotational speed of the paddle to 50 rpm. Withdraw a quantity of the solution after exactly 45 minutes and filter. Measure the absorbances of the successive filtrate and that of methotrexate CRS solution at 306 nm (Appendix IV A). Calculate the dissolution of $C_{20}H_{22}N_8O_5$ from each tablet, not less than 75% of the labelled amount is dissolved.

Other requirements Comply with the general requirements for tablets (Appendix I A).

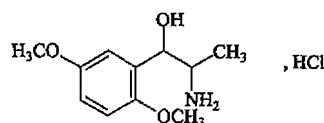
Assay Weigh accurately and powder 10 tablets. To an accurately weighed quantity of the powder, equivalent to about 10 mg of methotrexate in 25 ml volumetric flask add 20 ml of the mobile phase, dissolve methotrexate by ultrasonic treatment, dilute to volume with mobile phase, mix well and filter. Inject 10 μ l of the successive filtrate into the column. Complete the Assay described under Methotrexate.

Category As described under Methotrexate.

Strength 2.5 mg

Storage Preserve in tightly closed containers, protected from light.

Methoxamine Hydrochloride



$C_{11}H_{17}NO_3 \cdot HCl$ 247.72

[61-16-5]

Methoxamine Hydrochloride is α -(1-aminoethyl)-2,5-dimethoxy-benzenemethanol hydrochloride. It contains not less than 99.0% of $C_{11}H_{17}NO_3 \cdot HCl$, calculated on the dried basis.

Description White crystals or a crystalline powder; odourless or

almost odourless; taste, bitter.

Freely soluble in water; soluble in ethanol; practically insoluble in chloroform or ether.

Melting range 214-219°C, with decomposition (Appendix VI C).

Specific absorbance Measure the absorbance of a solution of 30 µg per ml in water at 290 nm (Appendix IV A), the values of A (1%, 1 cm) is 133-141.

Identification (1) To 1 mg add 3 drops of formaldehyde-sulfuric acid TS; a purple colour is produced changing slowly to brown and then to green.

(2) To 20 mg add 2 ml of water and 0.5 ml of silver nitrate TS; a white curdy precipitate is produced, which is soluble in ammonia TS but insoluble in nitric acid.

(3) The infrared absorption spectrum (Appendix IV C) is concordant with the reference spectrum of methoxamine hydrochloride (Appendix XVI).

Acidity Dissolve 0.20 g in 10 ml of water, pH 4.5-6.0 (Appendix VI H).

Ketonic amine The light absorbance of a solution of 1.5 mg per ml in water at 347 nm (Appendix IV A) is not greater than 0.06.

Loss on drying When dried at 105°C for 2 hours, loses not more than 0.5% of its weight (Appendix VIII L).

Residue on ignition Not more than 0.2% (Appendix VIII N).

Assay Dissolve about 0.2 g, accurately weighed, in 10 ml of glacial acetic acid and 5 ml of mercuric acetate TS by warming, if necessary, add 10 drops of naphtholbenzein IS, titrate with perchloric acid (0.1 mol/L) VS until the colour changes to yellowish-green. Perform a blank determination and make any necessary correction. Each ml of perchloric acid (0.1 mol/L) VS is equivalent to 24.77 mg of $C_{11}H_{17}NO_3 \cdot HCl$.

Category α-Adrenergic receptor stimulant.

Storage Preserve in tightly closed containers.

Preparation Methoxamine Hydrochloride Injection

Methoxamine Hydrochloride Injection

Methoxamine Hydrochloride Injection is a sterile solution of Methoxamine Hydrochloride in Water for Injection. It contains not less than 95.0% and not more than 105.0% of the labelled amount of methoxamine hydrochloride ($C_{11}H_{17}NO_3 \cdot HCl$).

Description A clear, colourless liquid.

Identification (1) Evaporate 2-3 drops to dryness in a porcelain dish, cool, add 3 drops of formaldehyde-sulfuric acid TS; a purple colour is produced, changing slowly to brown and finally to green.

(2) To 1 ml, add 0.5 ml of silver nitrate TS; a white curdy precipitate is produced, which is soluble in ammonia TS but insoluble in nitric acid.

pH value 3.0-5.5 (Appendix VI H).

Other requirements Complies with the general requirements for injections (Appendix I B).

Assay Measure accurately a quantity equivalent to about 100 mg of methoxamine hydrochloride to a 250 ml volumetric flask, dilute with water to volume and mix well. Measure accurately 10 ml to a 100 ml volumetric flask, dilute with

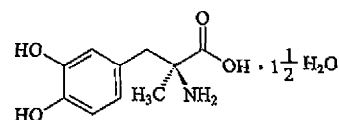
water to volume and mix well. Measure the absorbance of the resulting solution at 290 nm (Appendix IV A) and calculate the content of $C_{11}H_{17}NO_3 \cdot HCl$, taking 137 as the value of A (1%, 1 cm).

Category As described under Methoxamine Hydrochloride.

Strength (1) 1 ml : 10 mg (2) 1 ml : 20 mg

Storage Preserve in well closed containers.

Methyldopa



$C_{10}H_{13}NO_4 \cdot 1 \frac{1}{2} H_2O$ 238.24

[41372-08-1]

Methyldopa is L-3 (3,4-dihydroxyphenyl)-2-methylalanine sesquihydrate. It contains not less than 98.0% of $C_{10}H_{13}NO_4$, calculated on the dried basis.

Description A white or almost white crystalline powder; odourless.

Sparingly soluble in water; slightly soluble in ethanol; very slightly soluble in ether; freely soluble in dilute hydrochloric acid.

Specific optical rotation -25° to -30° , in a solution of 44 mg per ml of aluminium trichloride solution (to 65 g of aluminium trichloride hexahydrate, add water to 100 ml and 0.5 g of active carbon, shake for 10 minutes, filter and adjust the pH of the filtrate to 1.5 with 1% sodium hydroxide solution) (Appendix VI E).

Identification (1) The light absorption of a solution of 0.04 mg per ml in 0.1 mol/L hydrochloric acid solution exhibits maximum at 280 nm; the absorbance is about 0.48 (Appendix IV A)

(2) To about 10 mg add 3 drops of ninhydrin TS, a deep purple colour is produced on standing.

Acidity Dissolve 1.0 g in 100 ml of freshly boiled and cooled water, add 1 drop of methyl red IS, the red colour produced, becomes yellow on the addition of 0.5 ml of sodium hydroxide (0.1 mol/L) VS.

Chloride Carry out the limit test for chlorides (Appendix VIII A), using 0.25 g. Any opalescence produced is not more pronounced than that of a reference solution using 7.0 ml of sodium chloride standard solution (0.028%).

Related substances Carry out the method for thin-layer chromatography (Appendix V B), using silica gel HF₂₅₄ as the coating substance and a mixture of n-butanol-glacial acetic acid-water (65 : 15 : 25) as the mobile phase. Apply separately to the plate 20 µl each of two solutions in methanol containing (1) 10 mg per ml (2) 0.1 mg per ml of the substance being examined. After developing and removal of the plate, dry in air and spray with p-nitroaniline solution [to 0.3 g of p-nitroaniline add a mixture of 100 ml of hydrochloric acid solution (9→10) and 5% sodium nitrite (9 : 1)], dry in air, then spray with 25% sodium carbonate solution, any spot, other than the principal spot, obtained with solution (1) is not more intense than the principal spot obtained with solution (2).

Loss on drying When dried to constant weight at 125 °C, loses 10.0%-13.0% of its weight (Appendix VIII L).

Residue on ignition Not more than 0.1% (Appendix VIII N), using 1.0 g.

Heavy metals Carry out the limit test for heavy metals (Appendix VIII H, method 2), using the residue obtained under Residue on ignition; not more than 0.001%.

Assay Dissolve about 0.15 g, accurately weighed, in 20 ml of glacial acetic acid, add 1 drop of crystal violet IS, titrate with perchloric acid (0.1 mol/L) VS until the colour changes to bluish-green. Perform a blank determination and make any necessary correction. Each ml of perchloric acid (0.1 mol/L) VS is equivalent to 21.12 mg of $C_{10}H_{13}NO_4$.

Category Antihypertensive.

Storage Preserve in tightly closed containers, protected from light.

Preparation Methyldopa Tablets

Methyldopa Tablets

Methyldopa Tablets contain not less than 95.0% and not more than 105.0% of the labelled amount of methyldopa ($C_{10}H_{13}NO_4$).

Description Sugar coated tablets with white core.

Identification (1) Dissolve a quantity of the powdered tablets in 0.1 mol/L hydrochloric acid solution to produce a solution of methyldopa of 0.04 mg per ml and filter. The light absorption of the filtrate exhibits a maximum at 280 nm (Appendix IV A).

(2) To a quantity of powdered tablets equivalent to about 10 mg of methyldopa add a few drops of ninhydrin TS, a deep purple is produced gradually on heating.

Dissolution Carry out dissolution test (Appendix X C, method 1), using 900 ml of hydrochloric acid solution (9→1000) as dissolution medium, adjust the rotational speed of the basket to 100 rpm. Withdraw a quantity of the solution after exactly 45 minutes and filter. Dilute 2 ml of the successive filtrate, accurately measured, with dissolution medium to 10 ml and mix well. Dissolve methyldopa CRS, in hydrochloric acid solution (9→1000) to produce a solution of 0.04 mg per ml. Measure the absorbances of the resulting solutions at 280 nm (Appendix IV A). Calculate the dissolution of $C_{10}H_{13}NO_4$ from each tablet, not less than 70% of the labelled amount is dissolved.

Other requirements Comply with the general requirements for tablets (Appendix I A).

Assay Weigh accurately and powder 10 tablets with sugar coating removed. Transfer a quantity of the powder equivalent to about 0.1 g of methyldopa, accurately weighed, in a 100 ml volumetric flask, add a quantity of 0.05 mol/L sulfuric acid solution, shake to dissolve methyldopa, dilute with 0.05 mol/L sulfuric acid solution to volume, mix well and filter. Measure accurately 5 ml of successive filtrate into another 100 ml volumetric flask, add 2 ml of citric acid ferrous sulfate solution [Dissolve 1 g of sodium pyrosulfite in 200 ml of water, add 1 ml of hydrochloric acid (1 mol/L) VS, 1.5 g of ferrous sulfate and 10 g of sodium citrate, shake thoroughly. Be prepared freshly] and 8 ml of amino acetate BS [Shake 42 g of sodium bicarbonate and 50 g of potassium bicarbonate with 180 ml of water as solution 1. Dissolve 37.5 g of amino acetic acid in 15 ml of concentrated ammonia TS and 180 ml of water as solution 2. Mix the two solutions, make up to 500 ml with water], add water to volume and mix well. Weigh accurately 0.1 g of methyldopa CRS in 100 ml volumetric

flask, dilute with 0.05 mol/L sulfuric acid solution to the volume and mix well. Transfer 5 ml of the above solution in a 100 ml volumetric flask, measured accurately, prepare a solution as described above, beginning at the words "add 2 ml of citric acid ferrous sulfate solution...". Measure the absorbances of the solutions at 550 nm (Appendix IV B). Weigh accurately 0.1 g of methyldopa CRS to a 100 ml volumetric flask, add sulfuric acid solution (0.05 mol/L) to volume and mix well. Measure accurately 5 ml of the solution to a 100 ml volumetric flask, proceed as described above beginning at the words "add 2 ml of citric acid ferrous sulfate solution...". Calculate the content of $C_{10}H_{13}NO_4$.

Category As described under Methyldopa.

Strength 0.25 g

Storage Preserve in tightly closed containers, protected from light.

Methylenediphosphonate and Stannous Chloride for Injection

Methylenediphosphonate and Stannous Chloride for Injection is a sterile, lyophilized mixture of Methylenediphosphonic Acid and Stannous Chloride. It contains not less than 80.0% and not more than 120.0% of the labelled amount of Methylenediphosphonic acid ($CH_6O_6P_2$).

Description A white lyophilized powder. Freely soluble in water.

Identification (1) To the diluted solution of the residue obtained after ignition in the Assay add ammonium molybdate TS, a yellow colour is produced.

(2) Dissolve the contents of 1 container in 0.5 ml of Sodium Chloride Injection, apply 1 drop of the solution to a strip of ammonium phosphomolybdate TP, a blue colour is produced.

Clarity and colour of solution Dissolve the contents of 1 container in 5 ml of Sodium Chloride Injection, the solution is clear and colourless.

Stannous chloride Dissolve the contents of 5 containers separately in 3 ml of 1 mol/L hydrochloric acid solution, previously saturated with nitrogen. Carry out the method for potentiometric titration (Appendix VII A) under a current of nitrogen, titrate with potassium iodate (0.001667 mol/L) VS. Not less than 0.07 ml is consumed for each container. Repeat the test with another 5 containers if one of them failed to comply with the requirement, all the containers in the second test must comply with the requirement.

Acidity The pH value of the solution obtained in the test for Clarity and colour of solution is 5.0-7.0 (Appendix VI H).

Bacterial endotoxin Carry out the test for bacterial endotoxin (Appendix XI E), using suitable amount of the solution by dissolving the content in 5 ml of water BET and diluted to 10 times of its volume with water BET; not more than 75 EU each container.

Other requirements Complies with the general requirements for injections (Appendix I B).

Assay Dissolve the contents of 3 containers respectively in 2 ml of water, measured accurately, combine the solutions and mix well. To 2 ml of the solution add 2 ml of 2% hydrochloric acid solution, both measured accurately, mix well and pass hydrogen sulfide into the solution until precipitation is complete. Centrifuge and decant the supernate liquid, expel the excess hydrogen sulfide with a current of air.

Transfer 1 ml of the liquid, measured accurately, to a crucible containing 0.2 g of calcium hydroxide, stir well and evaporate to dryness on a water bath. Ignite until the residue is greyish-white in colour, cool and dissolve it in 10 ml of dilute hydrochloric acid. Transfer the solution to a 50 ml volumetric flask, dilute with water to volume and mix well. Transfer 4 ml, measured accurately, to a 25 ml volumetric flask, add 5 ml of molybdo-ascorbic acid solution (mix 9 ml of dilute sulfuric acid with 3 ml each of 2.5% ammonium molybdate solution and 10% ascorbic acid solution), dilute with water to volume and mix well. Warm for 30 minutes in a water bath at 45°C, measure the absorbance (E_1) of the resulting solution at 550 nm (Appendix IV A). Transfer 1 ml of the liquid removed from hydrogen sulfide, measured accurately to a 50 ml volumetric flask, add 0.2 g of calcium hydroxide and 10 ml of dilute hydrochloric acid, dilute with water to volume and mix well. Proceed as described above, beginning at the words "Transfer 4 ml, measured accurately..." Measure the absorbance (E_2) of the solution at the same wavelength.

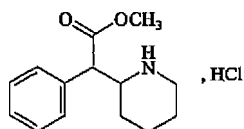
Place 2 ml of potassium dihydrogen phosphate standard solution (0.05 mg phosphorus per ml), measured accurately, pass hydrogen sulfide into the solution, then expel the excess hydrogen sulfide with a current of air. Transfer 1 ml of the solution to a 25 ml volumetric flask, add 5 ml of molybdo-ascorbic acid solution, dilute to volume with water. Proceed as described above, beginning at the words "mix well...". Measure the absorbance (E_3). Calculate the content of phosphorus (P) in the sample multiplied with 7.102, representing the content of methylenediphosphonic acid ($\text{CH}_3\text{O}_3\text{P}_2$).

Category Used for the preparation of Technetium [$^{99\text{m}}\text{Tc}$] Methylenediphosphonate Injection.

Strength 5 mg of methylenediphosphonic acid and 0.5 mg of stannous chloride ($\text{SnCl}_2 \cdot 2\text{H}_2\text{O}$).

Storage Preserve in tightly closed containers, stored at 2-8°C in a dark place.

Methylphenidate Hydrochloride



$\text{C}_{14}\text{H}_{19}\text{NO}_2 \cdot \text{HCl}$ 269.77

[298-59-9]

Methylphenidate Hydrochloride is α -phenyl-2-piperidine methylacetate hydrochloride. It contains not less than 98.0% of $\text{C}_{14}\text{H}_{19}\text{NO}_2 \cdot \text{HCl}$, calculated on the dried basis.

Description A white crystalline powder; odourless. Freely soluble in water or methanol; soluble in ethanol; slightly soluble in chloroform; practically insoluble in acetone.

Identification (1) The light absorption of a 1.0 mg per ml solution in ethanol exhibits three maxima at 252 nm, 258 nm and 264 nm (Appendix IV A).

(2) The infrared absorption spectrum (Appendix IV C) is concordant with the reference spectrum of methylphenidate hydrochloride (Appendix XVI).

(3) The aqueous solution yields the reactions characteristic of chlorides (Appendix III).

Related substances Carry out the method for thin-layer

chromatography (Appendix V B), using silica gel G as the coating substance and chloroform-methanol-concentrated ammonia solution (19 : 1 : 0.1) as the mobile phase. Apply separately to the plate 10 μl each of two solutions of the substance being examined in methanol containing (1) 100 mg per ml (2) 1.0 mg per ml. After developing and removal of the plate, dry it in air and spray with potassium iodobismuthate TS. Any spot other than the principal spot in the chromatogram obtained with solution (1) is not more intense than the principal spot obtained with solution (2).

Loss on drying When dried in vacuum at 60°C to constant weight, loses not more than 1.0% of its weight (Appendix VIII L).

Residue on ignition Not more than 0.1% (Appendix VIII N).

Heavy metals Carry out the limit test for heavy metals (Appendix VIII H, method 1) using 1.0 g; not more than 0.0010%.

Assay Dissolve about 0.2 g, accurately weighed, in 15 ml of glacial acetic acid and 5 ml of mercuric acetate TS, add 4 drops of naphtholbenzein IS. Titrate with perchloric acid (0.1 mol/L) VS until the solution changes to green. Perform a blank determination and make any necessary correction. Each ml of perchloric acid (0.1 mol/L) VS is equivalent to 26.98 mg of $\text{C}_{14}\text{H}_{19}\text{NO}_2 \cdot \text{HCl}$.

Category Central stimulant.

Storage Preserve in tightly closed containers, protected from light.

Preparation Methylphenidate Hydrochloride Tablets

Methylphenidate Hydrochloride Tablets

Methylphenidate Hydrochloride Tablets contain not less than 90.0% and not more than 110.0% of the labelled amount of methylphenidate hydrochloride ($\text{C}_{14}\text{H}_{19}\text{NO}_2 \cdot \text{HCl}$).

Description White tablets.

Identification To the filtrate obtained in the Assay add methanol to produce a solution of 1.0 mg per ml. It complies with test (1) for Identification described under Methylphenidate Hydrochloride.

Other requirements Comply with the general requirements for tablets (Appendix I A).

Assay Weigh accurately and powder 60 tablets. Transfer an accurately weighed quantity of the powdered tablets, equivalent to about 0.25 g of methylphenidate hydrochloride to a 50 ml volumetric flask. Add 30 ml of methanol, warm and shake thoroughly. Cool, dilute with methanol to volume and mix well. Filter, measure accurately 20 ml of the successive filtrate evaporate to dryness on a water bath. Then proceed as directed in the Assay described under Methylphenidate hydrochloride, beginning at the words "Dissolve in 15 ml of glacial acetic acid...". Each ml of perchloric acid (0.1 mol/L) VS is equivalent to 26.98 mg of $\text{C}_{14}\text{H}_{19}\text{NO}_2 \cdot \text{HCl}$.

Category As described under Methylphenidate Hydrochloride.

Strength 10 mg

Storage Preserve in tightly closed containers.

Methylrosanilinium Chloride

Methylrosanilinium Chloride is a mixture of tetrapenta- and hexamethylpararosanine chloride.

Description Dark greenish-violet granular powders or greenish-violet pieces with a metallic lustre; odour, very slight.

Soluble in ethanol and chloroform; sparingly soluble in water; insoluble in ether.

Identification (1) Sprinkle about 1 mg to 1 ml of sulfuric acid, it dissolves in the acid, an orange or brownish-red colour is produced. Dilute cautiously with water, the colour changes to brown, then to green, and finally to blue.

(2) Dissolve about 20 mg in 10 ml of water, add 5 drops of hydrochloric acid, mix well. To 5 ml of this solution add tannic acid TS dropwise; a deep blue precipitate is produced.

(3) To the remainder of the solution prepared for test (2) add about 0.5 g of zinc powder and warm the mixture; rapid decolourisation occurs. Place 1 drop of the decolourised solution adjacent to 1 drop of ammonia TS on a filter paper; the region of contact assumes a blue colour.

Ethanol-insoluble matter Boil 1.0 g with 50 ml of ethanol under reflux for 15 minutes, filter with a sintered glass crucible, previously dried to constant weight at 105°C. Wash the residue with hot ethanol until the washings cease to be violet, dry to constant weight at 105°C, the residue is not more than 0.5%.

Loss on drying When dried to constant weight at 105°C, loses not more than 7.5% of its weight (Appendix VIII L).

Residue on ignition Not more than 1.5% (Appendix VIII N); using 0.5 g.

Heavy metals Carry out the limit test for heavy metals (Appendix VIII H, method 2), using the residue obtained in the test for residue on ignition; not more than 0.005%.

Arsenic Mix 0.20 g with 0.5 g of calcium hydroxide, add small amount of water, mix well and allow to dry. Heat gently to carbonization then ignite at 500-600°C, until the incineration is complete. Cool, dissolve it in 5 ml of hydrochloric acid and 23 ml of water. Complies with the limit test for arsenic (Appendix VIII J, method 1) (0.001%).

Category Antiseptic, Disinfectant.

Storage Preserve in tightly closed containers, protected from light.

Preparation Methylrosanilinium Chloride Solution

Methylrosanilinium Chloride Solution

Methylrosanilinium Chloride Solution contains not less than 0.85% (g/ml) and not more than 1.05% (g/ml) of Methylrosanilinium Chloride.

Formula	Methylrosanilinium Chloride	10 g
	Ethanol	sufficient quantity
	Water	sufficient quantity

To make	1000 ml
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Processing Dissolve Methylrosanilinium Chloride in sufficient quantity of ethanol, add water to 1000 ml and filter.

Description Violet liquid.

Identification (1) To 5 ml add 2 drops of hydrochloric acid and add tannic acid TS dropwise; a deep blue precipitate is produced.

(2) Evaporate 2 ml on a water bath to dryness. Sprinkle a small amount of the residue to 1 ml of sulfuric acid; it dissolves in the acid, an orange or brownish-red colour is produced. Dilute cautiously with water, the colour changes to brown, then to green and finally to blue.

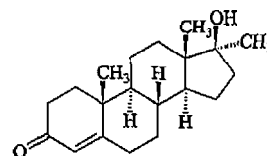
Fill Comply with the requirements for Minimum Fill (Appendix X F).

Assay Measure accurately 10 ml to an evaporating dish, previously dried to constant weight at 105°C. Evaporate on a water bath to dryness, dry to constant weight at 105°C. Calculate the content of Methylrosanilinium Chloride.

Category As described under Methylrosanilinium Chloride

Storage Preserve in tightly closed containers, protected from light.

Methyltestosterone



$C_{20}H_{30}O_2$ 302.46

[58-18-4]

Methyltestosterone is 17 β -hydroxy-17 α -methyl-androst-4-en-3-one. It contains not less than 97.0% and not more than 103.0% of $C_{20}H_{30}O_2$, calculated on the dried basis.

Description A white or almost white crystalline powder; odourless, tasteless; slightly hygroscopic.

Freely soluble in ethanol, acetone or chloroform; sparingly soluble in ether; slightly soluble in vegetable oil; insoluble in water.

Melting range 163-167°C (Appendix VI C).

Specific optical rotation +79° to +85°, in a solution of about 10 mg per ml in ethanol (Appendix VI E).

Identification (1) Dissolve a quantity mg in 1 ml of sulfuric acid-ethanol (2 : 1), a yellow colour is produced with a yellowish-green fluorescence.

(2) The retention time of principal peak of the substance being examined is identical with that of principal peak of the reference solution in the chromatogram obtained in Assay.

(3) The infrared absorption spectrum (Appendix IV C) is concordant with the reference spectrum of methyltestosterone (Appendix XVI).

Related substances Carry out the method as described under Assay. Inject 10 μ l of the solution into the column, adjust the attenuation so that the principal peak height is about 25% of full scale of the chart. Dissolve a quantity of the substance being examined, accurately weighed, in methanol to produce solutions of 0.6 mg per ml (solution 1) and 0.012 mg per ml (solution 2), inject separately 10 μ l each of solution (1) and (2) into the column, and record the chromatograms for twice the retention times of the principal peak. Not more than three secondary peaks in the chromatogram are obtained with solution (1), each secondary peak area and the sum of the areas of all secondary peaks are not greater than 1/2 and 3/4 of the principal peak area in the chromatogram obtained

with solution (2) correspondingly.

Loss on drying When dried at 105°C for 2 hours, loses not more than 1.0% of its weight (Appendix VIII L).

Assay Carry out the method for high performance liquid chromatography (Appendix V D), with an octadecylsilane bonded silica gel column, using methanol-water (72 : 28) as the mobile phase and the detection wavelength is 241 nm. The number of the theoretical plates of the column is not less than 1500, calculated with reference to the peak of methyltestosterone. The resolution factor between the peaks of methyltestosterone and internal standard complies with the related requirements.

Internal Standard Solution Dissolve about 10 mg of norethisterone, accurately weighed, in methanol in a 10 ml volumetric flask, dilute to volume and mix well.

Procedure Dissolve about 12 mg of methyltestosterone CRS, accurately weighed, in methanol in a 10 ml volumetric flask, dilute to volume and mix well. Transfer 1 ml each of the solution and the internal standard solution, both accurately measured, in a 10 ml volumetric flask, dilute with methanol to volume, mix well. Inject 10 µl of the resulting solution into the column, repeat the operation, using the substance being examined instead of methyltestosterone CRS, calculate the content of $C_{20}H_{30}O_2$ with respect to the peak area obtained in the chromatogram by the

Category Androgen.

Storage Preserve in tightly closed containers, protected from light.

Preparation Methyltestosterone Tablets

Methyltestosterone Tablets

Methyltestosterone Tablets contain not less than 90.0% and not more than 110.0% of the labelled amount of methyltestosterone ($C_{20}H_{30}O_2$).

Description White tablets.

Identification To a quantity of finely powdered tablet equivalent to 10 mg of methyltestosterone add 10 ml of ethanol or chloroform, stir well, filter, evaporate the filtrate to dryness on a water bath, the residue complies with tests (1) and (3) for Identification described under Methyltestosterone.

Content uniformity Dissolve 1 tablet in a 50 ml volumetric flask in a quantity of absolute ethanol, shake well, dilute to volume with absolute ethanol and mix well, filter. Measure accurately 5 ml of the successive filtrate to another 50 ml volumetric flask, add absolute ethanol to volume and mix well. Determine the content of methyltestosterone as described under Assay. The content of each of the ten tablets comply with the requirements (Appendix X E).

Dissolution Carry out dissolution test (Appendix X C, method 2), using 500 ml of ethanol (5 → 100) as the dissolution medium, adjust the rotation speed of the paddle to 100 rpm. Withdraw the solution after exactly 45 minutes and filter. Discard the initial filtrate. Measure the absorbance of the successive filtrate at 249 nm (Appendix IV A). Treat a quantity of methyltestosterone CRS instead of the substance being examined in the same manner. Calculate the dissolution of $C_{20}H_{30}O_2$ from each tablet. Not less than 75% of the labelled amount is dissolved.

Other requirements Comply with the general requirements

for tablets (Appendix I A).

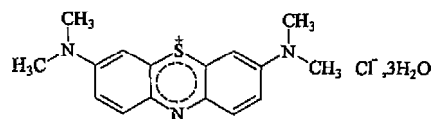
Assay Weigh accurately and powder 10 tablets, transfer an accurately weighed quantity of the powder equivalent to about 20 mg of methyltestosterone into a 100 ml volumetric flask, add dehydrated ethanol and shake to dissolve the methyltestosterone, dilute with dehydrated ethanol to volume and mix well, filter, discard the initial filtrate, transfer 5 ml of the successive filtrate, accurately measured, to another 100 ml volumetric flask, add dehydrated ethanol to volume and mix well. Measure the absorbance of the resulting solution at 240 nm (Appendix IV A). Calculate the content of $C_{20}H_{30}O_2$, taking 540 as the value of A (1%, 1 cm).

Category As described under Methyltestosterone.

Strength 5 mg

Storage Preserve in tightly closed containers, protected from light.

Methylthioninium Chloride



$C_{16}H_{18}ClN_3S \cdot 3H_2O$ 373.90

[7220-79-3]

Methylthioninium Chloride is 3,7-bis (dimethylamino)-phenothiazine-5-ium chloride trihydrate. It contains not less than 98.5% of $C_{16}H_{18}ClN_3S$, calculated on the dried basis.

Description Dark green crystals or crystalline powder with a bronzelike luster; odourless. Freely soluble in water or ethanol; soluble in chloroform.

Identification (1) Dissolve about 10 mg in 50 ml of water, a deep blue colour is produced. To 10 ml of this solution add a mixture of 1 ml of sulfuric acid and 0.1 g of zinc powder, the blue colour of the solution disappears. Filter, the filtrate changes to blue again on standing in air or by adding 1 drop of hydrogen peroxide TS. Add a few drops of potassium iodide TS to 10 ml of this solution, a deep blue flocculent precipitate is produced, while the colour of supernatant liquid is pale blue. Add a few drops of 0.1 mol/L iodine solution to 10 ml of this solution, a deep brown colour is produced; add 0.1 mol/L sodium thiosulfate solution, the blue colour is produced again.

(2) The infrared absorption spectrum (Appendix IV C) is concordant with the reference spectrum of methylthioninium chloride (Appendix XVI).

Loss on drying When dried to constant weight at 105°C, loses not more than 18.0% of its weight (Appendix VIII L).

Residue on ignition Not more than 1.2% (Appendix VIII N).

Zinc Moisten 0.10 g with a few drops of sulfuric acid and ignite. Add 5 ml of dilute hydrochloric acid and 5 ml of water to the residue, boil, add 5 ml of ammonia TS and filter. Add 2 drops of ammonium sulfide TS to the filtrate, no precipitate or turbidity is produced.

Arsenic Mix 0.20 g with 0.5 g of calcium hydroxide and a small amount of water, stir and dry. Heat gently until it is charred, then ignite at 600-700°C until the incineration is completed. Cool, dissolve the residue in 5 ml of hydrochloric acid and 23 ml of water. It complies with the limit test for arsenic (Appendix VIII J, method 1) (0.001%).

Assay Dissolve about 0.2 g, accurately weighed, in 40 ml of water in a beaker, heat on a water bath to 75°C. Add accurately 25 ml of potassium dichromate (0.01667 mol/L) VS, mix well and keep at 75°C for 20 minutes. Cool, filter with a sintered-glass funnel. Wash the beaker and funnel with water for 4 times, each o 2.5 ml. Filter, combine the filtrates and washings, transfer to a stoppered flask. Add 250 ml of water, 25 ml of sulfuric acid solution (1→5) and 10 ml of potassium iodide TS, mix well. Titrate with sodium thiosulfate (0.1 mol/L) VS, adding 2 ml of starch IS towards the end of the titration and continue the titration until the blue colour just disappears. Perform a blank determination and make any necessary correction. Each ml of potassium dichromate (0.01667 mol/L) VS, is equivalent to 10.66 mg of $C_{16}H_{18}ClN_3S$.

Category Antidote.

Storage Preserve in tightly closed containers, protected from light.

Preparation Methylthioninium Chloride Injection

Methylthioninium Chloride Injection

Methylthioninium Chloride Injection is a sterile solution of Methylthioninium chloride in Water for Injection. It contains not less than 90.0% and not more than 110.0% of the labelled amount of $C_{16}H_{18}ClN_3S \cdot 3H_2O$.

It may contain 5 % of glucose.

Description A clear, deep blue liquid.

Identification Complies with test (1) for identification described under Methylthioninium Chloride.

pH value 3.5-5.0 (Appendix V H).

Other requirements Complies with the general requirements for injections (Appendix I B).

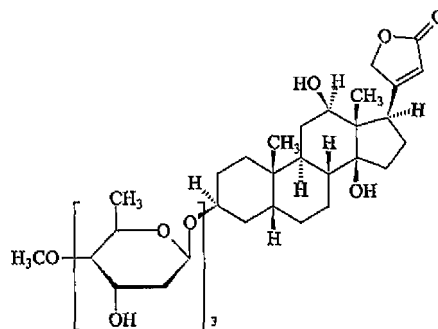
Assay Dissolve an accurately measured quantity equivalent to about 20 mg of Methylthioninium Chloride in dilute ethanol to produce a solution of 2 µg per ml. Measure the absorbance at 661 nm (Appendix IV A). Repeat the operation using a quantity of methylthioninium chloride CRS instead of the substance being examined. Calculate the content of $C_{16}H_{18}ClN_3S \cdot 3H_2O$, and multiply by 1.169.

Category As described under Methylthioninium Chloride.

Strength (1) 2 ml : 20 mg (2) 5 ml : 50 mg
(3) 10 ml : 100 mg

Storage Preserve in well closed containers, protected from light.

Metildigoxin



$C_{42}H_{66}O_{14}$ 794.98

[30685-43-9]

Metildigoxin is 3β -[(*O*-2,6-dideoxy-4-*O*-methyl- β -D-ribo-hexopyranosyl-(1→4))-*O*-2,6-dideoxy- β -D-ribo-hexopyranosyl-(1→4))-2,6-dideoxy- β -D-ribo-hexopyranosyl]oxy]-12 β , 14-dihydroxy-5 β , 14 β -card-20(22)-enolide. It contains not less than 95.0% of $C_{42}H_{66}O_{14}$, calculated on the dried basis.

Description A white or almost white crystalline powder; odourless; taste, bitter.

Sparingly soluble in chloroform; very slightly soluble in methanol or ethanol; practically insoluble in water.

Identification (1) Dissolve about 1 mg in 1 ml of glacial acetic acid solution containing ferric chloride (to 10 ml of glacial acetic acid add 1 drop of ferric chloride TS) in a test tube, add alongside the wall to form a subjacent layer, a violet colour formed at the junction of the liquids, and the glacial acetic acid layer turns to blue after standing.

(2) The retention time of principal peak of the substance being examined in the chromatogram obtained in the Assay is identical with that of the principal peak of metildigoxin CRS.

(3) The infrared absorption spectrum (Appendix IV C) is concordant with reference spectrum of Metildigoxin (Appendix XI).

Related substances Dissolve a quantity of the substance being examined, accurately weighed, in mobile phase to produce two solutions of 0.25 mg per ml [solution (1)] and 0.0125 mg per ml [solution (2)]. Carry out the method as described under the Assay except using a mixture of acetonitrile-water (34 : 66) as the mobile phase. Inject 20 µl of solution (2) into the column, adjust the attenuation so that the principal peak height in the chromatogram is 20%-25% full scale of the chart. Then inject separately 20 µl each of solution (1) and (2) into the column and record the chromatogram for triple the retention time of the principal peak. The sum of the areas of all peaks other than the principal peak is not greater than the area of the principal peak in the chromatogram obtained with solution (2).

Loss on drying When dried in vacuum over phosphorous pentoxide to constant weight, loses not more than 1.0% of its weight (Appendix VII L).

Assay Carry out the method for high performance liquid chromatography (Appendix V D), using a column packed with octadecylsilane bonded silica gel and a mixture of acetonitrile-water (40 : 60) as the mobile phase. Detection wavelength is 218 nm and the number of the theoretical plates of the column is not less than 1000, calculated with reference to the peak of metildigoxin. The resolution factor between the peaks of metildigoxin and internal standard

complies with the related requirements.

Internal standard solution Dissolve a quantity of digitoxin CRS, accurately weighed, in mobile phase to produce a solution of 0.1 mg per ml, mix well.

Procedure Dissolve a quantity of metildigoxin CRS, accurately weighed, in mobile phase to produce a reference solution of 0.1 mg per ml. Transfer each 2 ml of the reference solution and the internal standard solution, accurately measured, in a 10 ml volumetric flask, dilute with mobile phase to volume and mix well, inject 20 μ l into the column. Repeat the operation, using the substance being examined instead of metildigoxin CRS, calculate the content of $C_{42}H_{66}O_{14}$.

Category Cardiotonic.

Storage Preserve in tightly closed containers.

Preparation Metildigoxin Tablets

Metildigoxin Tablets

Metildigoxin Tablets contain not less than 85.0% and not more than 115.0% of the labelled amount of metildigoxin ($C_{42}H_{66}O_{14}$).

Description White or almost white tablets.

Identification (1) To a quantity of the powdered tablets equivalent to about 1 mg of metildigoxin add 5 ml of a mixture of ethanol-chloroform (1 : 1). Shake vigorously for a few minutes and centrifuge, evaporate the centrifugate to dryness on a water bath at 60-70°C. The residue complies with test (1) for Identification described under Metildigoxin. (2) The retention time of principal peak of the metildigoxin in the substance being examined in the chromatogram obtained in the Assay is identical with that the principal peak of metildigoxin CRS.

Content uniformity Comply with the requirements (Appendix X E). Transfer 1 tablet to a 5 ml volumetric flask. Carry out the procedure described under the Assay beginning at the words "Add 1 ml of the internal standard solution... measure accurately". Calculate the content of $C_{42}H_{66}O_{14}$. The limit of content uniformity is $\pm 20\%$.

Dissolution Comply with dissolution test (Appendix X C, method 3), using 100 ml of 0.1 mol/L hydrochloric acid solution as the dissolution medium, adjust the rotational speed of the paddle to 60 rpm. Withdraw a quantity of the solution after exactly 60 minutes and filter through a membrane with pores of less than 0.45 μ m in diameter. Use the successive filtrate as the test solution. Dissolve metildigoxin CRS in 0.1 mol/L hydrochloric acid solution to produce a solution of 1 μ g per 1 ml as the reference solution. Measure accurately 1 ml each of the solutions to two 10 ml volumetric flasks, respectively. Add 3.0 ml of 0.1% ascorbic acid in methanol solution and 0.2 ml of 0.009 mol/L hydrogen peroxide solution, dilute with 0.1 mol/L hydrochloric acid to volume, mix well. Allow to stand for 90 minutes at 30°C, cool to room temperature. Measure the fluorescence intensity of the resulting solutions (Appendix IV E), the excitation wavelength and the emission wavelength are 356 nm and 485 nm, respectively. Calculate the dissolution of $C_{42}H_{66}O_{14}$ from each tablet, not less than 65% of the labelled amount is dissolved.

Other requirements Comply with the general requirements for tablets (Appendix I A).

Assay Weigh and powder 20 tablets. Transfer a quantity of the powder equivalent to about 0.1 mg of metildigoxin,

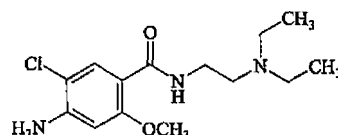
accurately weighed, to a 5 ml volumetric flask. Add 1 ml of internal standard solution, accurately measured. Add a quantity of mobile phase to dissolve the metildigoxin by ultrasonic treatment. Dilute with mobile phase to volume and filter. Use the successive filtrate as test solution. Carry out the Assay described under Metildigoxin, inject 20 μ l of the solution into the column. Repeat the operation. Calculate the content of $C_{42}H_{66}O_{14}$ with respect to the peak area obtained in the chromatogram by the internal standard method.

Category As described under Metildigoxin.

Strength 0.1 mg

Storage Preserve in tightly closed containers.

Metoclopramide



$C_{14}H_{22}ClN_3O_2$ 299.80

[364-62-5]

Metoclopramide is 4-amino-5-chloro-N-[2-(diethylamino)ethyl]-2-methoxy-benzamide. It contains not less than 99.0% of $C_{14}H_{22}ClN_3O_2$, calculated on the dried basis.

Description A white crystalline powder; odourless; taste, bitter.

Soluble in chloroform, sparingly soluble in ethanol or acetone, very slightly soluble in ether; practically insoluble in water; soluble in acid solutions.

Melting range 147-151°C (Appendix VI C).

Identification (1) To about 5 mg in a test tube add 1 ml of sulfuric acid, heat gently until the solution exhibits a violet-black colour. Add a few drops into 5 ml of water, mix well, a green fluorescence is produced, when made alkaline the fluorescence disappears.

(2) The light absorption of a solution of 10 μ g per ml in standard potassium tetraoxalate BS (Appendix VI H) exhibits a maximum at 309 nm, and a minimum at 290 nm (Appendix IV A).

(3) The infrared absorption spectrum (Appendix IV C) is concordant with reference spectrum of Metoclopramide (Appendix XVI).

Clarity of acid solution Dissolve 0.20 g in 1.5 ml of hydrochloric acid solution (9 \rightarrow 100), add water to 20 ml, the solution is clear.

Related substances Carry out the method for thin-layer chromatography (Appendix V B), using silica gel GF₂₅₄ as the coating substance and a mixture of *n*-butanol-concentrated ammonia solution (19 : 1) as the mobile phase. Apply separately to the plate 10 μ l each of two solutions of the substance being examined in methanol containing (1) 10 mg per ml (2) 50 μ g per ml. After developing and removal of the plate, dry it at 80°C for 30 minutes and examine under ultraviolet light at 254 nm. Any secondary spot in the chromatogram obtained with solution (1) is not more intense than the principal spot obtained with solution (2).

Loss on drying When dried to constant weight at 105°C, loses not more than 0.5% of its weight (Appendix VIII L).

Residue on ignition Not more than 0.1% (Appendix VIII N).

volumetric flask and dilute to volume, mix well, measure accurately a quantity, add the mobile phase to produce a solution of 0.3 mg per ml. Repeat the operation, calculate the content of $[(C_{15}H_{25}NO_3)_2 \cdot C_4H_6O_6]$ with respect to the peak area obtained in the chromatogram by external standard method.

Sodium chloride Dilute 5 ml, accurately measured, with 40 ml of water, add 5 ml of 2% dextrin solution and 5 to 8 drops of fluorescent yellow IS, titrate with silver nitrate (0.1 mol/L) VS. Each ml of silver nitrate (0.1 mol/L) VS is equivalent to 5.844 mg NaCl.

Category As described under Metoprolol Tartrate.

Strength (1) 2 ml : 2 mg of metoprolol tartrate + 18 mg of sodium chloride
(2) 5 ml : 5 mg of metoprolol tartrate + 45 mg of sodium chloride

Storage Preserve in tightly closed containers, protected from light.

Metoprolol Tartrate Sustained-release Tablets

Metoprolol Tartrate Sustained-release Tablets contain not less than 90.0% and not more than 110.0% of the labelled amount of metoprolol tartrate $[(C_{15}H_{25}NO_3)_2 \cdot C_4H_6O_6]$.

Description White tablets or film coated tablets with white or almost white core.

Identification (1) Shake a quantity of powdered tablets, equivalent to about 0.3 g of metoprolol tartrate, with 10 ml of water to dissolve metoprolol tartrate, filter. Transfer the filtrate in a clean test tube, add an excess of silver nitrate TS, a white precipitate is produced. Add a sufficient amount of ammonia TS to dissolve the precipitate. Heat on a water bath, silver is deposited on the inner wall of the test tube as a mirror.

(2) To a quantity of the powdered tablets, add water to produce a solution of about 20 µg per ml and filter. The light absorption of the filtrate exhibits maxima at 223 nm and 274 nm (Appendix IV A).

Drug Release Carry out the method for dissolution test (Appendix X D, method 1 and Appendix X C, method 2), using 900 ml of water as the release medium and adjust the rotational speed of the paddle to 50 rpm. Withdraw a sample of 10 ml of the solution at exact 1, 4 and 8 hours respectively, filter and supply 10 ml of water accordingly in the vessel immediately. Measure the absorbance of the filtrate at 274 nm (Appendix IV A); dissolve an accurately weighed quantity of metoprolol tartrate CRS in water to produce a solution of 0.1 mg per ml, repeat the operation. Calculate the content of $(C_{15}H_{25}NO_3)_2 \cdot C_4H_6O_6$ dissolved from each tablet at 1, 4 and 8 hours separately. The dissolution of metoprolol tartrate complies with the requirement; the quantity dissolved of each tablet is not less than 25%-45%, 40%-75% and over 75% of the labelled amount of $(C_{15}H_{25}NO_3)_2 \cdot C_4H_6O_6$ at 1, 4 and 8 hours respectively.

Other requirements Comply with the general requirements for tablets (Appendix I A).

Assay Weigh accurately and powder finely 20 tablets with film coating removed. Weigh accurately a quantity of the powder equivalent to about 0.3 g of metoprolol tartrate into a 200 ml volumetric flask, add a quantity of water to dissolve

metoprolol tartrate, dilute with water to volume and shake thoroughly. Filter and transfer 5 ml of the successive filtrate to a 50 ml volumetric flask, dilute with water to volume and mix well. Measure the absorbance of the resulting solution at 274 nm (Appendix IV A). Dissolve an accurately weighed quantity of metoprolol tartrate CRS in water to produce a solution of 0.15 mg per ml, measure the absorbance in the same manner. Calculate the content of $(C_{15}H_{25}NO_3)_2 \cdot C_4H_6O_6$.

Category As described under Metoprolol Tartrate.

Strength (1) 100 mg (2) 150 mg

Storage Preserve in tightly closed containers.

Metoprolol Tartrate Tablets

Metoprolol Tartrate Tablets contain not less than 95.0% and not more than 105.0% of the labelled amount of metoprolol tartrate $[(C_{15}H_{25}NO_3)_2 \cdot C_4H_6O_6]$.

Description White tablets.

Identification (1) To a quantity of the powdered tablets, equivalent to 0.3 g of metoprolol tartrate, add 10 ml of water, shake to dissolve metoprolol tartrate. Filter. The filtrate complies with test (1) for Identification described under Metoprolol Tartrate.

(2) The light absorption of a solution obtained in the Assay exhibits a maximum at 274 nm (Appendix IV A).

Dissolution Carry out the dissolution test (Appendix X C, method 1), using 900 ml (for strength 100 mg) or 500 ml (for strength 25 mg, for strength 50 mg) of sodium chloride solution in hydrochloric acid (add 7 ml of hydrochloric acid to 2 g of sodium chloride, dilute with water to 1000 ml) as the dissolution medium, adjust the rotational speed of the basket to 100 rpm. Withdraw a quantity of the solution after exactly 30 minutes and filter. Measure the absorbance of the successive filtrate at 274 nm (Appendix IV A). Dissolve an accurately weighed quantity of Metoprolol Tartrate CRS in the dissolution medium to produce a solution of 100 µg per ml, repeat the operation. Calculate the dissolution of $(C_{15}H_{25}NO_3)_2 \cdot C_4H_6O_6$ from each tablet. Not less than 75% of the labelled amount is dissolved.

Other requirements Comply with the general requirements for tablets (Appendix I A).

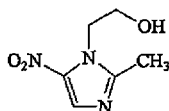
Assay Weigh accurately and powder 20 tablets. Weigh accurately a quantity of the powdered tablets equivalent to about 0.12 g of metoprolol tartrate into a 100 ml volumetric flask, add a quantity of 2% sodium chloride solution, shake to dissolve metoprolol tartrate, dilute with water to volume and mix well. Filter. Measure accurately 5 ml of the successive filtrate into a 50 ml volumetric flask, dilute with water to volume and mix well. Measure the absorbance of the resulting solution at 274 nm (Appendix IV A). Dissolve a quantity of metoprolol tartrate CRS in water to produce a solution of about 0.12 mg per ml, measure the absorbance in the same manner. Calculate the content of $[(C_{15}H_{25}NO_3)_2 \cdot C_4H_6O_6]$.

Category β-Adrenergic blocker.

Strength (1) 25 mg (2) 50 mg (3) 100 mg

Storage Preserve in tightly closed containers, protected from light.

Metronidazole



$C_6H_9N_3O_3$ 171.16

[443-48-1]

Metronidazole is 2-methyl-5-nitroimidazole-1-ethanol. It contains not less than 99.0% of $C_6H_9N_3O_3$, calculated on the dried basis.

Description A white or slightly yellow crystalline powder or crystal; odour, slight; taste, bitter and slightly saline. Sparingly soluble in ethanol; slightly soluble in water or chloroform; very slightly soluble in ether.

Melting range 159-163°C (Appendix VI C).

Specific absorbance Measure the absorbance of a solution of about 13 µg per ml in hydrochloric acid solution (9→1000) at 277 nm (Appendix IV A), the value of A (1%, 1 cm) is 365-389.

Identification (1) To about 10 mg add 2 ml of sodium hydroxide TS and warm, a violet-red colour is produced; acidify the solution with dilute hydrochloric acid, the colour changes to yellow; add dropwise an excess of sodium hydroxide TS, the solution becomes orange-red.

(2) About 0.1 g should be soluble in 4 ml of sulfuric acid solution (3→100). Add 10 ml of trinitrophenol TS to the solution, a yellow precipitate is produced on standing.

(3) The light absorption of a solution obtained in the measurement of specific absorbance, exhibits a maximum at 277 nm and a minimum at 241 nm (Appendix IV A).

(4) The infrared absorption spectrum (Appendix IV C) is concordant with the reference spectrum of metronidazole (Appendix XVI).

2-Methyl-5-nitroimidazole Dissolve about 100 mg, weighed accurately, in methanol and dilute to 100 ml, mix well. Measure accurately a quantity, dilute with the mobile phase to produce a solution of 0.1 mg per ml as the test solution; Dissolve about 25 mg of 2-Methyl-5-nitroimidazole CRS, weighed accurately, in methanol and dilute to 100 ml, mix well. Measure accurately a quantity, dilute with the mobile phase to produce a solution of 1 µg per ml as the reference solution. Carry out the method for high performance liquid chromatograph (Appendix V D), using a column packed with octadecylsilane bonded silica gel and a mixture of methanol-water (20 : 80) as the mobile phase. Detection wavelength is 300 nm and the number of the theoretical plates of the column is not less than 2000, calculated with reference to the peak of metronidazole. Inject 20 µl of the reference solution into the column, adjust the attenuation so that the principal peak height in the chromatogram is 10%-30% of the full scale of the chart. Inject separately 20 µl of the test solution and the reference solution into the column, and record the chromatogram for two times the retention time of the principal peak. The peak area of 2-Methyl-5-nitroimidazole in the test solution is not greater than 1.0%.

Clarity and colour of ethanol solution A solution of 5 mg per ml in ethanol is clear; any opalescence produced is not more pronounced than that of reference suspension 1 (Appendix IX B); any colour produced is not more intense than that of reference solution Y₂ or YG₂ (Appendix IX A).

Loss on drying When dried to constant weight at 105°C,

loses not more than 0.5% of its weight (Appendix VII L).

Residue on ignition Not more than 0.1%, using 1.0 g (Appendix VII N).

Heavy metals Carry out the limit test for heavy metals (Appendix VII H, method 2), using the residue obtained in the test for residue on ignition; not more than 0.001%.

Assay Dissolve about 0.13 g, accurately weighed, in 10 ml of glacial acetic acid, add 2 drops of naphtholbenzein IS, titrate with perchloric acid (0.1 mol/L) VS until the solution becomes green. Perform a blank determination and make any necessary correction. Each ml of perchloric acid (0.1 mol/L) VS is equivalent to 17.12 mg of $C_6H_9N_3O_3$.

Category Anti-trichomonacide and anti-anaerobic bacteria agent.

Storage Preserve in tightly closed containers, protected from light.

Preparation (1) Metronidazole and Glucose Injection
(2) Metronidazole Capsules
(3) Metronidazole Injection
(4) Metronidazole Suppositories
(5) Metronidazole Tablets
(6) Metronidazole Vaginal Effervescent Tablets

Metronidazole Capsules

Metronidazole Capsules contain not less than 90.0% and not more than 110.0% of the labelled amount of Metronidazole ($C_6H_9N_3O_3$).

Description Capsules containing white or pale yellow crystalline powder.

Identification (1) To a quantity of the contents equivalent to about 10 mg of Metronidazole, add 2 ml of sodium hydroxide TS, gently warm the solution; a purplish red colour is produced. Add dilute hydrochloric acid dropwisely to acidify the solution; the colour changes to yellow which changes to orange-red on addition of excessive sodium hydroxide TS.

(2) Shake a quantity of the contents equivalent to about 0.1 g of Metronidazole with 4 ml of 0.5mol/L sulfuric acid solution and filter. To the filtrate add 10 ml of trinitrophenol TS and allow to stand; a yellow precipitate is produced.

(3) The light absorption of the solution described under the Assay exhibits a maximum at 277 nm and a minimum at 241 nm (Appendix IV A).

Other requirements Comply with the general requirements for capsules (Appendix I E).

Assay To an accurately weighed quantity of the mixed contents in the test for Weight variation, equivalent to about 50 mg of Metronidazole, carry out the Assay described under Metronidazole Tablets beginning at the words "in a 100 ml volumetric flask. . ." Calculate the content of $C_6H_9N_3O_3$.

Category As described under Metronidazole.

Strength 0.2 g

Storage Preserve in tightly closed containers, protected from light.

Metronidazole Injection

Metronidazole Injection is a sterile solution of Metronidazole in Water for Injection. It contains not less than 93.0% and not more than 107.0% of the labelled amount of metronidazole ($C_6H_9N_3O_3$). It is an isotonic solution containing sodium chloride.

Description A clear, colourless or almost colourless liquid.

Identification (1) Complies with test (1) for Identification described under Metronidazole, using a quantity equivalent to 10 mg of metronidazole.

(2) Evaporate a quantity equivalent to 0.1 g of metronidazole on a water bath to dryness, the residue complies with Identification test (2) described under Metronidazole.

(3) The light absorption of the solution obtained in the Assay exhibits a maximum at 277 nm and a minimum at 241 nm (Appendix IV A).

(4) Yields the reactions characteristic of sodium salts and chlorides (Appendix III).

pH value 4.5-7.0 (Appendix VI H).

2-Methyl-5-nitroimidazole Dilute a quantity with water to produce a solution containing 0.1 mg of metronidazole per ml as the test solution, complies with test of 2-Methyl-5-nitroimidazole described under Metronidazole.

Chloride Measured accurately a quantity equivalent to about 50 mg, add 50 ml of water, 5 ml of 2% of dextrin solution, 0.1 g of calcium carbonate and 5-8 drops of fluorescein IS, mix well. Titrate with silver nitrate (0.1 mol/L) VS until the colour of the turbid solution changes from yellowish-green to slightly red; not less than 13.2 ml and not more than 14.6 ml or not less than 35.1 ml and not more than 38.8 ml (for strength 250 ml : 500 ml) are required.

Bacterial endotoxin Carry out the test for bacterial endotoxin (Appendix XI E); not more than 0.35 EU per mg.

Sterility Complies with the test for sterility (Appendix XI H, membrane filtration method), use clostridium sporogenes suspension as positive control.

Other requirements Complies with the general requirements for injection (Appendix I B).

Assay Dilute an accurately measured quantity with hydrochloric acid solution (9→1000) to produce a solution containing about 12.5 µg of metronidazole per ml. Measure the absorbance at 277 nm (Appendix IV A) and calculate the content of $C_6H_9N_3O_3$, taking 377 as the value of A (1%, 1 cm).

Category As described under Metronidazole.

Strength (1) 10 ml : 50 mg (2) 20 ml : 100 mg
(3) 100 ml : 500 mg (4) 250 ml : 1.25 g
(5) 250 ml : 500 ml

Storage Preserve in well closed containers, protected from light.

Metronidazole Suppositories

Metronidazole Suppositories contain not less than 93.0% and not more than 107.0% of the labelled amount of metronidazole ($C_6H_9N_3O_3$).

Description Creamy white to pale yellow liposoluble

suppositories.

Identification Melt 1 suppository with 20 ml of ethanol by heating on a water bath, allow to cool until the mass just sets and filter. Evaporate the filtrate on a water bath to dryness, the residue complies with test (1)(2) and (3) for Identification described under Metronidazole.

Other requirements Comply with the general requirements for suppositories (Appendix I D).

Assay Weigh accurately 10 suppositories, cut in chips. Melt a quantity equivalent to about 0.1 g of metronidazole, accurately weighed, with 20 ml of acetic anhydride on a water bath with shake, allow to cool, add 2 drops of malachite green IS, titrate with perchloric acid (0.1 mol/L) VS until the colour changes to yellowish-green. Perform a blank determination and make any necessary correction. Each ml of perchloric acid (0.1 mol/L) VS is equivalent to 17.12 mg of $C_6H_9N_3O_3$.

Category As described under Metronidazole.

Strength (1) 0.5 g (2) 1 g

Storage Preserve in tightly closed containers, protected from light and stored at a temperature below 30°C.

Metronidazole Tablets

Metronidazole Tablets contain not less than 93.0% and not more than 107.0% of the labelled amount of metronidazole ($C_6H_9N_3O_3$).

Description White or almost white tablets.

Identification (1) Comply with test (1) for Identification described under Metronidazole, using a quantity of the powdered tablets equivalent to about 10 mg of metronidazole.

(2) To a quantity of the powdered tablets equivalent to about 0.2 g of metronidazole add 4 ml of sulfuric acid solution (3→100), shake well and filter. To the filtrate add 10 ml of trinitrophenol TS; a yellow precipitate is produced on standing.

(3) The light absorption of the solution obtained in the Assay exhibits a maximum at 277 nm and a minimum at 241 nm (Appendix IV A).

Dissolution Comply with the requirements for dissolution test (Appendix X C, method 1), using 900 ml of hydrochloric acid solution (9→1000) as the dissolution medium, adjust the rotational speed of the basket to 100 rpm. Withdraw a quantity of the solution after exactly 30 minutes and filter. Dilute 3 ml of the successive filtrate, accurately measured, with hydrochloric acid solution (9→1000) to 50 ml and mix well. Measure the absorbance at 277 nm (Appendix IV A), calculate the dissolution of $C_6H_9N_3O_3$ from each tablet, taking 377 as the value of A (1%, 1 cm). Not less than 70% of the labelled amount is dissolved.

Other requirements Comply with the general requirements for tablets (Appendix I A).

Assay Weigh accurately and powder 10 tablets. To an accurately weighed quantity equivalent to about 50 mg of metronidazole in a 100 ml volumetric flask add about 80 ml of hydrochloric acid solution (9→1000) and warm to dissolve metronidazole, add hydrochloric acid solution (9→1000) to volume and mix well. Filter, measure accurately 5 ml of the successive filtrate to a 200 ml volumetric flask, add hydrochloric acid solution (9→1000) to volume and mix well. Measure the absorbance of the resulting solution at 277

nm (Appendix IV A) and calculate the content of $C_6H_9N_3O_3$, taking 377 as the value of A (1%, 1 cm).

Category As described under Metronidazole.

Strength 0.2 g

Storage Preserve in tightly closed containers, protected from light.

Metronidazole Vaginal Effervescent Tablets

Metronidazole Vaginal Effervescent Tablets contain not less than 90.0% and not more than 110.0% of the labelled amount of metronidazole ($C_6H_9N_3O_3$).

Description White or almost white tablets, with faintly visible spots on the surface of the tablets.

Identification A quantity of powdered tablets complies with tests for Identification described under Metronidazole Tablets.

Acidity Triturate 5 tablets and dissolve in 50 ml of water: pH 4.0-5.5 (Appendix VI H).

Effervescence Add 2 ml each of water, accurately measured, to ten 25 ml graduated test tubes with stopper (the internal diameter is about 1.5 cm) separately, place in a water bath at $37^\circ\text{C} \pm 1^\circ\text{C}$ for 5 minutes. Add 1 tablet each to the ten test tubes, stopper the test tubes for 20 minutes. The maximum volume of effervescence is not greater than 10.0 ml, and not more than 2 tablets lower than 6.0 ml.

Other requirements Comply with the general requirements for tablets except disintegration test (Appendix I A).

Assay Weigh accurately and powder 10 tablets. Shake well an accurately weighed powder equivalent to about 50 mg of metronidazole in a 200 ml volumetric flask with 180 ml of hydrochloric acid solution (9→1000), dilute to volume and mix well, filter, measure accurately 5 ml of the successive filtrate to a 100 ml volumetric flask, add hydrochloric acid solution (9→1000) to volume and mix well. Measure the absorbance of the solution at 277 nm (Appendix IV A). Calculate the content of $C_6H_9N_3O_3$, taking 377 as the value of A (1%, 1 cm).

Category As described under Metronidazole.

Strength 0.2 g

Storage Preserve in tightly closed containers, stored in a cool and dry place.

Metronidazole and Glucose Injection

Metronidazole and Glucose Injection is a sterile solution of Metronidazole and Glucose in Water for Injection. It contains not less than 93.0% and not more than 107.0% of the labelled amount of metronidazole ($C_6H_9N_3O_3$) and glucose ($C_6H_{12}O_6 \cdot H_2O$).

Description A clear, colourless or pale yellow liquid.

Identification (1) Heat and evaporate 50 ml to about 8 ml, cool, allow to stand until crystals are formed in refrigerator. Filter, wash the crystals with a little water for 3 times. Transfer to a small beaker, the residue complies with test (1) for Identification described under Metronidazole.

(2) Heat and evaporate 50 ml to about 8 ml, cool, allow to stand until crystals are formed in refrigerator. Filter, wash the crystals with a little water for 3 times. Transfer to a small beaker, evaporate to dryness. The residue complies with test (2) for Identification described under Metronidazole.

(3) The light absorption of the solution obtained in the Assay exhibits a maximum at 277 nm and a minimum at 241 nm (Appendix IV A).

(4) Add dropwise 5 ml of the injection to hot alkaline cupric tartrate TS, a red precipitate of cuprous oxide is produced.

pH value 4.5-6.0 (Appendix VI H).

2-Methyl-5-nitroimidazole Dilute a quantity with water to produce a solution containing 0.1 mg of metronidazole per ml as the test solution, complies with test of 2-Methyl-5-nitroimidazole described under Metronidazole.

Heavy metals Measure a quantity equivalent to about 3 g of glucose, evaporate to about 20 ml on a water bath, allow to cool, add 2 ml of acetate BS (pH 3.5) and sufficient water to produce 25 ml. Carry out the limit test for heavy metals (Appendix VIII H, method 1); not more than 0.0005%.

Bacterial endotoxin Carry out the test for bacterial endotoxin (Appendix XI E); not more than 0.5 EU per ml.

Sterility Complies with the test for sterility (Appendix XI, H), treat as described under the Membrane filtration method, using clostridium sporogenes bacterial suspension as the control.

Other requirements Complies with the general requirements for injections (Appendix I B).

Assay Metronidazole To a quantity of the injection, accurately measured, add hydrochloric acid solution (9→1000) to produce a solution of 10 µg per ml, measure the absorbance at 277 nm (Appendix IV A). Calculate the content of $C_6H_9N_3O_3$, taking 377 as the value of A (1%, 1 cm).

Glucose Carry out the determination of optical rotation (Appendix VI E). The observed rotation in degree multiplied by 2.0852 represents the weight in g of $C_6H_{12}O_6 \cdot H_2O$ of the testing volume.

Category As described under Metronidazole.

Strength 250 ml : 0.5 g of metronidazole and 12.5 g of glucose

Storage Preserve in well closed containers, protected from light.

Metronidazole, Clotrimazole and Chlohexidine Acetate Suppositories

Metronidazole, Clotrimazole and Chlohexidine Acetate Suppositories contain not less than 90.0% and not more than 110.0% of the labelled amount of metronidazole ($C_6H_9N_3O_3$) and clotrimazole ($C_{22}H_{17}ClN_2$); Contain not less than 85.0% and not more than 115.0% of the labelled amount of chlohexidine acetate ($C_{22}H_{30}Cl_2N_{10} \cdot 2 C_2H_4O_2$).

Formula	Metronidazole	200 g
	Clotrimazole	160 g
	Chlohexidine Acetate	8 g
	Lanolin	sufficient quantity
	Parafin wax	sufficient quantity
	Semi-synthesized fatty	

glyceride (type 38)

sufficient quantity

to make

suppositories

Description Cream yellow suppositories.

Identification (1) To a quantity of the suppositories equivalent to about 0.1 g of Metronidazole add 8 ml of sodium hydroxide TS and warm, a violet-red colour is produced. Cool the solution to room temperature, extract with 8 ml of ethyl ether, shake and separate the water layer, acidify with dilute hydrochloric acid TS, a yellow colour is produced, an orange-red colour appears on adding excess sodium hydroxide.

(2) To the ethyl ether layer obtained in the test for Identification (1) add 5 ml of 1% cetyl-trimethyl-ammonium bromide solution, 1 ml of bromide TS and 1 ml of sodium hydroxide TS, shake and allow to stand, a red colour is produced in the water layer.

(3) Carry out the method for thin-layer chromatography (Appendix V B), using silica gel G as the coating substance and xylene-propanol-concentrated ammonia solution (180 : 20 : 1) as the mobile phase. Apply separately to the plate 10 ml each of two solutions in chloroform containing (1) 2 mg per ml of Clotrimazole CRS, (2) a quantity of suppositories being examined equivalent to about 2 mg of Clotrimazole per ml. After developing and removal of the plate, dry it in air and view with iodine vapour. The principal spot in the chromatography obtained with the solution (2) is identical in colour and position to that in the chromatography obtained with solution (1).

Other requirement Comply with the general requirements for suppositories (Appendix I D).

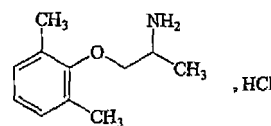
Assay Carry out the method for high performance liquid chromatography (Appendix V D), using a column packed with octylsilane bonded silica gel and a mixture of methanol-water-triethylamine (70 : 30 : 0.3) (containing 10 mmol/L heptane sodium sulfonate and adjust pH to 4.0 by phosphoric acid) as the mobile phase. Detection Wavelength is 260 nm. The number of the theoretical plates of the column is not less than 2500, calculated with reference to the peak of clotrimazole and the resolution factor between the peaks of metronidazole, clotrimazole and chlorhexidine should comply with the related requirements.

Procedure Take 10 suppositories, weighed accurately, to a beaker, warm on a 70-80°C water bath to melt, mix well and cool to room temperature. Transfer a quantity of the melted suppositories, weighed accurately, equivalent to about 20 mg of metronidazole into a 100 ml volumetric flask, add a quantity of mobile phase, shake on a 70-80°C water bath to dissolve the suppositories, then cool to room temperature, dilute with mobile phase to volume, mix well. Cool for 2 hours in a ice bath, then filter immediately, put the successive filtrate to room temperature as the test solution. Inject 20 µl of solution (1) into the column and record the chromatogram. Dissolve a quantity of metronidazole, clotrimazole and chlorhexidine acetate CRS in mobile phase to produce a solution of containing 200 µg of metronidazole, 160 µg of clotrimazole and 8 µg of chlorhexidine acetate per ml. Repeat the operations instead of the substance being examined, calculate the content of $C_6H_9N_3O_2$, $C_{22}H_{17}ClN_2$ and $C_{22}H_{30}Cl_2N_{10} \cdot 2C_2H_4O_2$ with respect to the peak area obtained in the chromatogram by the external standard method.

Category Antibacterial agent.

Storage Preserve in tightly closed containers, protected from light, stored below 30°C.

Mexiletine Hydrochloride


 $C_{11}H_{17}NO \cdot HCl$ 215.72

[5370-01-4]

Mexiletine Hydrochloride is 1-(2,6-dimethylphenoxy)-2-propanamine hydrochloride. It contains not less than 98.5% of $C_{11}H_{17}NO \cdot HCl$, calculated on the dried basis.

Description A white or almost white, crystalline powder; almost odourless; taste, bitter.

Freely soluble in water or ethanol; practically insoluble in ether.

Melting range 200-204°C (Appendix VI C).

Identification (1) Dissolve 0.1 g in 2 ml of water, add 2 drops of iodine TS, a brownish-red precipitate is produced.

(2) The light absorption of a 0.40 mg per ml solution in water exhibits a maximum at 261 nm; the absorbance is 0.44-0.48 (Appendix IV A).

(3) The infrared absorption spectrum (Appendix IV C) is concordant with the reference spectrum of mexiletine hydrochloride (Appendix XVI).

(4) The aqueous solution yields the reactions characteristic of chlorides (Appendix III).

Acidity Dissolve 1.0 g in 10 ml of water, pH 4.0-5.5 (Appendix VI H).

Clarity and colour of solution A solution of 0.5 g in 10 ml of water is clear and colourless; any colour produced is not more intense than that of reference solution Y₃, (Appendix IX A, method 1).

2,6-Dimethylphenol Carry out the method for thin-layer chromatography (Appendix V B), using silica gel G as the coating substance and a mixture of chloroform-methanol-concentrated ammonia TS (85 : 14 : 1) as the mobile phase. Apply separately to the plate 10 µl each of two solutions in methanol containing (1) 50 mg of the substance being examined per ml, (2) 0.1 mg of 2,6-dimethylphenol CRS per ml. After developing, dry it in air and spray with 0.1% Fast Blue BB salt in methanol solution, heat at 90°C for 10 minutes and spray with 3 mol/L solution of potassium hydroxide. Any spot in the chromatogram other than the principal spot obtained with solution (1) is not more intense than the principal spot obtained with solution (2).

Loss on drying When dried to constant weight at 105°C, loses not more than 1.0% of its weight (Appendix VIII L).

Residue on ignition Not more than 0.1% (Appendix VIII N); use 2.0 g.

Heavy metals Carry out the limit test for heavy metals (Appendix VIII H, method 2), using the residue obtained in the test for Residue on ignition; not more than 0.001%.

Assay. Dissolve about 0.16 g, accurately weighed, in 20 ml of glacial acetic acid and 5 ml of mercuric acetate TS, add 1 drop of crystal violet IS. Titrate with perchloric acid (0.1 mol/L) VS until the solution becomes blue. Perform a blank determination and make any necessary correction. Each ml of perchloric acid (0.1 mol/L) VS is equivalent to 21.57 mg of $C_{11}H_{17}NO \cdot HCl$.

Category Antiarrhythmic.

Storage Preserve in tightly closed containers.

Preparation (1) Mexiletine Hydrochloride Capsules
(2) Mexiletine Hydrochloride Injection
(3) Mexiletine Hydrochloride Tablets

Mexiletine Hydrochloride Capsules

Mexiletine Hydrochloride Capsules contain not less than 90.0% and not more than 110.0% of the labelled amount of Mexiletine Hydrochloride ($C_{11}H_{17}NO \cdot HCl$).

Description Capsules containing white powder.

Identification (1) Shake a quantity of the contents equivalent to about 0.25 g of Mexiletine Hydrochloride with 5 ml of water and filter. The filtrate complies with the following tests.

(i) To 1 ml of the filtrate, add 2 drops of iodine TS; a brownish-red precipitate is produced.

(ii) To 1 ml of the filtrate, add 2 drops of 0.01 mol/L sodium tetraphenylboron solution; a white turbidity is produced.

(iii) Yields the reactions characteristic of chlorides (Appendix III).

(2) Shake a quantity of the contents with water to produce a solution containing 0.4 mg of Mexiletine Hydrochloride per ml and filter. The light absorption of the filtrate exhibits a maximum at 261 nm (Appendix IV A).

Other requirements Comply with the general requirements for capsules (Appendix I E).

Assay Dissolve an accurately weighed quantity of the mixed contents in the test for Weight variation, equivalent to about 0.16 g of Mexiletine Hydrochloride, in 20 ml of glacial acetic acid, add 5 ml of mercuric acetate TS and a drop of crystal violet IS, titrate with perchloric acid (0.1 mol/L) VS until the colour changes to blue. Perform a blank determination and make any necessary correction. Each ml of perchloric acid (0.1 mol/L) VS is equivalent to 21.57 mg of $C_{11}H_{17}NO \cdot HCl$.

Category Antiarrhythmic agent.

Strength (1) 50 mg (2) 100 mg

Storage Preserve in tightly closed containers, protected from light.

Mexiletine Hydrochloride Injection

Mexiletine Hydrochloride Injection is sterile solution of Mexiletine Hydrochloride in Water for Injection. It contains not less than 95.0% and not more than 105.0% of the labelled amount of mexiletine hydrochloride ($C_{11}H_{17}NO \cdot HCl$).

Description A clear, colourless liquid.

Identification (1) To 1 ml add 2 drops of iodine TS, a brownish-red precipitate is produced.

(2) To 1 ml add 2 drops of 0.01 mol/L sodium tetraphenylborate, a white turbidity is produced.

(3) Dilute a quantity of the injection with water to produce a solution of 0.4 mg per ml, the solution complies with test

(2) for Identification described under Mexiletine Hydrochloride.

(4) The aqueous solution yields the reactions characteristic

of chlorides (Appendix III).

pH value 4.5-6.5 (Appendix VI H).

Related substances Carry out the method for thin-layer chromatography (Appendix V B), using silica gel G as the coating substance and a mixture of chloroform-methanol-concentrated ammonia solution (85 : 14 : 1) as the mobile phase. Apply separately to plate 10 μ l each of the following solutions. Add 16 ml of methanol to a quantity of the injection equivalent to 0.1 g of mexiletine hydrochloride, mix well, evaporate to dryness and dissolve the residue in methanol to produce a solution of 50 mg per ml as solution (1). Dilute an accurately measured quantity of solution (1) with methanol to produce a solution of 0.25 mg per ml as solution (2). After developing and removal of the plate, dry in air, spray with ninhydrin TS and heat at 105°C for 15 minutes. Any spot, other than the principal spot, in the chromatogram obtained with solution (1) is not more intense than the principal spot obtained with solution (2).

2,6-Dimethylphenol Comply with the test for 2,6-Dimethylphenol described under Mexiletine Hydrochloride, using the solution prepared under test for Related substances.

Other requirements Complies with the general requirements for injections (Appendix I B).

Assay Measure accurately 2 ml to a 200 ml volumetric flask, dilute with (0.01 mol/L) hydrochloric acid solution to volume, mix well. Measure the absorbance at 261 nm (Appendix IV A). Dissolve an accurately weighed quantity of mexiletine hydrochloride CRS in 0.01 mol/L hydrochloric acid solution to produce a solution of about 0.5 mg per ml. Measure the absorbance in the same manner, calculate the content of $C_{11}H_{17}NO \cdot HCl$ accordingly.

Category As described under Mexiletine Hydrochloride.

Strength 2 ml : 100 mg

Storage Preserve in well closed containers, stored in a cool and dark place.

Mexiletine Hydrochloride Tablets

Mexiletine Hydrochloride Tablets contain not less than 93.0% and not more than 107.0% of the labelled amount of Mexiletine Hydrochloride ($C_{11}H_{17}NO \cdot HCl$).

Description White tablets.

Identification (1) To a quantity of the powder equivalent to about 0.5 g of mexiletine hydrochloride add 10 ml of water, stir well and filter. The filtrate complies with tests (1) and (4) for Identification described under Mexiletine Hydrochloride. (2) Dissolve a quantity in water to produce a solution containing 0.4 mg of mexiletine hydrochloride per ml, filter. The light absorption of this solution exhibits a maximum at 261 nm (Appendix IV A).

Other requirements Comply with the general requirements for tablets (Appendix I A).

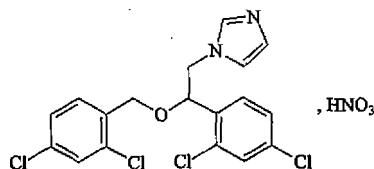
Assay Weigh accurately and powder finely 20 tablets. To a quantity of the powder equivalent to about 0.6 g of mexiletine hydrochloride, accurately weighed, in a 100 ml volumetric flask add 25 ml of water, shake thoroughly, dilute with water to volume, mix well and filter. Measure accurately 25 ml of the successive filtrate, evaporate to dryness on a water bath. Dry the residue at 105°C, complete the Assay described under Mexiletine Hydrochloride, beginning at the words "in 20 ml of glacial

acetic acid, add 5 ml of mercuric acetate TS. . .". Each ml of perchloric acid (0.1 mol/L) VS is equivalent to 21.57 mg of $C_{11}H_{17}NO \cdot HCl$.

Category, Storage As described under Mexiletine Hydrochloride.

Strength (1) 50 mg (2) 100 mg

Miconazole Nitrate



$C_{18}H_{14}Cl_4N_2O \cdot HNO_3$ 479.15

[22832-87-7]

Miconazole Nitrate is 1-[2,4-dichloro-β (2,4-dichlorobenzoyloxy) phenethyl] imidazole Nitrate. It contains not less than 98.5% and not more than 101.5% of $C_{18}H_{14}Cl_4N_2O \cdot HNO_3$, calculated on dried basis.

Description White or almost white crystals or crystalline powder, odourless or almost odourless. Sparingly soluble in methanol, slightly soluble in ethanol or chloroform, insoluble in ether or water.

Melting range 178-184°C with decomposition.

Identification (1) To 3 mg add one drop of diphenylamine TS, a deep blue colour develops.

(2) The light absorption of the solution of about 0.4 mg per ml in a mixture of methanol and 0.1 mol/L hydrochloric acid solution (9 : 1) exhibits three maxima at 264 nm, 272 nm and 280 nm, respectively.

(3) The infrared absorption spectrum (Appendix IV C) is concordant with the reference spectrum of miconazole nitrate (Appendix XVI).

(4) Carry out the oxygen flask combustion (Appendix VII C), using about 20 mg, and 5 ml of 0.5% sodium hydroxide solution as absorbing solution. Shake thoroughly, to the resulting solution add 15 ml of water and acidify with dilute nitric acid. The solution yields reactions characteristic of chloride (Appendix III).

Related substances Carry out the method for thin-layer chromatography (Appendix V B) using silica gel G as the coating substance and a mixture of hexane-chloroform and methanol (54 : 28 : 18) as the mobile phase. Apply separately to the plate 50 μl of each of two solutions of the substance being examined in chloroform and methanol (1 : 1) containing (1) 10 mg and (2) 25 μg per ml, respectively. Place a beaker with 5 ml of concentrated ammonia solution in chromatographic chamber. After developing and removal of the plate, allow it to dry in air and expose the plate to iodine vapour. Any secondary spot in the chromatogram obtained with solution (1) is not more intense than the principal spot in the chromatogram obtained with solution (2).

Loss on drying Dry it at 105°C to constant weight, loses not more than 0.5% (Appendix VIII L).

Residue on ignition Not more than 0.2% (Appendix VIII N).

Assay Dissolve 0.25 g accurately weighed in 35 ml of a mixture of equal volume of glacial acetic acid and acetic anhydride. Carry out the method for potentiometric titration (Appendix VII A). Titrate with perchloric acid (0.1 mol/L)

VS. Perform a blank determination and make any necessary correction. Each ml of 0.1 mol/L of perchloric acid is equivalent to 47.92 mg of $C_{18}H_{14}Cl_4N_2O \cdot HNO_3$.

Category Antifungal.

Storage Preserve in tightly close container.

Preparations (1) Miconazol Nitrate Capsules
(2) Miconazol Nitrate Cream
(3) Miconazol Nitrate Liniment

Miconazol Nitrate Capsules

Miconazol Nitrate Capsules contains not less than 90.0% and not more than 110.0% of labelled quantity of miconazol nitrate ($C_{18}H_{14}Cl_4N_2O \cdot HNO_3$).

Description Capsules containing white or almost white crystalline powder; odourless or almost odourless.

Identification (1) To a small quantity add a drop of diphenylamine solution (to 0.1 g add the mixture of 10 ml of sulfuric acid and 2 ml of water, cool), a deep blue develops. (2) The light absorption of the solution of 0.4 mg per ml in methanol and hydrochloric acid solution 0.1 mol/L exhibits three maxima at 264 nm, 272 nm and 280 nm, respectively, with corresponding absorbances of 0.40, 0.54 and 0.44.

(3) Carry out the method of oxygen flask combustion (Appendix VII C) using 5 ml of 5% sodium hydroxide as the absorption solution. When the combustion is complete. To the result solution add 15 ml of water, it yields a reaction characteristic of chloride (Appendix III).

Other requirements Comply with the general requirements for capsules (Appendix I E).

Assay Carry out the method for high performance liquid chromatography (Appendix V D), using a column packed with octadecylsilane bonded silica gel and a mixture of acetonitrile-methanol-0.5% ammonium acetate solution (42.5 : 42.5 : 15) as the mobile phase. Detection Wavelength is 230 nm. The number of the theoretical plates of the column is generally 7000, calculated with reference to the peak of miconazole nitrate.

Procedure Transfer an accurately weighed quantity of mixed contents from test for weight variation of content, be equivalent to about 0.25 g of miconazole nitrate, to a 100 ml volumetric flask, add methanol to dissolve miconazole nitrate and dilute to volume, mix well and filter. Measure accurately 2 ml of the successive filtrate to a 10 ml volumetric flask and dilute with methanol to volume, mix well as the test solution. Inject 20 μl of the test solution into the column and record the chromatogram. Dissolve a quantity of miconazole nitrate CRS, weighed accurately, with methanol to produce a solution of about 0.5 mg per ml as the reference solution. Repeat the operations instead of the test solution, calculate the content of $C_{18}H_{14}Cl_4N_2O \cdot HNO_3$ with respect to the peak area obtained in the chromatogram by the external standard method.

Category As described under miconazol nitrate.

Strength 0.25 g

Storage Preserve in tightly closed container and protected from light.

Miconazole Nitrate Cream

Miconazole Nitrate Cream contains not less than 90.0% and not more than 110.0% of labelled amount of miconazole nitrate ($C_{18}H_{14}Cl_4N_2O \cdot HNO_3$).

Description A white or almost white cream.

Identification Carry out the method for thin-layer chromatography as described under relative substance of miconazol nitrate (Appendix V B). Apply separately to the same plate 10 μ l of each of the following solution. Solution (1) is the supernatant liquid centrifuged with the solution of substance being examined (equivalent to about 40 mg of miconazol nitrate) dissolved in 10 ml of anhydrous ethanol by heating on water bath and cool. Solution (2) is solution of 10 mg of miconazole nitrate CRS in 10 ml of anhydrous ethanol. The position and colour of the principle spot obtained from the solution (1) corresponds to that obtained from solution (2).

Other requirement Complies with the general requirement for creams (Appendix I F).

Assay Carry out the method for high performance liquid chromatography (Appendix V D), using a column packed with octadecylsilane bonded silica gel and a mixture of 0.5% ammonium acetate solution-acetonitrile-methanol (15 : 42.5 : 42.5) as the mobile phase. Detection wavelength is 230 nm. The resolution factor between the peaks of miconazol nitrate and internal standard complies with the related requirements.

Internal standard solution Dissolve a quantity of dibutyl phthalate with a mixture of methanol-chloroform (1 : 1) to produce a solution of about 1.6 mg per ml.

Procedure Transfer about 2.5 g of accurately weighed cream to a 50 ml volumetric flask, add 25 ml of internal standard solution, dilute to volume with a mixture of methanol-chloroform (1 : 1) and mix well, filter. Inject 10 μ l of the successive filtrate into the column. Repeat the operation, using miconazole nitrate CRS instead of the substance being examined, calculate the content of $C_{18}H_{14}Cl_4N_2O \cdot HNO_3$.

Category As described under miconazol nitrate.

Strength 2%

Storage Preserve in tightly closed container.

Miconazole Nitrate Liniment

Miconazole Nitrate Liniment contains not less than 90.0% and not more than 110.0% of labelled amount of miconazole nitrate ($C_{18}H_{14}Cl_4N_2O \cdot HNO_3$).

Description A clear, colourless to slight yellow liquid.

Identification The retention time of the principal peak in the chromatogram of the test preparation obtained under the Assay is identical with that of the principal peak in the chromatogram of the reference preparation.

Other requirements Complies with the requirements for Liniments (Appendix I T).

Assay Carry out the method for high performance liquid chromatography (Appendix V D), using a column packed with octadecylsilane bonded silica gel and a mixture of acetonitrile-methanol-0.5% ammonium acetate solution

(42.5 : 42.5 : 15) as the mobile phase. Detection wavelength is 230 nm and the number of the theoretical plates of the column is generally 7000, calculated with reference to the peak of miconazole nitrate.

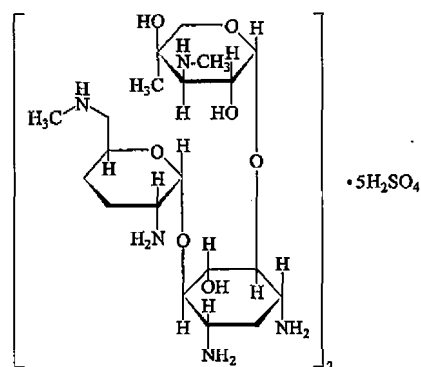
Procedure Transfer accurately 2 ml of the liniment, equivalent to 40 mg of miconazole nitrate, into a 100 ml volumetric flask, dilute to volume with methanol and mix well, as test solution. Inject 20 μ l of the test solution into the column and record the chromatogram. Repeat the operation, using a reference solution containing 0.4 mg of miconazole nitrate CRS per ml in methanol instead of the test solution. Calculate the content of $C_{18}H_{14}Cl_4N_2O \cdot HNO_3$ with respect to the peak area obtained in the chromatogram by the external standard method.

Category As described under Miconazole Nitrate.

Strength 2%

Storage Preserve in tightly closed containers, protected from light.

Micronomicin Sulfate



$(C_{20}H_{41}N_5O_7)_2 \cdot 5H_2SO_4$ 1417.52

Micronomicin sulfate is O-3-amino-2,3,4,6-tetradeoxy-6-methylamino- α -D-erythro-hexopyranosyl-(1 \rightarrow 4)-O-[3-deoxyl-4-C-methyl-3-methylamino- β -L-arabinopyranosyl-(1 \rightarrow 6)]-2-deoxyl-D-streptamine hemihydrate sulfate. It has a potency of not less than 590 micronomicin Units per mg, calculated on the anhydrous basis.

Description A white or almost white powder; odourless; hygroscopic; freely soluble in water, practically insoluble in methanol, ethanol, acetone, ethyl acetate or chloroform.

Specific optical rotation +110° to +130° (Appendix VI E), in a solution of 10 mg per ml in water.

Identification (1) To about 5 mg, add water to dissolve, then mix with 1 ml of 0.1% ninhydrin in n-butanol saturated with water and 0.5 ml of pyridine, heat on a water bath for a few minutes. A violet colour is produced immediately.

(2) Carry out the method for thin-layer chromatography (Appendix V B), using silica gel G as the coating substance and the lower layer of a mixture of chloroform-methanol-ammonia (4 : 3 : 2) as the mobile phase. Apply separately to the plate 5 μ l each of the two solutions in water containing (1) 5 mg per ml of the substance being examined and (2) 5 mg per ml of micronomicin CRS. After developing and removal of the plate, allow to dry at 20-25°C and expose it to iodine vapor. The position and colour of the principal spot in the chromatogram obtained with solution (1) correspond to

that of the principal spot obtained with solution (2).

(3) The retention time of the principal peak in the test solution in the chromatogram obtained in the Purity is identical with that of the principal peak of micronomicin CRS in the chromatogram of the reference solution correspondingly.

(4) The aqueous solution yields the reaction characteristic of sulfate (Appendix III).

Test (2) and (3) are alternative.

Acidity An aqueous solution of 50 mg per ml, pH 4.0-6.5 (Appendix VI H).

Clarity and colour of solution Dissolve 1.0 g each of 5 portions in 10 ml of water respectively, the solutions are clear and colourless; any opalescence produced is not more pronounced than that of reference suspension 1 (Appendix IX B); any colour produced is not intense than that of reference solution Y₂ or YG₂ (Appendix IX A method 1) for injection.

Sulphate Dissolve about 0.125 g, accurately weighed, in 100 ml of distilled water, adjust the pH value of the solution to 11 with concentrated ammonia solution. Add accurately 10 ml of 0.1 mol/L barium chloride VS and five drops of phthalein purple IS. Titrate with 0.05 mol/L disodium edetate VS (Notice: keep the pH value at 11 during the titration), adding 50 ml of alcohol when the colour of the solution begins to change and continue the titration until the violet-blue colour disappears. Perform a blank determination and make any necessary correction. Each ml of barium chloride VS (0.1 mol/L) is equivalent to 9.606 mg of SO₄; not less than 32.0% and not more than 37.0%, calculated on the anhydrous basis.

Water Not more than 12.0% (Appendix VIII M, method 1 A).

Residue on ignition Not more than 0.5% (Appendix VIII N).

Bacterial endotoxin Carry out the test for bacterial endotoxin (Appendix XI E), less than 0.5 EU per 1000 micronomicin Units (for injection).

Purity Carry out the method for high-performance liquid chromatography (Appendix V D), using a column packed with octadecylsilane bonded silica gel (pH adaptive value is 0.8-8.0) and a mixture of 0.2 mol/L trifluoroacetic acid-methanol (94 : 6) as the mobile phase. The flow rate is 0.6 ml per minute. The drift tube temperature of evaporative light-scattering detector (ELSD) is 110°C, the flow rate of the carrier gas is 2.8 L per minute and Impactor is off (these parameters can be adjusted if necessary). Dissolve an amount of gentamycin C_{1a} CRS and micronomicin CRS in water to obtain a solution containing 0.2 mg each of the two substances per ml. Inject 20 µl of the solution into the column. The resolution factor between the peaks of gentamycin C_{1a} and micronomicin complies with the related requirements. The relative standard deviation (RSD) for replicate 5 injections is less than 2.0%.

Procedure Dissolve an accurately weighed quantity of micronomicin CRS in water to produce solutions of 0.2, 0.5, 1.0 mg per ml respectively as reference solution (1), (2), (3). Inject 20 µl each of the three solutions into the column. Based on the corresponding concentrations (C) and areas (A) of micronomicin in reference solution (1), (2), (3), the linear regression equation of logA versus logC can be determined. The correlation coefficient (r) of the regression equation should be greater than 0.99; Dissolve an accurately weighed quantity of the substance being examined with water to produce a solution of about 0.4 mg per ml as test solution. Inject 20 µl of the solution into the column. Calculate the content of C₂₀H₄₁N₅O₇ based on the regression equation and the corresponding peak area of micronomicin in the

chromatogram of test solution. Not less than 85.0% of C₂₀H₄₁N₅O₇ of the labelled amount.

Assay Carry out the method for Microbiological Assay of Antibiotics (Appendix XI A), using a solution of 1000 Units per ml in sterile water. The confidence-limit rate is not more than 7%. 1000 micronomicin units is equivalent to 1 mg of micronomicin.

Category Aminoglycoside Antibiotics.

Storage Preserve in tightly closed containers, stored in a dry place.

Preparation (1) Micronomicin Sulfate Injection
(2) Micronomicin Sulfate Oral Solution
(3) Micronomicin Sulfate Tablets

Micronomicin Sulfate Injection

Micronomicin Sulfate Injection is a sterile solution of micronomicin sulfate in water for injection. It contains not less than 90.0% and not more than 110.0% of the labelled amount of micronomicin (C₂₀H₄₁N₅O₇).

Description A clear, colourless or almost colourless liquid.

Identification Complies with the tests for Identification described under Micronomicin Sulfate.

pH Value pH 5.5-7.5 (Appendix VI H).

Colour of solution The solution is colourless; any colour produced is not intense than that of reference solution Y₂ or YG₂ (Appendix IX A, method 1).

Purity Transfer an accurately measured volume of the sample solution and dilute with sterile water to produce a solution of 0.4 mg of micronomicin per ml as the test solution. Carry out the Purity described under Micronomicin Sulfate. Not less than 81.0% of micronomicin of the labelled amount.

Sterility Transfer the samples to not less than 500 ml of 0.9% sterile sodium chloride solution, mix well, carry out the test for sterility (Appendix XI H, membrane filtration method).

Bacterial endotoxin Carry out the test for bacterial endotoxin (Appendix XI E), less than 0.50 EU per 1000 micronomicin Units.

Other requirements Complies with the general requirements for injections (Appendix I B).

Assay Dilute an accurately measured volume of the sample solution with sterile water to produce a solution of 1000 Units per ml, carry out the Assay described under Micronomicin Sulfate.

Category As described under Micronomicin Sulfate.

Strength (1) 1 ml : 30 mg (30000 micronomicin Units)
(2) 2 ml : 60 mg (60000 micronomicin Units)
(3) 2 ml : 80 mg (80000 micronomicin Units)

Storage Preserve in well closed containers, stored in a cool and dark place.

Micronomicin Sulfate Oral Solution

Micronomicin Sulfate Oral Solution contains not

less than 90.0% and not more than 110.0% of the labelled amount of micronomicin ($C_{20}H_{41}N_5O_7$).

Description A clear, almost colourless to yellow liquid; sweet.

Identification Comply with the tests for Identification described under Micronomicin Sulfate.

pH Value pH 3.5-5.5 (Appendix VI H).

Purity Transfer an accurately measured volume of the sample solution and dilute with sterile water to produce a solution of 0.4 mg of micronomicin per ml as the test solution. Carry out the Purity described under Micronomicin Sulfate. Not less than 81.0% of micronomicin of the labelled amount.

Other requirements Complies with the general requirements for oral solutions (Appendix I O).

Assay Dilute an accurately measured volume of the sample solution with sterile water to produce a solution of 1000 Units per ml, carry out the Assay described under Micronomicin Sulfate.

Category As described under Micronomicin Sulfate.

Strength 10 ml : 80 mg (80000 micronomicin Units)

Storage Preserve in tightly closed containers, stored in a cool and dark place.

Micronomicin Sulfate Tablets

Micronomicin Sulfate Tablets contain not less than 90.0% and not more than 110.0% of the labelled amount of micronomicin ($C_{20}H_{41}N_5O_7$).

Description Sugar coated or film coated tablets with white to pale yellow core.

Identification To a quantity of powdered tablets, equivalent to 25 mg of micronomicin, add 5 ml of water, filter, the successive filtrate complies with the tests for Identification described under Micronomicin Sulfate.

Purity Dissolve an accurately weighed quantity of powdered tablets with sterile water and dilute to produce a solution of 0.4 mg of micronomicin per ml as the test solution. Carry out the Purity described under Micronomicin Sulfate. Not less than 81.0% of micronomicin of the labelled amount.

Other requirements Comply with the general requirements for tablets (Appendix I A).

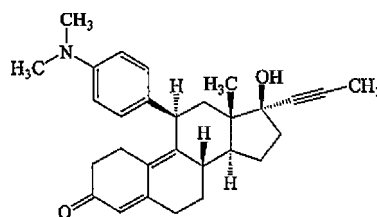
Assay Take and powder 5 tablets. Dissolve a quantity of the powdered tablets in sterile water and dilute to produce a solution of 1000 Units per ml, carry out the Assay described under Micronomicin Sulfate.

Category As described under Micronomicin Sulfate.

Strength 40 mg (40000 micronomicin Units)

Storage Preserve in tightly closed containers, stored in a cool and dark place.

Mifepristone



$C_{29}H_{35}NO_2$ 429.61

Mifepristone is 11-β [4-(N, N-Dimethylamino)-1-phenyl]-17β-hydroxy-17α-(1-propynyl)-estra-4,9-dien-3-one. It contains not less than 98.5% of $C_{29}H_{35}NO_2$, calculated on the dried basis.

Description A pale yellow crystalline powder; odourless, tasteless. Very soluble in methanol or dichloromethane; soluble in ethanol or ethyl acetate; practically insoluble in water.

Melting point 192-196°C (Appendix VI C).

Specific optical rotation +124° to +129°, in a solution of 5 mg per ml in dichloromethane (Appendix VI E).

Identification (1) The light absorption of a solution of 10 µg per ml in ethanol exhibits maxima at 304 nm and 260 nm (Appendix IV A).

(2) The infrared absorption spectrum (Appendix IV C) is concordant with the reference spectrum of mifepristone (Appendix XVI).

Related substances To a quantity, add methanol to produce a solution of 0.5 mg per ml as test solution. Measure accurately 2 ml of the test solution, to a 100 ml volumetric flask, dilute with methanol to volume, mix well, taking the solution as reference solution. Carry out the method for high performance liquid chromatography (Appendix V D), using a column packed with octadecylsilane bonded silica gel and a mixture of methanol-water-triethylamine (75 : 25 : 0.05) as the mobile phase. Detection wavelength is 304 nm and the number of the theoretical plates of the column is not less than 2000, calculated with reference to the peak of mifepristone. Inject 10 µl of the reference solution into the column, adjust the attenuation so that the principal peak height in the chromatogram is about 10% of full scale of the chart. Inject 10 µl each of the test solution and the reference solution into the column separately, and record the chromatogram for twice the retention time of the principal peak. The sum of the area of secondary peaks other than the principal peak is not greater than the area of the principal peak in the chromatogram obtained with the reference solution.

Loss on drying when dried to constant weight at 105°C, loses are not more than 0.5% of its weight (Appendix VIII L).

Assay Dissolve about 0.3 g, accurately weighed, in 20 ml of glacial acetic acid, add 1 drop of crystal violet IS, titrate with perchloric acid (0.1 mol/L) VS until the colour changes to bluish green. Perform a blank determination and make any necessary correction. Each ml of perchloric acid (0.1 mol/L) VS is equivalent to 42.96 mg of $C_{29}H_{35}NO_2$.

Category Earlier period conceived terminator.

Storage Preserve in tightly closed containers, protected from light.

Preparation mifepristone tablets

Mifepristone Tablets

Mifepristone Tablets contain not less than 90.0% and not more than 110.0% of the labelled amount of mifepristone ($C_{29}H_{35}NO_2$).

Description Slightly yellow tablets.

Identification A quantity of powdered tablets, equivalent to about 20 mg of mifepristone, complies with the test (1) for Identification as described under Mifepristone.

Content uniformity Comply with the requirements for content uniformity (Appendix X E). Transfer 1 tablet (for strength 10 mg) to a 100 ml volumetric flask, add a quantity of 0.1 mol/L hydrochloric acid solution, shake to dissolve mifepristone, dilute with 0.1 mol/L hydrochloric acid solution to volume and shake thoroughly, filter. Transfer 5 ml of the successive filtrate, accurately measured, to a 50 ml volumetric flask, dilute with 0.1 mol/L hydrochloric acid solution to volume and mix well, measure the absorbance of the resulting solution at 310 nm (Appendix IV A). Calculate the content of $C_{29}H_{35}NO_2$, taking 463 as the value of A (1%, 1 cm).

Dissolution Carry out the test for the dissolution (Appendix X C, method 1), using 900 ml of 0.1 mol/L hydrochloric acid solution as the dissolution medium and adjust the rotational speed of the basket to 100 rpm. Withdraw 15 ml of the solution after exact 30 minutes and filter. Dilute 10 ml of the successive filtrate, accurately measured, with dissolution medium to produce a solution of 10 µg per ml. Measure the absorbance of the resulting solution at 310 nm (Appendix IV A). Calculate the dissolution of $C_{29}H_{35}NO_2$ from each tablet, taking 463 as the value of A (1%, 1 cm). Not less than 75% of the labelled amount is dissolved.

Other requirements Comply with the general requirements for tablets (Appendix I A).

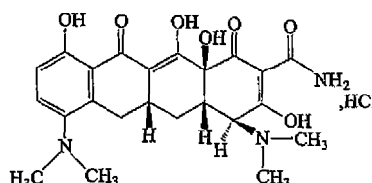
Assay Weigh accurately and powder 20 tablets. Weigh accurately a quantity of the powdered tablets, equivalent to about 50 mg of mifepristone, to a 100 ml volumetric flask, add a quantity of 0.1 mol/L hydrochloric acid solution and shake to dissolve mifepristone, dilute with 0.1 mol/L hydrochloric acid solution to volume and shake thoroughly, filter. Transfer 2 ml of the successive filtrate, accurately measured, to a 100 ml volumetric flask, dilute with 0.1 mol/L hydrochloric acid solution to volume and mix well, measure the absorbance of the resulting solution at 310 nm (Appendix IV A). Calculate the content of $C_{29}H_{35}NO_2$, taking 463 as the value of A (1%, 1 cm).

Category As described under mifepristone.

Strength (1) 10 mg (2) 25 mg (3) 0.2 g

Storage Preserve in tightly closed containers, protected from light.

Minocycline Hydrochloride



$C_{23}H_{27}N_3O_7 \cdot HCl$ 493.94

Minocycline Hydrochloride is [4S-(4 α , 4a α , 5a α , 12a α)]-4,7-bis(dimethylamino)-1,4,4a,5,5a,6,11,12a-octahydro-3,10,12,12 α -tetrahydroxy-1,11-dioxo-2-tetracyclic-carboxamide hydrochloride. It contains not less than 89.0% and not more than 95.0% of $C_{23}H_{27}N_3O_7$, calculated on the anhydrous basis.

Description A yellow crystalline powder; odourless; taste bitter; hygroscopic.

Soluble in methanol; sparingly soluble in water; slightly soluble in ethanol; practically insoluble in ether.

Identification (1) The retention time of the principal peak of the substance being examined in the chromatogram obtained in the Assay is identical with that of minocycline CRS in the chromatogram.

(2) The infrared absorption spectrum (Appendix IV C) is concordant with the reference spectrum of minocycline hydrochloride (Appendix XVI).

(3) The aqueous solution yields the reactions characteristic of chloride (Appendix III).

Crystallinity Complies with the test for crystallinity (Appendix IX D).

Acidity An aqueous solution of 10 mg per ml, pH 3.5-4.5 (Appendix VI H).

Water 4.3%-8.0% (Appendix VIII M, method 1 A).

Residue on ignition Not more than 0.5% (Appendix VIII N).

Heavy metals Carry out the limit test for heavy metals (Appendix VIII H, method 2), using the residue obtained in the test for Residue on ignition; not more than 0.005%.

Related substances Protect from light throughout the procedure. Carry out the method described under Assay. Dissolve a quantity of the substance being examined, accurately weighed, in water to produce solutions of 0.5 mg per ml (solution 1) and 5 µg per ml (solution 2). Inject 10 µl of solution (2) into the column, adjust the attenuation so that the principal peak height is 20%-25% of the full scale of the chart. Inject separately 10 µl each of solution (1) and (2), and record the chromatogram for 2.6 times the retention time of the principal peak. The peak area of 4-epiminocycline is not greater than 1.2 times of the principal peak area in the chromatogram obtained with solution (2) and any other peak area and the sum of the areas of all peaks other than the principal peak are not greater than 1.2 times and twice of the principal peak area in the chromatogram obtained with solution (2) respectively. (Disregard any peak with an area less than 0.05 times of area of the principal peak in the chromatogram obtained with solution (2).)

Assay Carry out the method for high performance liquid chromatography (Appendix V D), using a column packed with octylsilane bonded silica gel and a mixture of 0.2 mol/L ammonium acetate solution-N, N-dimethylformamide-tetrahydrofuran (600 : 398 : 2, with 0.01 mol/L disodium

edetate) as the mobile phase. Detection wavelength is 280 nm. Weigh about 10 mg of minocycline hydrochloride CRS into a 25 ml volumetric flask, add 5 ml of water to dissolve minocycline, heat the solution in a water bath at 100°C for 60 minutes, cool and dilute with water to volume and mix well. Inject 10 μ l of the resulting solution into the column and record the chromatogram. The tail factor of the peak of minocycline is not less than 0.9 and not more than 1.35. The resolution factor between the peaks of minocycline and 4-epiminocycline (relative retention time is about 0.8) is not less than 2.5. The number of theoretical plates of the column is not less than 3000, calculated with reference to the peak of minocycline.

Procedure Dissolve a quantity of the substance being examined, equivalent to about 50 mg of minocycline, accurately weighted, in water in a 100 ml volumetric flask and dilute to volume, mix well. Inject 10 μ l into the column and record the chromatogram. Repeat the operation, using minocycline CRS instead of the substance being examined. Calculate the content of $C_{23}H_{27}N_3O_7$ with respect to the peak area obtained in the chromatogram by the external standard method.

Category Tetracycline antibiotic.

Storage Preserve in tightly closed containers, protected from light.

Preparation (1) Minocycline Hydrochloride Capsules
(2) Minocycline Hydrochloride Tablets

Minocycline Hydrochloride Capsules

Minocycline Hydrochloride Capsules contain not less than 90.0% and not more than 110.0% of the labelled amount of minocycline ($C_{23}H_{27}N_3O_7$).

Description The contents are yellow or dark yellow powder or granules.

Identification (1) The retention time of the principal peak of the substance being examined in the chromatogram obtained in the Assay is identical with that of minocycline CRS in the chromatogram.

(2) To a quantity of the contents of capsules, equivalent to about 20 mg of minocycline, add 20 ml of water, shake to dissolve minocycline and filter. The successive filtrate yields the reactions characteristic of chloride (Appendix III).

Dissolution Carry out the dissolution test (Appendix X C, method 2), using 900 ml of water as the dissolution medium, adjust the rotational speed of the paddle to 50 rpm. Withdraw a quantity of the solution after exactly 45 minutes and filter. Dilute a quantity of the successive filtrate with water to produce a solution of about 15 μ g per ml. Dissolve an accurately weighed quantity of minocycline hydrochloride CRS in water to produce a solution of 15 μ g per ml. Measure the absorbances of the resulting solutions at 348 nm (Appendix IV A). Calculate the dissolution of $C_{23}H_{27}N_3O_7$ from each capsule. Not less than 80% of the labelled amount is dissolved.

Related substances Protect from light throughout the procedure. Dissolve an accurately weighed quantity of the mixed contents obtained in weight variation in water to produce solutions of 0.5 mg per ml (solution 1) and 5 μ g per ml (solution 2). Carry out the Related substances described under Minocycline Hydrochloride.

Water Not more than 12.0% (Appendix VIII M, method 1 A), using a quantity of the contents of the capsules.

Other requirements Comply with the general requirements

for capsules (Appendix I E).

Assay Weigh accurately a quantity of the mixed contents obtained in weight variation, equivalent to about 50 mg of minocycline, into a 100 ml volumetric flask, add 80 ml of water and ultrasonic for 5 minutes to dissolve minocycline, dilute with water to volume and mix well. Filter and use the successive filtrate as the test solution. Carry out the Assay described under Minocycline Hydrochloride.

Category As described under Minocycline Hydrochloride.

Strength Calculate as $C_{23}H_{27}N_3O_7$ (1) 50 mg (2) 100 mg

Storage Preserve in tightly closed containers, protected from light.

Minocycline Hydrochloride Tablets

Minocycline Hydrochloride Tablets contain not less than 90.0% and not more than 110.0% of the labelled amount of minocycline ($C_{23}H_{27}N_3O_7$).

Description Yellow tablets or sugar or film coated tablets with yellow core.

Identification (1) The retention time of the principal peak of the substance being examined in the chromatogram obtained in the Assay is identical with that of minocycline CRS in the chromatogram.

(2) To a quantity of powdered tablets, equivalent to about 20 mg of minocycline, add 20 ml of water, shake to dissolve minocycline and filter. The successive filtrate yields the reactions characteristic of chloride (Appendix III).

Dissolution Carry out the dissolution test (Appendix X C, method 2), using 900 ml of water as the dissolution medium, adjust the rotational speed of the paddle to 50 rpm. Withdraw a quantity of the solution after exactly 45 minutes and filter. Dilute a quantity of the successive filtrate with water to produce a solution of about 15 μ g per ml. Dissolve an accurately weighed quantity of minocycline hydrochloride CRS in water to produce a solution of 15 μ g per ml. Measure the absorbances of the resulting solutions at 348 nm (Appendix IV A). Calculate the dissolution of $C_{23}H_{27}N_3O_7$ from each tablet. Not less than 80% of the labelled amount is dissolved.

Related substances Protect from light throughout the procedure. Weigh accurately and powder 10 tablets. Dissolve an accurately weighed quantity of the powdered tablets in water to produce solutions of 0.5 mg per ml (solution 1) and 5 μ g per ml (solution 2). Carry out the Related substances described under Minocycline Hydrochloride.

Water Not more than 12.0% (Appendix VIII M, method 1 A), using a quantity of powdered tablets.

Other requirements Comply with the general requirements for tablets (Appendix I A).

Assay Weigh accurately and powder 10 tablets. Weigh accurately a quantity of the powdered tablets, equivalent to about 50 mg of minocycline, into a 100 ml volumetric flask, add 80 ml of water and ultrasonic for 5 minutes to dissolve minocycline, dilute with water to volume and mix well. Filter and use the successive filtrate as the test solution. Carry out the Assay described under Minocycline Hydrochloride.

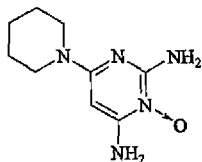
Category As described under Minocycline Hydrochloride.

Strength Calculate as $C_{23}H_{27}N_3O_7$
(1) 50 mg (2) 100 mg

Storage Preserve in tightly closed containers, protected from

light.

Minoxidil



$C_9H_{15}N_5O$ 209.25

[38304-91-5]

Minoxidil is 2,4-diamino-6-piperidinopyrimidine 3-oxide. It contains not less than 98.0% of $C_9H_{15}N_5O$, calculated on the dried basis.

Description A white or almost white crystalline powder. Soluble in glacial acetic acid; sparingly soluble in ethanol; slightly soluble in chloroform or water; very slightly soluble in acetone.

Identification (1) The light absorption of a solution of 6 μ g per ml in ethanol exhibits a maximum at 231 nm (Appendix IV A).

(2) The infrared absorption spectrum (Appendix IV C) is concordant with the reference spectrum of minoxidil (Appendix XVI).

Chlorinate compound Carry out the method for oxygen flask combustion (Appendix VII C), using about 20 mg, accurately weighed, and 10 ml of sodium hydroxide (0.1 mol/L) VS as the absorbing liquid. When the combustion is complete, shake vigorously the flask for a few minutes, wash the stopper and the platinum wire with a little water, transfer the combined washings and absorbing liquid to a 50 ml Nessler cylinder quantitatively. Carry out the limit test for chlorides (Appendix VIII B), using the resulting solution. Any opalescence produced is not more pronounced than that of a reference solution prepared in the same manner using 4.0 ml of sodium chloride standard solution (0.2%).

Loss on drying When dried to constant weight at 105°C, loses not more than 0.5% of its weight (Appendix VIII L).

Residue on ignition No more than 0.15% (Appendix VIII N); using 1.0 g.

Heavy metals Carry out the limit test for heavy metals (Appendix VIII H, method 2), using the residue obtained in the test for Residue on ignition; not more than 0.002 %.

Assay To about 0.2 g, accurately weighed, add 10 ml of glacial acetic acid and 1 drop of crystal violet IS, titrate with perchloric acid (0.1 mol/L) VS until the colour changes to bluish-green. Perform a blank determination and make any necessary correction. Each ml of perchloric acid (0.1 mol/L) VS is equivalent to 20.93 mg of $C_9H_{15}N_5O$.

Category Antihypertensive agent.

Storage Preserve in tightly closed containers, protected from light.

Preparation Minoxidil Tablets

Minoxidil Tablets

Minoxidil Tablets contain not less than 90.0% and not more than 110.0% of the labelled amount of

minoxidil ($C_9H_{15}N_5O$).

Description White tablets.

Identification (1) Shake a quantity of the powdered tablets, equivalent to about 5 mg of minoxidil, with 3 ml of ethanol, filter, evaporate the filtrate to dryness. To the residue add 1 ml of acetic anhydride and 10 mg of citric acid, heat in a water bath for 2 minutes, a red colour is produced gradually.

(2) The light absorption of solution obtained in the Assay exhibits two maxima at 281 nm and 229 nm (Appendix IV A).

Content uniformity Comply with the requirements (Appendix X E). Shake 1 tablet in a 100 ml volumetric flask with a quantity of hydrochloric acid solution (9→1000) to dissolve minoxidil, dilute with hydrochloric acid solution (9→1000) to volume and mix well. Filter, measure accurately 2 ml of the successive filtrate to a 10 ml volumetric flask, dilute with hydrochloric acid solution (9→1000) to volume and mix well. Carry out the determination as described under Assay. Calculate the content of $C_9H_{15}N_5O$.

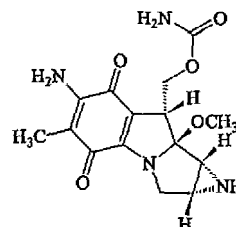
Other requirements Comply with the general requirements for tablets (Appendix I A).

Assay Weigh accurately and powder 20 tablets. To a quantity of the powdered tablets, equivalent to about 20 mg of, minoxidil, accurately weighed, in a 100 ml volumetric flask, add about 60 ml of hydrochloric acid solution (9→1000), shake to dissolve minoxidil, dilute with hydrochloric acid solution (9→1000) to volume and mix well. Filter, measure accurately 2 ml of the successive filtrate to another 100 ml volumetric flask, dilute with hydrochloric acid solution (9→1000) to volume and mix well. Dissolve minoxidil CRS in hydrochloric acid solution (9→1000) to produce a solution of about 4 μ g per ml. Measure the absorbances of the resulting solutions at 281 nm (Appendix IV A). Calculate the content of $C_9H_{15}N_5O$.

Category, Storage As described under Minoxidil.

Strength 2.5 mg

Mitomycin



$C_{15}H_{18}N_4O_5$ 334.33

[50-07-7]

Mitomycin contains not less than 90.0% of $C_{15}H_{18}N_4O_5$, calculated on the dried basis.

Description A dark purple, crystalline powder, odourless, unstable when exposed to acid, alkaline or sunlight. Slightly soluble in water, methanol or ethanol, practically insoluble in ether.

Identification (1) The light absorption of a solution containing 0.01 mg per ml in water exhibits maxima at 217 nm and 365 nm (Appendix IV A).

(2) The retention time of the principal peak for the substance being examined in the chromatogram obtained in the Assay is identical with that of the principal peak obtained in the chromatogram of the reference solution.

(3) The infrared absorption spectrum (Appendix IV C) is concordant with the reference spectrum of mitomycin (Appendix XI).

Crystallinity Complies with the test for crystallinity (Appendix IX D).

Acidity or alkalinity A suspension of 5 mg per ml in water pH 5.5-7.5 (Appendix VI H).

Loss on drying When dried in vacuum over phosphorous pentoxide to constant weight at 60°C, loses not more than 2.0% of its weight (Appendix VIII L).

Bacterial endotoxin Carry out the test for bacterial endotoxin (Appendix XI E): less than 10 EU per mg.

Assay Carry out the method for high performance liquid chromatography (Appendix V D), using a column packed with benzolsilane bonded silica gel and a mixture of methanol-ammonia acetate BS (dissolve 2.05 g of ammonia acetate in water, add 6.7 ml of 0.83 mol/L acetic acid solution, dilute to 1000 ml with water) (25 : 75) as the mobile phase. Detection wavelength is 365 nm. Dissolve 5 mg of Mitomycin CRS and 75 mg of 3-ethoxycarbonyl-4-hydroxyl benzaldehyde in N,N-dimethylacetamide in a 10 ml volumetric flask and dilute to volume, mix well. Inject 5 µl into the column and record the chromatogram. The resolution factor between the peak of Mitomycin and 3-ethoxycarbonyl-4-hydroxyl benzaldehyde is not less than 1.8. The tailing factor of Mitomycin is not more than 1.3.

Procedure Dissolve an accurately weighed quantity of the substance being examined in N, N-dimethylacetamide to produce a solution of 0.2 mg of Mitomycin per ml. Inject 5 µl, accurately measured, into the column and record the peak areas obtained in the chromatogram. Repeat the operation, using mitomycin CRS instead of the substance being examined, calculate the content of $C_{15}H_{18}N_4O_5$ by the external standard method.

Category Antitumor Antibiotic.

Storage Preserve in hermetically sealed containers, stored in a cool and dark place.

Preparation Mitomycin for Injection

Mitomycin for Injection

Mitomycin for Injection is a sterile mixed powder of mitomycin and sodium chloride. It contains not less than 90.0% and not more than 110.0% of the labelled amount of mitomycin ($C_{15}H_{18}N_4O_5$), calculated on the basis of the average contents.

Description A bluish-purple powder or grey-purple lyophilized powder, unstable on exposure to light.

Identification Complies with the tests for Identification described under Mitomycin.

Acidity or alkalinity Dissolve a quantity in water to produce a solution containing 5 mg per ml, pH 5.5-7.5 (Appendix VI H).

Loss on drying When dried in vacuum over phosphorous pentoxide to constant weight about 0.2 g at 60°C, loses not more than 1.0%, using about 0.2 g (Appendix VIII L).

Content uniformity Carry out the method described under Assay, using 10 vials. Calculate the content of $C_{15}H_{18}N_4O_5$ in each vial and the average content of 10 vials. Not more than 1 vial of the individual content deviates from the average content by more than 15% of the content variation, and none

of the individual content deviates by more than 20% of the content variation.

Bacterial endotoxin Carry out the test described under Mitomycin.

Sterility Complies with the test for sterility (Appendix XI H, Membrane Filtration Method), dissolving content in a suitable solvent and transferring all of the solution to 0.9% sterile sodium chloride solution.

Other requirements Complies with the general requirements for injections (Appendix I B).

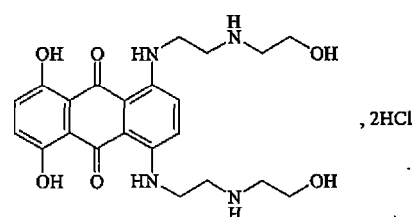
Assay Carry out the Assay described under Mitomycin, using 10 vials. Determine the content of each vial and calculate the average content of 10 vials.

Category As described under Mitomycin.

Strength (1) 2 mg (2) 4 mg (3) 8 mg (4) 10 mg

Storage Preserve in tightly closed containers, protected from light.

Mitoxantrone Hydrochloride



$C_{22}H_{28}N_4O_6 \cdot 2HCl$ 517.41

Mitoxantrone Hydrochloride is 1,4-dihydroxy-5,8-di[[2-[(2-hydroxyethyl) amino] ethyl] amino]-9,10-quinone dihydrochloride. It contains not less than 97.0% and not more than 102.0% of $C_{22}H_{28}N_4O_6 \cdot 2HCl$, calculated on the dried basis.

Description A dark blue crystalline powder; odourless; hygroscopic. Soluble in water; slightly soluble in ethanol; insoluble in chloroform.

Identification (1) Dissolve 5 mg in 1 ml of water, add 1 ml of strong sulfuric acid, a blue colour turns to violetish-red.

(2) Dissolve 2 mg in 1 ml of water, add sodium Nitrite crystalline powder and 5 drops of hydrochloric acid solution (1→2), a violet colour is produced.

(3) The light absorption of the solution obtained in Assay exhibits maxima at 242 nm, 275 nm, 609nm and 663 nm (Appendix IV A).

(4) The infrared absorption spectrum (Appendix IV C) is concordant with the reference spectrum of mitoxantrone hydrochloride (Appendix XVI).

(5) Yields the reactions characteristic of chlorides (Appendix III).

Acidity Dissolve 0.1g in 10 ml of water, pH 3.0-5.5 (Appendix VI H).

Related substances Carry out the method for thin-layer chromatography (Appendix V B), using silica gel G as the coating substance and a mixture of chloroform-methanol-ammonia (17 : 3 : 0.5) as the mobile phase. Apply separately to the plate 10 µl of each of four solutions of substance being examined in ethanol containing (1) 1 mg per ml, (2) 0.01 mg per ml, (3) 0.02 mg per ml, (4) 0.03 mg per ml. After developing and removal of the plate, allow it to dry in air, and then examine. The number of the

secondary spots in the chromatogram obtained with solution (1) is not more than 3. Any secondary spot is not more intense than the principal spot obtained with solution (4). the total impurity is not more than 7%.

Loss on drying When dried to constant weight at 100°C for 4 hours, loses not more than 5.0% of its weight (Appendix VIII L).

Residue on ignition Not more than 0.2% (Appendix VIII N), using 1.0 g.

Heavy metals Carry out the limit test for heavy metals (Appendix VIII H, method 2), using the residue obtained in the test for Residue on ignition; not more than 0.002%.

Assay Dissolve 10 mg, accurately weighed, in 1 ml of water in a 100 ml volumetric flask, dilute with dehydrated ethanol to volume and shake well, measure accurately 5 ml into a 50 ml volumetric flask, add 5 ml of 0.1 mol/L hydrochloric acid solution, dilute with dehydrated ethanol to volume and shake well. Measure the absorbance at 663 nm (Appendix IV B), calculate the content of $C_{22}H_{28}N_4O_6 \cdot 2HCl$, taking 570 as the value of A (1%, 1 cm).

Category Antineoplastic.

Storage Preserve in tightly closed container, protected from light.

Preparation Mitoxantrone Hydrochloride for Injection

Mitoxantrone Hydrochloride for Injection

Mitoxantrone Hydrochloride for Injection is a sterile powder of Mitoxantrone Hydrochloride. It contains not less than 90.0% and not more than 110.0% of the labelled amount of mitoxantrone hydrochloride ($C_{22}H_{28}N_4O_6$).

Description A bluish-black colour solid hygroscopic.

Identification Complies with the tests (1), (2), (3) and (5) for Identification described under Mitoxantrone Hydrochloride.

Acidity Dissolve 5 mg in 1 ml of water, pH 4.0-6.0 (Appendix VI H).

Loss on drying When dried in vacuum to constant weight at 100°C for 4 hours, loses not more than 6.0% of its weight (Appendix VIII L).

Content uniformity The content determined in the Assay complies with the requirement of content uniformity (Appendix X E).

Sterility Dissolve the contents in a quantity of sodium chloride injection, and transfer the solution to 100 ml of sodium chloride injection respectively. The resulting solutions comply with the test for sterility (Appendix XI H, membrane filtration method).

Other requirements Complies with the general requirements for injections (Appendix I B).

Assay Add 1 ml of water respectively to 10 containers, allow to dissolve, and then transfer them to 50 ml volumetric flask, respectively. Wash the containers with dehydrated ethanol several times, combine the washings to the volumetric flask and dilute to volume, shake well. Carry out the method described under Mitoxantrone Hydrochloride beginning at the words "measure accurately 5 ml". Calculate the contents of each container and the average contents of 10

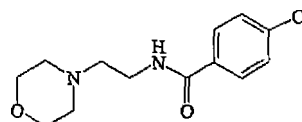
containers. Each mg of mitoxantrone hydrochloride ($C_{22}H_{28}N_4O_6 \cdot 2HCl$) is equivalent to 0.8591 mg of mitoxantrone ($C_{22}H_{28}N_4O_6$).

Category As described under Mitoxantrone Hydrochloride.

Strength 5 mg (calculated on Mitoxantrone)

Storage Preserve in tightly closed container, protected from light.

Moclobemide



$C_{13}H_{17}ClN_2O_2$ 268.74

[71320-77-9]

Moclobemide is 4-chloro-*N*-[2-(4-morpholinoethyl)]benzamide. It contains not less than 99.0% of $C_{13}H_{17}ClN_2O_2$, calculated on the dried basis.

Description White or almost white crystals or a crystalline powder; odourless; taste slightly bitter.

Freely soluble in methanol, ethanol, chloroform or glacial acetic acid; soluble in acetone; slightly soluble in water.

Melting point 136-140°C (Appendix VI C).

Specific absorbance Measure the absorbance of a solution of 10 µg per ml in 0.1 mol/L hydrochloric acid solution at 240 nm (Appendix IV A), the value of A (1%, 1 cm) is 557-591.

Identification (1) Dissolve about 10 mg in 5 ml of dilute hydrochloric acid and 20 ml of water, to 5 ml add 2 drops of potassium iodobismuthate TS; an orange-red precipitate is produced.

(2) The light absorption of the solution obtained in Specific absorbance exhibits a maximum at 240 nm, and a minimum at 214 nm (Appendix IV A).

(3) The infrared absorption spectrum (Appendix IV C) is concordant with the reference spectrum of moclobemide (Appendix XVI).

(4) Place 0.1 g in a suitable crucible, mix with 1 g of anhydrous sodium carbonate. Heat until the mixture turns to brown, then keep heating for 10 minutes. Dissolve the cooled residue in 10 ml of water and filter. The filtrate yields the reactions characteristic of chlorides (Appendix III).

Chloride Add 50 ml of water to 0.60 g of the substance being examined, shake for 5 minutes to dissolve and filter. Carry out the limit test for chloride (Appendix VII A), using 25 ml of the successive filtrate. Any opalescence produced is not more pronounced than that of a reference solution using 6.0 ml of sodium chloride standard solution (0.020%).

Sulfate Add 50 ml of water to 2.0 g of the substance being examined, treat in a ultrasonic bath for 5 minutes and filter. Carry out the limit test for sulfate (Appendix VII B), using 25 ml of the successive filtrate. Any opalescence produced is not more pronounced than that of a reference solution using 3.0 ml of potassium sulfate standard solution (0.030%).

Related substances Carry out the method for high performance liquid chromatography (Appendix V D), using a column packed with cyanosilane bonded silica gel and a mixture of 0.14% triethylamine solution [adjust pH to 6.0 with phosphoric acid (1 → 2)]-methanol (6 : 1) as the

mobile phase. The detection wavelength is 235 nm. The number of the theoretical plates of the column is not less than 2000, calculated with reference to the peak of moclobemide. Dissolve a quantity of the substance being examined, accurately weighed, in mobile phase to produce solutions of 1.5 mg per ml (solution 1) and 15 µg per ml (solution 2). Inject 20 µl of solution (2) into the column. Adjust the attenuation so that the principal peak height in the chromatogram is about 25% of full scale of the chart. And then inject separately 20 µl each of solution (1) and (2) into the column, and record the chromatogram for 2.5 times of the retention time of the principal peak. Each peak area and the sum of the areas of all peaks other than the principal peak in the chromatogram obtained with solution (1) are not greater than 1/2 the area and the area of the principal peak in the chromatogram obtained with solution (2) respectively.

Loss on drying When dried to constant weight at 105°C, loses not more than 0.5% of its weight (Appendix VIII L).

Residue on ignition Not more than 0.1% (Appendix VIII N), using 1.0 g.

Heavy metals Carry out the limit test for heavy metals (Appendix VIII H, method 2), using the residue obtained in the test for Residue on ignition; not more than 0.002%.

Arsenic Mix well 1.0 g with 1 g of calcium hydroxide and a small amount of water, stir and dry. Heat gently to carbonize, then ignite at 500-600°C until free from carbon. Dissolve the cooled residue in 5 ml of hydrochloric acid and 23 ml of water. Carry out the limit test for arsenic (Appendix VIII J, method 1); not more than 0.0002%.

Assay Dissolve about 0.2 g, accurately weighed, in 20 ml of glacial acetic acid, add 1 drop of crystal violet IS. Titrate with perchloric acid (0.1 mol/L) VS until the colour changes to blue. Perform a blank determination and make any necessary correction. Each ml of perchloric acid (0.1 mol/L) VS is equivalent to 26.87 mg of $C_{13}H_{17}ClN_2O_2$.

Category Antidepressant.

Storage Preserve in tightly closed containers, protected from light.

Preparation (1) Moclobemide Capsules
(2) Moclobemide Tablets

Moclobemide Capsules

Moclobemide Capsules contain not less than 93.0% and not more than 107.0% of the labelled amount of moclobemide ($C_{13}H_{17}ClN_2O_2$).

Description Content white or almost white powder.

Identification (1) Dissolve a quantity of the contents of the capsules, equivalent to about 50 mg of moclobemide, in 25 ml volumetric flask in ethanol by shaking, dilute to volume and mix well. Filter and use the successive filtrate as test solution. Prepare a reference solution by dissolving a quantity of moclobemide CRS in ethanol to produce a solution of 2 mg per ml. Carry out the thin-layer chromatography (Appendix V B), using silica gel GF₂₅₄ as the coating substance and a mixture of ethyl acetate-ethanol-concentrated ammonia solution (8 : 2 : 1) as the mobile phase. Apply separately to the plate 15 µl each of above two solutions, after developing and removal of the plate, dry in air and examine under ultra-violet light at 254 nm. The position and colour of the principal spot in the chromatogram obtained with the test solution correspond to the principal spot obtained with the reference solution.

(2) The light absorption of the solution obtained in Assay exhibits a maximum at 240 nm, and a minimum at 214 nm (Appendix IV A).

(3) Place a quantity of the contents of capsules, equivalent to about 0.1 g of moclobemide, in a suitable crucible, mix with 1 g of anhydrous sodium carbonate. Heat until it is thoroughly charred, then keep heating for 10 minutes. Dissolve the cooled residue in 5 ml of water and filter. The filtrate yields the reactions characteristic of chlorides (Appendix III).

Dissolution Carry out the method for dissolution test (Appendix X C, method 2), using 900 ml of 0.1 mol/L hydrochloric acid solution as the dissolution medium, adjust the rotational speed of the paddle at 50 rpm. Withdraw a quantity of the solution after exactly 30 minutes, filter. Measure accurately a quantity of the successive filtrate, dilute with 0.1 mol/L hydrochloric acid solution to produce a solution of 10 µg per ml. Carry out the procedure as described under Assay, beginning at the words "Dissolve a quantity of moclobemide CRS". Calculate the dissolution of $C_{13}H_{17}ClN_2O_2$ from each capsule. Not less than 80% of the labelled amount is dissolved.

Other requirements Comply with the general requirements for capsules (Appendix I E).

Assay Weigh accurately a quantity of the mixed contents of capsules, equivalent to about 20 mg of moclobemide, into a 100 ml volumetric flask, add a quantity of 0.1 mol/L hydrochloric acid solution and shake to dissolve, dilute with 0.1 mol/L hydrochloric acid solution to volume and mix well, filter. Dilute 5 ml of the successive filtrate, accurately measured, with 0.1 mol/L hydrochloric acid solution to 100 ml, mix well as the test solution. Dissolve a quantity of moclobemide CRS, accurately weighed, with 0.1 mol/L Hydrochloric acid solution to produce a solution of 10 µg per ml as the reference solution. Measure the absorbance of the two solutions at 240 nm (Appendix IV A), calculate the content of $C_{13}H_{17}ClN_2O_2$.

Category As described under moclobemide.

Strength 0.1 g

Storage Preserve in tightly closed containers, protected from light.

Moclobemide Tablets

Moclobemide Tablets contain not less than 93.0% and not more than 107.0% of the labelled amount of moclobemide ($C_{13}H_{17}ClN_2O_2$).

Description White or almost white tablets or film coated tablets with white or almost white core.

Identification (1) Dissolve a quantity of the powdered tablets, equivalent to about 50 mg of moclobemide, in a 25 ml volumetric flask in ethanol by shaking, dilute to volume, and mix well. Filter and use the successive filtrate as test solution. Prepare a reference solution by dissolving a quantity of moclobemide CRS to produce a solution of 2 mg per ml. Carry out the thin-layer chromatography (Appendix V B), using silica gel GF₂₅₄ as the coating substance and a mixture of ethyl acetate-ethanol-concentrated ammonia solution (8 : 2 : 1) as the mobile phase. Apply separately to the plate 15 µl each of the above two solutions, after developing and removal of the plate, dry in air and examine under ultra-violet light (254 nm). The position and colour of the principal spot in the chromatogram obtained with the test solution correspond to the principal spot obtained with the reference solution.

(2) The light absorption of the solution obtained in Assay exhibits a maximum at 240 nm, and a minimum at 214 nm (Appendix IV A).

(3) Place a quantity of the powdered tablets, equivalent to about 0.1 g of moclobemide, in a suitable crucible, mix with 1 g of anhydrous sodium carbonate. Heat until it is thoroughly charred, then keep heating for 10 minutes. Dissolve the cooled residue in 5 ml of water and filter. The filtrate yields the reactions characteristic of chlorides (Appendix III).

Dissolution Carry out the method for dissolution test (Appendix X C, method 1), using 900 ml of 0.1 mol/L hydrochloric acid solution as the dissolution medium, adjust the rotational speed of the paddle at 100 rpm. Withdraw a quantity of the solution after exactly 30 minutes, filter. Measure accurately a quantity of the successive filtrate, dilute with 0.1 mol/L Hydrochloric acid solution to produce a solution of 10 µg per ml. Carry out the procedure as described under Assay, beginning at the words "Dissolve a quantity of moclobemide CRS". Calculate the dissolution of $C_{13}H_{17}ClN_2O_2$ from each tablet. Not less than 80% of the labelled amount is dissolved.

Other requirements Comply with the general requirements for tablets (Appendix I A).

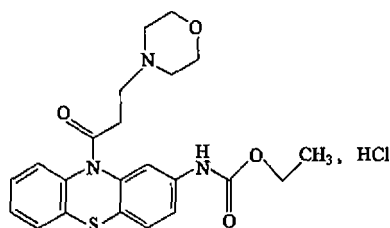
Assay Weigh accurately and powder 20 tablets, with film coat removed if necessary. Weigh accurately a quantity of the powder, equivalent to about 20 mg of moclobemide, into a 100 ml volumetric flask, add a quantity of 0.1 mol/L hydrochloric acid solution and shake to dissolve, dilute with 0.1 mol/L hydrochloric acid solution to volume and mix well, filter. Dilute 5 ml of the successive filtrate, accurately measured, with 0.1 mol/L hydrochloric acid solution to 100 ml and mix well as the test solution. Dissolve a quantity of moclobemide CRS, accurately weighed, with 0.1 mol/L hydrochloric acid solution to produce a solution of 10 µg per ml as the reference solution. Measure the absorbance of the two solutions at 240 nm (Appendix IV A), calculate the content of $C_{13}H_{17}ClN_2O_2$.

Category As described under moclobemide.

Strength (1) 75 mg (2) 0.1 g (3) 0.15 g

Storage Preserve in tightly closed containers, protected from light.

Moracizine Hydrochloride



$C_{22}H_{25}N_3O_4S \cdot HCl$ 463.98

Moracizine Hydrochloride is 10-(3-morpholinyl)-phenothiazine-2-carbamic acid ethylester hydrochloride. It contains not less than 99.0% of $C_{22}H_{25}N_3O_4S \cdot HCl$, calculated on the dried basis.

Description A white or almost white powder. Very soluble in methanol, soluble in water or ethanol, slightly soluble in acetone, insoluble in ethyl acetate; freely soluble in glacial acetic acid.

Specific absorbance Dissolve an accurately weighed quantity of the substance being examined, in a mixture of ethanol-water (1 : 1) to produce a solution of 0.1 mg per ml, measure accurately a quantity of the solution, dilute with water to produce a solution of 10 µg per ml. Measure the absorbance of the resulting solution at 268 nm (Appendix IV A), the value of A (1%, 1 cm), calculated on the dried basis, is 360-375.

Identification (1) Dissolve about 10 mg in 5 ml of water, add 1 drop of potassium heptaiodobismuthate TS, an orange red precipitate is produced immediately.

(2) Dissolve about 15 mg in 2 ml of water, add 0.5 ml of 1 mol/L hydroxylamine hydrochloride solution. Make the solution alkaline by adding dropwise 5 mol/L ethanolic potassium hydroxide solution, a white precipitate is produced. Boil the mixture for a few minutes, cool, acidify the solution with dilute hydrochloric acid, colour changes to pale violet. Add 1 or 2 drops of ferric chloride TS, the colour changes to intense violet.

(3) The infrared absorption spectrum (Appendix IV C) is concordant with the reference spectrum of moracizine Hydrochloride (Appendix XVI).

(4) Yields the reactions characteristic of chlorides (Appendix III)

Related substances Carry out the method for thin-layer chromatography (Appendix V B), using silica gel G as the coating substance and a mixture of methanol-n-butanol (2 : 3) as mobile phase. Weigh accurately about 50 mg into a 5 ml volumetric flask, add a quantity of ethanol and 0.25 ml of ammonia TS, shake to dissolve, dilute with ethanol to volume as test solution. Transfer 1 ml of the test solution to a 200 ml volumetric flask, accurately measured, dilute with ethanol to volume as reference solution. Apply separately to the plate 10 µl each of the two solutions. After developing and removal of the plate, dry it in air, visualize with iodine vapor after staying for half an hour. No any thirdly spot other than the principal spot obtained with the test solution in the chromatogram is observed. The colour of the spot in the chromatogram other than the principal spot obtained with the test solution is not more intense than the principal spot obtained with the reference solution.

Loss on drying When dried to constant weight at 105°C, loses not more than 1.0% of its weight (Appendix VIII L).

Residue on ignition Not more than 0.1% (Appendix VIII N), using 1.0 g.

Heavy metals Carry out the limit test for heavy metals (Appendix VIII H, method 2), using the residue obtained in the test for Residue on ignition; not more than 0.002%.

Assay Dissolve about 0.4 g, accurately weighed, in 20 ml of glacial acetic acid, add 5 ml of mercuric acetate TS and 1 drop of crystal violet IS. Titrate with perchloric acid (0.1 mol/L) VS until the colour changes to blue. Perform a blank determination and make any necessary correction. Each ml of perchloric acid (0.1 mol/L) VS is equivalent to 46.40 mg of $C_{22}H_{25}N_3O_4S \cdot HCl$.

Category Antiarrhythmic.

Storage Preserve in tightly closed containers, protected from light.

Preparation Moracizine Hydrochloride Tablets.

Moracizine Hydrochloride Tablets

Moracizine Hydrochloride Tablets contain not less

than 90.0% and not more than 110.0% of the labelled amount of moracizine hydrochloride ($C_{22}H_{25}N_3O_4S \cdot HCl$).

Description Sugar coated tablets with a white or almost white core.

Identification (1) To a quantity of powdered tablets with sugar coating removed, equivalent to about 15 mg of moracizine hydrochloride, add 2 ml of water, shake to dissolve moracizine hydrochloride and filter. Add 0.5 ml of 1 mol/L hydroxylamine hydrochloride solution to filtrate, make the solution alkaline by adding dropwise 5 mol/L ethanolic potassium hydroxide solution, a white precipitate is produced. Boil the mixture for a few minutes, cool, acidify the solution with dilute hydrochloric acid, colour changes to pale violet. Add 1 or 2 drops of ferric chloride TS, the colour changes to intense violet.

(2) To a quantity of powdered tablets with sugar coating removed, equivalent to about 30 mg of moracizine hydrochloride, add 10 ml of water, shake to dissolve moracizine hydrochloride and filter. The filtrate yields the reaction characteristic of chlorides. (Appendix III).

Dissolution Comply with the requirements for dissolution test (Appendix X C, method 1), using 1000 ml of 0.1 mol/L hydrochloric acid solution as the dissolution medium, adjust the rotational speed of the basket to 50 rpm. Withdraw a quantity of the solution after exactly 60 minutes and filter. Measure accurately a quantity of the successive filtrate, dilute with the dissolution medium to produce a solution of containing moracizine hydrochloride 10 μ g per ml. Measure the absorbance of the resulting solution at 268 nm (Appendix IV A), calculate the dissolution of $C_{22}H_{25}N_3O_4S \cdot HCl$ from each tablet, taking 367 as the value of A (1%, 1 cm). Not less than 80% of the labelled amount is dissolved.

Other requirements Comply with the general requirements for tablets (Appendix I A).

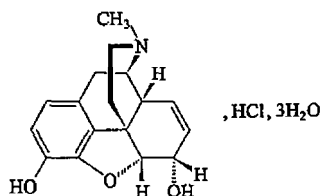
Assay Weigh accurately and powder 10 tablets with coating removed. Triturate an accurately weighed quantity of the powder, equivalent to about 50 mg of moracizine hydrochloride, in a 250 ml volumetric flask, add 25 ml of ethanol, shake thoroughly to dissolve moracizine hydrochloride, dilute with water to volume, shake well and filter. Transfer 5 ml of the solution into a 100 ml volumetric flask, accurately measured, dilute with water to volume and mix well. Measure the absorbance of the resulting solution at 268 nm (Appendix IV A), calculate the content of $C_{22}H_{25}N_3O_4S \cdot HCl$, taking 367 as the value of A (1%, 1 cm).

Category As described under Moracizine Hydrochloride.

Strength 50 mg

Storage Preserve in tightly closed containers, protected from light.

Morphine Hydrochloride



$C_{17}H_{19}NO_3 \cdot HCl \cdot 3H_2O$ 375.85

[52-26-6]

Morphine Hydrochloride is 7,8-didehydro-4,5-epoxy-17-methyl-(5 α , 6 α)-morphinan-3,6-diol hydrochloride trihydrate. It contains not less than 99.0% of $C_{17}H_{19}NO_3 \cdot HCl$, calculated on the dried basis.

Description White, silky needle crystals or a crystalline powder; odourless; deteriorated easily on exposure to light. Soluble in water; sparingly soluble in ethanol; practically insoluble in chloroform or ether.

Specific optical rotation -110.0° to -115.0° , dissolve 1 g of morphine hydrochloride in water in 50 ml volumetric flask (Appendix VI E). Dilute with water to volume.

Identification (1) To 1 mg add 1 drop of formaldehyde-sulfuric acid TS; an intense purple colour is produced.

(2) To 1 mg add 0.5 ml of molybdo-sulfuric acid TS, a violet colour is produced, turning to blue and then to brownish-green.

(3) Dissolve 1 mg in 1 ml of water, add 1 drop of dilute potassium ferricyanide TS; a bluish-green colour develops immediately (distinction from codeine).

(4) The infrared absorption spectrum (Appendix IV C) is concordant with the reference spectrum of morphine hydrochloride (Appendix XVI).

(5) The aqueous solution yields the reaction characteristic of chlorides (Appendix III).

Acidity To a solution of 0.20 g in 10 ml of water add 1 drop of methyl red IS, if a red colour is produced, not more than 0.20 ml of sodium hydroxide (0.02 mol/L) VS. is required to change it to yellow.

Clarity and colour of solution Dissolve 0.5 g with 25 ml of water, the solution is clear and colourless; any opalescence produced is not more pronounced than that of reference suspension 1 (Appendix IX B); any colour produced is not more intense than that of reference solution Y₂ or YG₂ (Appendix IX A, method 1).

Ammonium Heat 0.2 g with 5 ml of sodium hydroxide TS for 1 minute, the vapour evolved does not turn moistened red litmus paper to blue.

Apomorphine Dissolve 50 mg in 4 ml of water, add 0.10 g of sodium bicarbonate and 1 drop of iodine solution (0.1 mol/L) then shake with 5 ml of ether; the ether layer exhibits no red colour and the aqueous layer exhibits no green colour.

Meconate Dissolve 0.15 g in 5 ml of water, add 5 ml of dilute hydrochloric acid and 2 drops of ferric chloride TS; no red colour develops.

Foreign alkaloids Carry out the method for thin-layer chromatography (Appendix V B), using silica gel G as the coating substance and a mixture of 70% ethanol solution-toluene-acetone-concentrated ammonia solution (35 : 35 : 32.5 : 2.5) as the mobile phase. Apply separately to the plate 20 μ l each of the following two solutions. Dissolve 0.1 g of the substance being examined with 10 ml of a mixture of ethanol-water (1 : 1) as solution (1). Dissolve 50 mg of codeine phosphate CRS in 5 ml of solution (1) and dilute 0.1 ml with the mixture of ethanol-water (1 : 1) to 10 ml as solution (2). After developing and removal of the plate, dry it in air. Spray with bismuth potassium iodide TS. After 15 minutes, spray with hydrogen peroxide TS. The spot of codeine in the chromatogram obtained with solution (1) is not more intense than that of solution (2), any spot other than the principal spot obtained with solution (1) is not more intense than the principal spot obtained with solution (2).

Loss on drying When dried to constant weight at 105°C,

loses not more than 15.0% of its weight (Appendix VIII L).

Residue on ignition Not more than 0.1% (Appendix VIII N).

Assay Dissolve about 0.2 g, accurately weighed, in 10 ml of glacial acetic acid and 4 ml of mercuric acetate TS, add 1 drop of crystal violet IS. Titrate with perchloric acid (0.1 mol/L) VS until the colour changes to green. Perform a blank determination and make any necessary correction. Each ml of perchloric acid (0.1 mol/L) VS is equivalent to 32.18 mg of $C_{17}H_{19}NO_3 \cdot HCl$.

Category Analgesic.

Storage Preserve in tightly closed containers, protected from light.

Preparation (1) Morphine Hydrochloride Injection
(2) Morphine Hydrochloride Sustained-release Tablets
(3) Morphine Hydrochloride Tablets

Morphine Hydrochloride Injection

Morphine Hydrochloride Injection is a sterile solution of morphine hydrochloride in Water for Injection. It contains not less than 95.0% and not more than 105.0% of the labelled amount of morphine hydrochloride ($C_{17}H_{19}NO_3 \cdot HCl \cdot 3H_2O$).

Description A clear, colourless liquid; deteriorate easily on exposure to light.

Identification When evaporated to dryness on a water bath, the residue complies with tests (1), (2), (3) and (5) for Identification described under Morphine Hydrochloride.

pH value 3.0-5.0 (Appendix VI H).

Other requirements Complies with the general requirements for injections (Appendix I B).

Assay Measure accurately a quantity of the substance being examined and dilute with 0.1 mol/L sodium hydroxide solution to produce a solution of 20 µg per ml. Measure the absorbance at 250 nm (Appendix IV A). Dissolve an accurately weighed quantity of morphine CRS in 0.1 mol/L sodium hydroxide solution and dilute to produce a solution of 20 µg per ml. Repeat the operation, calculate the content and multiply with 1.317 as the content of $C_{17}H_{19}NO_3 \cdot HCl \cdot 3H_2O$.

Category As described under Morphine Hydrochloride.

Strength (1) 0.5 ml : 5 mg (2) 1 ml : 10 mg

Storage Preserve in well closed containers, protected from light.

Morphine Hydrochloride Sustained-release Tablets

Morphine Hydrochloride Sustained-release Tablets contain not less than 93.0% and not more than 107.0% of the labelled amount of morphine hydrochloride ($C_{17}H_{19}NO_3 \cdot HCl \cdot 3H_2O$).

Description Film coated tablets with white core.

Identification Triturate the tablets with coating removed. Transfer a quantity of the powdered tablets, equivalent to

about 20 mg of morphine hydrochloride, to mortar, add 10 ml of water, dissolve morphine hydrochloride and filter. Evaporate the filtrate to dryness. The residue complies with the test (1), (2), (3) and (5) for Identification as described under Morphine Hydrochloride.

Content uniformity Comply with the requirements for content uniformity (Appendix X E). Place 1 tablet in a mortar, add a quantity of water, triturate to dissolve morphine hydrochloride. Transfer the solution to 100 ml (10 mg per tablet), 250 ml (30 mg per tablet) or 500 ml (60 mg per tablet) volumetric flask, wash the mortar with water for several times, combine the wash solution, shake thoroughly, dilute to volume with water and mix well. Filter the resulting solution through a membrane with pores of 0.45 µm in diameter. Discard the initial filtrate and use the successive filtrate as the test preparation. Carry out the test as described under assay, beginning at the words "measure accurately 20 µl of the successive filtrate", and calculate the content of morphine hydrochloride.

Drug release Carry out the method for drug release test (Appendix X D, method 1) and use an apparatus for dissolution test (Appendix X C, method 1), using 500 ml of water as the release medium and adjust the rotational speed of the basket to 50 rpm. Withdraw a sample of 2 ml of the solution at exact 1, 2, 3, 4, 5 and 6 hours respectively, filter through a membrane with pores of 0.45 µm in diameter and supply 2 ml of same temperature water accordingly into the vessel immediately. Take the successive filtrate as test solution. Measure accurately a quantity of standard solution obtained under the assay, dilute with mobile phase to produce the solutions of 0.02 mg per ml (10 mg per tablet), 0.05 mg per ml (30 mg per tablet) and 0.1 mg per ml (60 mg per tablet) respectively. Carry out the method as described under the Assay. Calculate the content of $C_{17}H_{19}NO_3 \cdot HCl \cdot 3H_2O$ dissolved from each tablet at different release time separately. The dissolution of morphine hydrochloride complies with the requirement; the quantity dissolved of each tablet is 25%-45%, 40%-60%, 55%-75%, 65%-85%, 70%-90% and over 80% of the labelled amount of $C_{17}H_{19}NO_3 \cdot HCl \cdot 3H_2O$ respectively.

Other requirements Comply with the general requirements for tablets (Appendix I A).

Assay Carry out the method for high performance liquid chromatography (Appendix V D), using a column packed with octadecylsilane bonded silica gel and a mixture of potassium dihydrogen phosphate (0.05 mol/L)-methanol (4 : 1) as the mobile phase. Detection wavelength is 280 nm and the number of theoretical plates of the column is not less than 1000, calculated with reference to the peak of morphine.

Procedure Accurately weigh 10 tablets and triturate. Transfer a quantity of the powdered tablets, equivalent to about 35 mg of morphine hydrochloride, accurately weighed, to a 250 ml volumetric flask. Add a quantity of water and shake thoroughly to dissolve morphine hydrochloride, dilute to volume with water and mix well. Filter through a membrane with pores of 0.45 µm in diameter. Measure accurately 20 µl of the successive filtrate and inject it into the column and record the peak areas obtained in the chromatography correspondingly. Accurately weigh a quantity of morphine CRS, dissolve it with mobile phase to produce a solution of 0.1 mg per ml. Repeat the operation, and calculate the content of $C_{17}H_{19}NO_3 \cdot HCl \cdot 3H_2O$ with multiplying 1.317 by the peak area.

Category and Storage As described under Morphine Hydrochloride.

Strength (1) 10 mg (2) 30 mg (3) 60 mg

Morphine Hydrochloride Tablets

Morphine Hydrochloride Tablets contain not less than 93.0% and not more than 107.0% of the labelled amount of morphine hydrochloride ($C_{17}H_{19}NO_3 \cdot HCl \cdot 3H_2O$).

Description White tablets, deteriorated on exposure to light.

Identification To a quantity of powdered tablets, equivalent to about 20 mg of morphine hydrochloride, add 10 ml of water, shake well and filter. Evaporate the filtrate to dryness. The residue complies with the tests (1), (2), (3) and (5) for Identification described under Morphine Hydrochloride.

Content uniformity Comply with the requirements (Appendix X E). Place 1 tablet in a 100 ml (5 mg) or 200 ml (10 mg) volumetric flask, add 0.1 mol/L sodium hydroxide solution to volume, shake thoroughly and filter. Transfer 25 ml of the successive filtrate to 50 ml volumetric flask, dilute to volume with 0.1 mol/L sodium hydroxide solution and mix well. Measure the absorbance of the resulting solution at 250 nm (Appendix IV A), calculate the content of $C_{17}H_{19}NO_3 \cdot HCl \cdot 3H_2O$.

Dissolution Carry out dissolution test (Appendix X C, method 3), using 125 ml (5 mg) or 250 ml (10 mg) of water as dissolution medium, adjust the rotational speed to 50 rpm. Withdraw 10 ml of the solution after exactly 30 minutes and filter, transfer 5 ml of the successive filtrate, accurately measured, to 10 ml volumetric flask, add 1 ml of 1 mol/L sodium hydroxide solution and dilute with water to volume, mix well. Dissolve a quantity of anhydrous morphine CRS in 0.1 mol/L sodium hydroxide solution and dilute with 0.1 mol/L sodium hydroxide solution to produce a solution of 10 µg per ml. Measure the absorbance of two solutions at 250 nm (Appendix IV A). Calculate the content and multiply by 1.317 as the dissolution of $C_{17}H_{19}NO_3 \cdot HCl \cdot 3H_2O$ from each tablet, not less than 70% of the labelled amount is dissolved.

Other requirements Comply with the general requirements for tablets (Appendix I A).

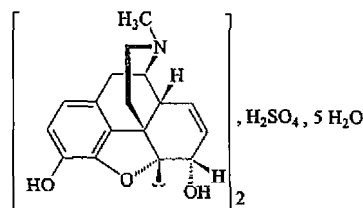
Assay Weigh accurately and powder 20 tablets. To a quantity of powder equivalent to 10 mg of morphine hydrochloride, accurately weighed, in a 100 ml volumetric flask add 50 ml of water and shake well. Dilute with water to volume and mix well and filter. Transfer 15 ml of the successive solution, accurately measured, to 50 ml volumetric flask, add 25 ml of 0.2 mol/L sodium hydroxide solution and dilute with water to volume, mix well [solution (1)]. Dissolve a quantity of anhydrous morphine CRS in 0.1 mol/L sodium hydroxide solution and produce a solution of 20 µg per ml with 0.1 mol/L sodium hydroxide solution [solution (2)]. Measure the absorbance of solution (1) and (2) at 250 nm (Appendix IV A). Calculate the content and multiply with 1.317 as the content of $C_{17}H_{19}NO_3 \cdot HCl \cdot 3H_2O$.

Category As described under Morphine Hydrochloride.

Strength (1) 5 mg (2) 10 mg

Storage Preserve in tightly closed containers, protected from light.

Morphine Sulfate



$(C_{17}H_{19}NO_3)_2 \cdot H_2SO_4 \cdot 5H_2O$ 758.83 [6211-15-0]

Morphine sulfate is 7,8-Didehydro-4,5 α-epoxy-17-methylmorphinan-3,6 α-diol sulphate (2 : 1) (salt) Pentahydrate. It contains not less than 98.0% and not more than 101.0% of $(C_{17}H_{19}NO_3)_2 \cdot H_2SO_4$, calculated on the dried basis.

Description White, needle crystals or a crystalline powder; odourless.

Soluble in water; slightly soluble in ethanol; practically insoluble in chloroform or ether.

Specific optical rotation -107.0° to -109.5° , in a solution of 20 mg per ml in water (Appendix VI E).

Identification (1) To about 1 mg add 1 drop of formaldehyde sulfuric acid TS, a intense purple colour is produced immediately.

(2) Dissolve 1 mg in 1 ml of water, add 1 drop of dilute potassium ferricyanide TS, a bluish-green colour is produced immediately.

(3) The light absorption of a solution of 0.015% in water in the range of 230-350 nm (Appendix IV A) exhibits a maximum at 285 nm; the absorbance is about 0.65. The light absorption of a solution of 0.015% in 0.1 mol/L sodium hydroxide solution exhibits a maximum at 298 nm; the absorbance is about 1.1.

(4) The infrared absorption spectrum (Appendix IV C) is concordant with the reference spectrum of morphine sulfate (Appendix XVI).

(5) The aqueous solution yields the reactions characteristic of sulfates (Appendix III).

Acidity To a solution of 0.20 g in 10 ml of water add 1 drop of methyl red IS, if a red colour is produced, not more than 0.20 ml of sodium hydroxide (0.02 mol/L) VS is required to change it to yellow.

Ammonium Heat 0.20 g with 5 ml of sodium hydroxide TS for 1 minute, the evolved vapour does not turn moistened red litmus paper to blue.

Foreign alkaloids Dissolve 0.50 g of dried substance being examined, accurately weighed, in 15 ml of water and 5 ml of sodium hydroxide TS in a separator. Shake and extract with three 10 ml portions of chloroform. Wash the combined chloroform extracts with 10 ml of 0.4% sodium hydroxide solution and followed two portions of 5 ml water. Evaporate the chloroform layer on a water bath to dry. The residue is not more than 7.5 mg after drying to constant weight at 105°C.

Loss on drying When dried at 145°C for 1 hour, loses 9.0%-12.0% of its weight (VII L).

Residue on ignition Not more than 0.1% (Appendix VII N).

Assay Dissolve about 0.25 g, accurately weighed, in 25 ml of glacial acetic acid, add 1 drop of crystal violet IS. Titrate

with perchloric acid (0.05 mol/L) VS until the colour changes to green. Perform a blank determination and make any necessary correction. Each ml of perchloric acid (0.05 mol/L) VS is equivalent to 33.44 mg of $(C_{17}H_{19}NO_3)_2 \cdot H_2SO_4$.

Category Analgesic.

Storage Preserve in tightly closed containers, protected from light.

Preparations Morphine Sulfate Sustained-release Tablets

Morphine Sulfate Sustained-release Tablets

Morphine Sulfate Sustained-release Tablets contain not less than 95.0% and not more than 105.0% of the labelled amount of morphine sulfate $[(C_{17}H_{19}NO_3)_2 \cdot H_2SO_4 \cdot 5H_2O]$.

Description Film coated tablets with white core.

Identification To a quantity of the powdered tablets, equivalent to 0.1 g of morphine sulfate, add 10 ml of water, shake to dissolve morphine sulfate and filter. Use the filtrate for the following tests.

(1) To 0.5 ml of the filtrate add 1 ml of formaldehyde sulfuric acid solution (to 0.5 ml of formaldehyde add 9.5 ml of sulfuric acid carefully); an intense purple colour is produced immediately.

(2) To 0.5 ml of the filtrate add 5 ml of water, and 1 drop each of potassium ferricyanide TS and ferric chloride solution (dissolve 5 g of ferric chloride in 100 ml of water); a bluish-green colour is produced and turns to blue immediately.

(3) To 5 ml of the filtrate add 1 ml of 2 mol/L hydrochloric acid solution, and 1 ml of barium chloride solution (dissolve 6.1 mg of barium chloride powder in 100 ml of water); a white precipitate develops immediately. Add 1 drop of iodine-potassium iodide solution (dissolve 2.0 g of iodine and 3.0 g of potassium iodide in 100 ml of water); a yellow precipitate is produced immediately. Add 2-3 drops of stannous chloride solution (Dissolve 33.0 g of stannous chloride in 10 ml of 2 mol/L hydrochloric acid solution, add water to 100 ml), boil and the colour of precipitate disappears.

Related substance To an accurately weighed quantity of the powdered tablets, equivalent to 20 mg of morphine sulfate, add 5 ml of hydroquinone solution (dissolve 30 mg of hydroquinone in 1000 ml of mobile phase), ultrasonic to dissolve morphine sulfate, shake thoroughly and filter, use the successive filtrate as test solution. Measure accurately a quantity of the successive filtrate in hydroquinone solution to produce a solution containing 40 µg per ml, use as reference solution. Carry out the method for high performance liquid chromatography (Appendix V D), using a column packed with octadecylsilane bonded silica gel (5 µm) and a mixture of methanol-sodium heptanesulfonate solution (dissolve 2.02 g of sodium heptanesulfonate in water, add 5 ml of glacial acetic acid, dilute to 1000 ml with water, mix well) (70 : 90) as the mobile phase. Detection wavelength is 233 nm and the number of theoretical plates of the column is not less than 1000, calculated with reference to the peak of morphine sulfate. Inject 10 µl of the reference solution into the column, adjust the attenuation so that the principal peak height in the chromatogram is about 20%-30% of full scale of the chart. Inject 10 µl of the reference solution and test solution respectively into the column, record the chromatogram for 4 times of the retention time of the principal peak. The sum of the areas of all peaks other than the principal peak of the

test solution is not greater than the area of the principal peak of the reference solution in the chromatogram.

Content uniformity Comply with the requirements (Appendix X E). Transfer 1 powdered tablet to a 50 ml volumetric flask with hydroquinone solution quantitatively. Carry out the method as described under Assay, beginning at the words "ultrasonic to dissolve the morphine sulfate", calculate the content of $(C_{17}H_{19}NO_3)_2 \cdot H_2SO_4 \cdot 5H_2O$.

Drug release Carry out the method for drug release test (Appendix X D, method 1) and the equipment comply with dissolution test (Appendix X C, method 2), using 900 ml of pH 6.5 phosphate buffer solution as the release medium and adjust the rotational speed of the paddle at 100 rpm. Withdraw a sample of 5 ml of the solution at exact 1, 2, 3, 4, 5 and 6 hours respectively, filter through membrane and supply 5 ml of pH 6.5 phosphate buffer solution accordingly in the vessel immediately. Use the filtrate as test solution. Dissolve a quantity of morphine sulfate CRS, accurately weighed, in pH 6.5 phosphate buffer solution to produce a solution of 0.03 mg per ml, use as reference solution. Proceed as described under Assay. Inject 10 µl of the test solution and reference solution into the column respectively, record the chromatogram and measure the peak areas. Calculate the content of $(C_{17}H_{19}NO_3)_2 \cdot H_2SO_4 \cdot 5H_2O$ dissolved from each tablet at 1, 2, 3, 4, 5 and 6 hours separately. The dissolution of morphine sulfate complies with the requirement; the quantity dissolved of each tablet is 30%-45%, 45%-65%, 55%-75%, 65%-85%, 75%-95% and over 80% of the labelled amount of $(C_{17}H_{19}NO_3)_2 \cdot H_2SO_4 \cdot 5H_2O$.

Other requirements Comply with the general requirements for tablets (Appendix I A).

Assay Carry out the method for high performance liquid chromatography (Appendix V D), using a column packed with octadecylsilane bonded silica gel and a mixture of methanol-sodium heptanesulfonate solution (dissolve 2.02 g of sodium heptanesulfonate in water, add 5 ml of glacial acetic acid, dilute to 1000 ml with water, mix well) (50 : 50) as the mobile phase. Detection wavelength is 233 nm and the number of theoretical plates of the column is not less than 1000, calculated with reference to the peak of morphine sulfate.

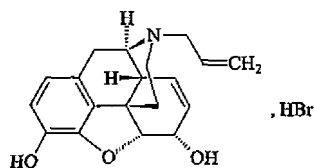
Procedure Weigh accurately and powder 20 tablets. Weigh accurately a quantity of the powder equivalent to about 30 mg of morphine sulfate into a 50 ml volumetric flask, add hydroquinone solution and ultrasonic to dissolve morphine sulfate, dilute to volume with hydroquinone solution and mix well. Filter. Transfer 2 ml of the successive filtrate, accurately measured, to a 25 ml volumetric flask, dilute with hydroquinone solution to volume, mix well. Inject 10 µl of the test solution into the column, record the chromatogram and measure the peak areas. Dissolve about 30 mg of morphine sulfate CRS, accurately weighed, in hydroquinone solution and dilute to produce a solution of 48 µg per ml. Repeat the operation, using the reference solution instead of the test solution. Calculate the content of $(C_{17}H_{19}NO_3)_2 \cdot H_2SO_4 \cdot 5H_2O$ with respect to the peak area obtained in the chromatogram by the external standard method.

Category Anesthetic and analgesic agent.

Strength 30 mg

Storage Preserve in tightly closed containers, protected from light.

Nalorphine Hydrobromide



$C_{19}H_{21}NO_3 \cdot HBr$ 392.29

[57-29-4]

Nalorphine Hydrobromide is 7, 8-didehydro-4,5 α -epoxy-17-(2-propenyl)-morphinan-3,6 α -diol Hydrobromide. It contains not less than 98.0% of $C_{19}H_{21}NO_3 \cdot HBr$, calculated on the dried basis.

Description A white or almost white, crystalline powder; odourless; darkens gradually in air. Soluble in water; sparingly soluble in ethanol; practically insoluble in chloroform or ether; soluble in dilute alkaline solution.

Specific optical rotation -100° to -105° , in a solution of 10 mg per ml in methanol (Appendix VI E).

Identification (1) Dissolve about 0.1 g in 5 ml of water, add 1 drop of ammonia TS, a white precipitate is produced, which is soluble in sodium hydroxide TS.

(2) Dissolve about 0.1 g in 5 ml of water, add 1 drop of ferric chloride TS, a blue colour is produced.

(3) Dissolve about 50 mg in 2 ml of carbon tetrachloride, add 1 ml of bromine TS, no colour is produced in carbon tetrachloride layer while the aqueous layer becomes reddish-brown.

(4) The aqueous solution yields the reaction characteristic of bromide (Appendix III).

Acidity Dissolve 0.20 g in 10 ml of water, pH 4.0-5.5 (Appendix VI H).

Clarity and colour of solution A solution of 0.20 g in 10 ml of water, fresh boiling and cool to room temperature, is clear and colourless; any opalescence produced is not more pronounced than that of reference suspension 1 (Appendix IX B); any colour produced is not more intense than that of reference solution Y₂ (Appendix IX A, method 1).

Related substances Carry out the method for thin-layer chromatography (Appendix V B), using silica gel G as the coating substance and a mixture of ethyl acetate-methanol-concentrated ammonia solution (8.6:1:0.4) as the mobile phase. Apply separately to the plate 10 μ l each of two solutions in methanol containing (1) 20 mg of the substance being examined per ml, (2) 0.2 mg of morphine CRS per ml. After developing and removal of the plate, allow it to dry and spray with concentrated potassium iodoplatinate TS. Any spot other than the principal spot in the chromatogram obtained with solution (1) is not more intense than the principal spot obtained with solution (2).

Loss on drying When dried to constant weight at $105^\circ C$, loses not more than 1.0% of its weight (Appendix VIII L), using 0.5 g.

Residue on ignition Not more than 0.1% (Appendix VIII N).

Assay Dissolve about 0.3 g, accurately weighed, in 30 ml of glacial acetic acid and 10 ml of mercuric acetate TS, add 1 drop of crystal violet IS. Titrate with perchloric acid (0.1 mol/L) VS until the solution becomes pure blue. Perform a

blank determination and make any necessary correction. Each ml of perchloric acid (0.1 mol/L) VS is equivalent to 39.23 mg of $C_{19}H_{21}NO_3 \cdot HBr$.

Category Morphine antagonist.

Storage Preserve in tightly closed containers, protected from light.

Preparation Nalorphine Hydrobromide Injection

Nalorphine Hydrobromide Injection

Nalorphine Hydrobromide Injection is a sterile solution of Nalorphine Hydrobromide in Water for Injections. It contains not less than 95.0% and not more than 105.0% of the labelled amount of nalorphine hydrobromide ($C_{19}H_{21}NO_3 \cdot HBr$).

Description A clear, colourless or almost colourless liquid.

Identification (1) To 10 ml add 1 drop of ferric chloride TS, a blue colour is produced.

(2) Yields the reaction characteristic of bromide (Appendix III).

pH value 2.7-3.3 (Appendix VI H).

Other requirements Complies with the general requirements for injections (Appendix I B).

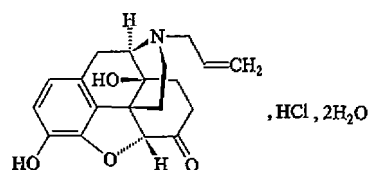
Assay To 20 ml, accurately measured, add 5 ml of ammonia TS, extract with 5 quantities, each 15 ml, of a mixture of isopropanol-chloroform (1:3) and wash each extract with the same 7 ml portion of water and allow to stand. Combine the extracts and evaporate to dryness on a water bath. To the residue add 2 ml of dehydrated ethanol and evaporate to dryness. Add further 2 ml of dehydrated ethanol and again evaporate to dryness, cool. To the residue add 20 ml of chloroform, 30 ml of glacial acetic acid, 3 ml of acetic anhydride and 2 drops of crystal violet IS. Titrate with perchloric acid (0.1 mol/L) VS until the solution becomes pure blue. Perform a blank determination and make any necessary correction. Each ml of perchloric acid (0.1 mol/L) VS is equivalent to 39.23 mg of $C_{19}H_{21}NO_3 \cdot HBr$.

Category As described under Nalorphine Hydrobromide.

Strength 1 ml:10 mg

Storage Preserve in well closed containers, protected from light.

Naloxone Hydrochloride



$C_{19}H_{21}NO_4 \cdot HCl \cdot 2H_2O$ 399.87

[51481-60-8]

Naloxone Hydrochloride is 17-allyl-4,5 α -epoxy-3,14-dihydroxy morphinan-6-one hydrochloride dihydrate. It contains not less than 98.0% and not more than 102.0% of $C_{19}H_{21}NO_4 \cdot HCl$, calculated on the dried basis.

Description White crystals or a crystalline powder; odourless.

Freely soluble in water; soluble in methanol; practically insoluble in chloroform or ether.

Specific optical rotation -170° to -181° , in a solution of 25 mg per ml in water (Appendix VI E).

Identification (1) Dissolve about 10 mg in 2 ml of water, add 2 drops of nitric acid and 1 drop of silver nitrate TS, a white curdy precipitate is formed which is soluble in ammonia TS and reprecipitated on addition of nitric acid.

(2) Transfer about 2 mg to a small test tube, add 3-4 drops of citric-acetic anhydride TS, heat in a water bath at $80-90^{\circ}\text{C}$ for 3-5 minutes, a purple colour is produced.

(3) Dissolve about 1 mg in 1 ml of water, add 1 drop of dilute potassium ferricyanide TS, a bluish-green colour is produced.

(4) The infrared absorption spectrum (Appendix IV C) is concordant with the reference spectrum of naloxone hydrochloride (Appendix XVI).

Loss on drying When dried at 90°C for 4 hours and then at 105°C to constant weight, loses not more than 11.0% of its weight (Appendix VIII L), using 0.5 g.

Related substances Protect from light in the procedure. Carry out the method for thin-layer chromatography (Appendix V B), using silica gel G as the coating substance and methanol-ammoniated butanol [shake 100 ml of butanol with 60 ml of concentrate ammonia solution (1 \rightarrow 100), discard the lower layer] (5:95) as the mobile phase. Apply separately to the plate 5 μl each of two solutions in methanol containing (1) 8 mg per ml of the substance being examined (2) 0.08 mg per ml of (–)-4,5 α -epoxy-3,14-dihydroxymorphinan-6-one CRS. After developing and removal of the plate, dry it in air, spray with potassium ferricyanide-ferric chloride solution (Dissolve 100 mg of potassium ferricyanide in 20 ml of 10% ferric chloride solution, be prepared freshly). Any spot, other than the principal spot in the chromatogram obtained with solution (1) is not more intense than the principal spot obtained with solution (2).

Chloride content Dissolve about 0.3 g, accurately weighed, in 30 ml of methanol, add 5 ml of water and 6-7 drops of fluorescein IS. Titrate with silver nitrate (0.1 mol/L) VS until the colour changes to pink. Each ml of silver nitrate (0.1 mol/L) VS is equivalent to 3.545 mg of Cl. The chloride content is not less than 9.54% and not more than 9.94%, calculated on the dried basis.

Assay Dissolve about 0.3 g, accurately weighed, in 40 ml of glacial acetic acid, 10 ml of acetic anhydride, add 10 ml of mercuric acetate TS and 1-2 drops of crystal violet IS. Titrate with perchloric acid (0.1 mol/L) VS until the colour changes to bluish-green. Perform a blank determination and make any necessary correction. Each ml of perchloric acid (0.1 mol/L) VS is equivalent to 36.38 mg of $\text{C}_{19}\text{H}_{21}\text{NO}_4 \cdot \text{HCl}$.

Category Morphine antagonist.

Storage Preserve in tightly closed containers, protected from light.

Preparation Naloxone Hydrochloride Injection

Naloxone Hydrochloride Injection

Naloxone Hydrochloride Injection is a sterile solution of naloxone hydrochloride in Water for

Injection. It contains not less than 90.0% and not more than 110.0% of the labelled amount of naloxone hydrochloride ($\text{C}_{19}\text{H}_{21}\text{NO}_4 \cdot \text{HCl}$).

Description A clear, colourless liquid.

Identification (1) Complies with tests (1) and (3) for Identification described under Naloxone Hydrochloride.

(2) Evaporate a quantity of the injection in a porcelain evaporating dish in a boiling water bath to dryness, add 1 drop of citric-acetic anhydride TS, heat in a water bath at $80-90^{\circ}\text{C}$ for 3-5 minutes, a violet red colour is produced.

(3) The light absorption of the injection exhibits a maximum at 280 nm and a minimum at 263 nm (Appendix IV A).

pH value 3.0-4.0 (Appendix VI H).

Other requirements Complies with the general requirements for injections (Appendix I B).

Assay Carry out the method for high performance liquid chromatography (Appendix V D), using a column packed with octadecylsilane bonded silica gel and a mixture of sodium octanesulfonate solution (mix 1.36 g of 1-octanesulfonate and 1.0 g of sodium chloride in 580 ml of water)-methanol-phosphoric acid (580 : 420 : 1) as the mobile phase. Detection wavelength is at 229 nm. Weigh 150 mg of disodium edetate to a 2000 ml volumetric flask, add 0.9 ml of hydrochloric acid, dissolve in water and dilute with water to the volume, mix well as the diluent. Dissolve a quantity of naloxone hydrochloride CRS and paracetamol CRS in the diluent and dilute to produce a solution of 20 μg of naloxone hydrochloride and 2.5 μg of paracetamol per ml as the solution (1). Inject 20 μl of the solution (1) into the column and record the chromatogram. The resolution factor between the peaks of naloxone hydrochloride and paracetamol is not less than 8.

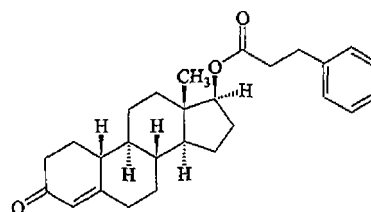
Procedure Dissolve about 10 mg of naloxone hydrochloride CRS, accurately weighed, in the diluent in a 100 ml volumetric flask and dilute to the volume. Transfer 1 ml to 10 ml volumetric flask, accurately measured, dilute with the diluent to the volume, mix well, as the solution (2). Measure accurately a quantity of naloxone hydrochloride injection, equivalent to 2 mg of naloxone hydrochloride, into a 200 ml volumetric flask and dilute with the diluent to the volume, as the solution (3). Inject separately 100 μl each of the solution (2) and (3) into the column, both accurately measured. Calculate the content of $\text{C}_{19}\text{H}_{21}\text{NO}_4 \cdot \text{HCl}$ with respect to the peak area obtained in the chromatogram by the external standard method.

Category As described under Naloxone hydrochloride.

Strength (1) 1 ml:0.4 mg (2) 1 ml:1 mg
(3) 2 ml:2 mg (4) 10 ml:4 mg

Storage Preserve in well closed containers, stored in a cool and dark place.

Nandrolone Phenylpropionate



$\text{C}_{27}\text{H}_{34}\text{O}_3$ 406.57

[62-90-8]

Nandrolone Phenylpropionate is the phenylpropionic ester of 17 β -hydroxyestr-4-en-3-one. It contains not less than 97.0% and not more than 103.0% of $C_{27}H_{34}O_3$, calculated on the dried basis.

Description A white or almost white crystalline powder with characteristic odour.

Soluble in ethanol; sparingly soluble in vegetable oil; practically insoluble in water.

Melting range 93–99°C (Appendix VI C).

Specific optical rotation +48° to +51°, in a solution of 10 mg per ml in dioxane (Appendix VI E).

Identification (1) The retention time of principal peak of the substance being examined is identical with that of principal peak of the reference solution in the chromatogram obtained in Assay.

(2) The infrared absorption spectrum (Appendix IV C) is concordant with the reference spectrum of nandrolone phenylpropionate (Appendix XVI).

Related substances Carry out the method with the solution described under Assay. Inject 8 μ l of the solution into the column, adjust the attenuation so that the principal peak height is full scale of the chart. Dissolve a quantity of the substance being examined, accurately weighed, in methanol to produce solutions of 2 mg per ml (solution 1) and 0.04 mg per ml (solution 2), inject separately 8 μ l each of solution (1) and solution (2) into the column, and record the chromatograms for 1.5 folds of the retention times of the principal peak. Not more than three secondary peaks area and the sum of the areas of all secondary peaks are not greater than 1/2 and 3/4 of area of the principal peak in the chromatogram obtained with solution (2) respectively.

Loss on drying When dried to constant weight in vacuum over phosphorus pentoxide, loses not more than 0.5% of its weight (Appendix VIII L).

Assay Carry out the method for high performance liquid chromatograph (Appendix V D), using a column of octadecylsilane bonded silica gel and methanol-water (82:18) as the mobile phase, and the wavelength of the detector is 241 nm. The number of the theoretical plates of the column is not less than 2300, calculated with reference to the peak of Nandrolone Phenylpropionate. The resolution factor between the peaks of Nandrolone Phenylpropionate and internal standard complies with the related requirements.

Internal standard solution Dissolve about 50 mg of progesterone, accurately weighed, in methanol in a 50 ml volumetric flask, dilute to volume and mix well.

Procedure Dissolve about 50 mg of Nandrolone Phenylpropionate CRS, accurately weighed, in methanol in a 25 ml volumetric flask and dilute to volume, mix well. Transfer 5 ml each of the solution and the internal standard solution, both accurately measured, in a 25 ml volumetric flask, dilute with methanol to volume, mix well. Inject 10 μ l of the resulting solution into the column. Repeat the operation, using the substance being examined instead of Nandrolone Phenylpropionate CRS, calculate the content of $C_{27}H_{34}O_3$.

Category Anabolic steroid.

Storage Preserve in tightly closed containers, protected from light.

Preparation Nandrolone Phenylpropionate Injection

Nandrolone Phenylpropionate Injection

Nandrolone Phenylpropionate Injection is a sterile solution of Nandrolone Phenylpropionate in oil. It contains not less than 90.0% and not more than 110.0% of the labelled amount of nandrolone phenylpropionate ($C_{27}H_{34}O_3$).

Description A pale yellow clear oily liquid.

Identification (1) To an amount of injection equivalent to 50 mg of nandrolone phenylpropionate add 8 ml of petroleum ether (boiling range 40–60°C), extract with three 8 ml portions of glacial acetic acid-water (7:3), wash the combined extracts with 10 ml of petroleum ether and discard the washing. To the washed solution add water until it is turbid, cool in an ice bath for 2 hours and filter. Wash the residue with water and dry it in vacuum over phosphorus pentoxide; a white crystalline powder is obtained. Dissolve this powder and nandrolone phenylpropionate CRS in acetone separately to produce two solutions of 5 mg per ml. Carry out the method for thin-layer chromatography (Appendix V B), using silica gel G as the coating substance and *n*-heptane-acetone (2:1) as the mobile phase. Apply separately to the plate 10 μ l each of the two solutions mentioned above. After developing and removal of the plate, dry it in air and spray with sulfuric acid-ethanol (1:49), heat at 110°C for 15 minutes. The principal spots in the chromatogram obtained with the two solutions are identical on colour and position.

(2) The retention time of principal peak of the substance being examined is identical with that of principal peak of the reference solution in the chromatogram obtained in Assay. Test (1) and (2) are alternative.

Other requirements Complies with the general requirements for injections (Appendix I B).

Assay Carry out the method for high performance liquid chromatography (Appendix V D), with an octadecylsilane bonded silica gel column using methanol-water (7:3) as the mobile phase. Wavelength of the detector is 254 nm. Number of theoretical plates of the column is not less than 600, calculated with reference to the peak of nandrolone phenylpropionate; the resolution factor between the peaks of nandrolone phenylpropionate, and internal standard complies with related requirements.

Internal Standard Solution Dissolve 50 mg of nandrolone phenylpropionate CRS, accurately weighed, in 25 ml of methanol.

Procedure Dissolve about 50 mg of testosterone propionate CRS, accurately weighed, in 25 ml of methanol. Transfer 5 ml each of the solution and internal standard solution to a 25 ml volumetric flask, dilute with methanol to volume and mix well, inject 5–10 μ l into the column, record the chromatogram. Transfer an accurately measured amount of the injection equivalent to about 50 mg of nandrolone phenylpropionate to a 25 ml volumetric flask, wash the interior of the pipet with several portions of ether, add the washings to the same volumetric flask, dilute with ether to volume and mix well. Transfer 5 ml of the ethereal solution, accurately measured, to a centrifuge tube with stopper, expel the ether on a water bath. Shake with 5 ml of methanol for 10 minutes and centrifuge for 15 minutes, repeat the extraction with 5 ml, 5 ml, 3 ml of methanol successively and transfer the methanol layers to another 25 ml volumetric flask. Add 5 ml of internal standard solution, dilute with methanol to volume and mix well, then inject

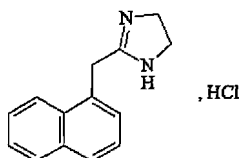
5-10 μ l into the column, record the chromatogram. Calculate the content of $C_{27}H_{34}O_3$.

Category As described under Nandrolone Phenylpropionate.

Strength (1) 1 ml:10 mg (2) 1 ml:25 mg

Storage Preserve in well closed containers, protected from light.

Naphazoline Hydrochloride



$C_{14}H_{14}N_2 \cdot HCl$ 246.74

[550-99-2]

Naphazoline Hydrochloride is 2-(1-naphthylmethyl)-2-imidazoline monohydrochloride. It contains not less than 98.5% of $C_{14}H_{14}N_2 \cdot HCl$, calculated on the dried basis.

Description A white crystalline powder; odourless; taste, bitter.

Freely soluble in water; soluble in ethanol; very slightly soluble in chloroform; insoluble in ether.

Identification (1) Dissolve about 20 mg in a few drops of dilute hydrochloric acid and 5 ml of water, add a few drops of ammonium reineckate TS, a purple precipitate is produced.

(2) The infrared absorption spectrum (Appendix IV C) is concordant with the reference spectrum of naphazoline hydrochloride (Appendix XVI).

(3) The aqueous solution yields the reactions characteristic of chloride (Appendix III).

Acidity Dissolve 0.2 g in 20 ml of water, pH 5.5-6.5 (Appendix VI H).

Related substances Carry out the method for thin-layer chromatography (Appendix V B), using silica gel G as the coating substance and a mixture of methanol-diethylamine (100:2) as the mobile phase. Apply separately to the plate 10 μ l each of four solutions of the substance being examined in methanol containing (1) 20 mg per ml, (2) 0.10 mg per ml, (3) 0.20 mg per ml and (4) 0.30 mg per ml. After developing and removal of the plate, dry it in air, heat at 105°C for an hour, visualize with iodine vapour until the chromatogram obtained with solutions (2), (3) and (4) show clearly visible spot respectively. Compare with any secondary spot in the chromatogram obtained with solution (1) with the principal spots obtained with solutions (2), (3) and (4), the total amount of impurities does not exceed 2.0%.

Loss on drying When dried to constant weight at 105°C, loses not more than 0.5% of its weight (Appendix VIII L).

Residue on ignition Not more than 0.2% (Appendix VIII N).

Assay Dissolve about 0.15 g, accurately weighed, in 10 ml of glacial acetic acid, add 3 ml of mercuric acetate TS and 1 drop of crystal violet TS. Titrate with perchloric acid (0.1 mol/L) VS until the colour changes to green. Perform a blank determination and make any necessary correction. Each ml of perchloric acid (0.1 mol/L) VS is equivalent to 24.67 mg of $C_{14}H_{14}N_2 \cdot HCl$.

Category Vasoconstrictor.

Storage Preserve in tightly closed containers, protected from light.

Preparation (1) Naphazoline Hydrochloride Eye Drops
(2) Naphazoline Hydrochloride Nasal Drops

Naphazoline Hydrochloride, Chlorphenamine Maleate and Vitamin B₁₂ Eye Drops

Naphazoline Hydrochloride, Chlorphenamine Maleate and Vitamin B₁₂ Eye Drops contain not less than 90.0% and not more than 110.0% of the labelled amount of Naphazoline Hydrochloride ($C_{14}H_{14}N_2 \cdot HCl$), Chlorphenamine Maleate ($C_{16}H_{19}ClN_2 \cdot C_4H_4O_4$) and Vitamin B₁₂ ($C_{63}H_{88}CoN_{14}O_{14}P$) respectively.

Formula Naphazoline Hydrochloride	0.02 g
Chlorphenamine Maleate	0.2 g
Vitamin B ₁₂	0.1 g
Excipient	a quantity
Water for Injection	a sufficient quantity

To make 1000 ml

Description A clear, pink liquid; odour, characteristic.

Identification (1) To 5 ml add 3 ml of sodium hydroxide TS and 3 ml of ether, shake and allow it to separate. Evaporate the ether extract to dryness at room temperature. Dissolve the residue in 0.5 ml of chloroform as test solution. Dissolve separately a quantity of naphazoline hydrochloride CRS and chlorphenamine maleate CRS in water to produce naphazoline hydrochloride solution of 20 μ g per ml and chlorphenamine maleate solution of 200 μ g per ml. Complete the procedure as described under test solution using 5 ml of the two solutions separately to produce reference solution (1) and reference solution (2). Carry out the thin-layer chromatography (Appendix V B), using silica gel G as the coating substance and a mixture of chloroform-methanol-acetone-concentrated ammonia solution (73:15:10:2) as the mobile phase. Apply separately to the plate 10 μ l each of above three solutions, after developing and removal of the plate, dry it in air, spray with dilute potassium iodobismuthate TS. The colour and position of the two principal spots in the chromatogram obtained with the test solution correspond to the principal spots obtained with reference solution (1) and reference solution (2).

(2) The absorbance of the solution obtained in Assay of Vitamin B₁₂ exhibits two maxima at 550 nm and 361 nm (Appendix IV A). The ratio of the absorbance at 550 nm to that at 361 nm is 0.29-0.32.

pH value 4.5-6.0 (Appendix VI H).

Other requirements Comply with the general requirements for eye preparations (Appendix I G).

Assay *Naphazoline hydrochloride and chlorphenamine maleate* Carry out the method for high performance liquid chromatography (Appendix V D), using a column packed with octylsilane bonded silica gel. Dissolve 4.32 g of octane sulfonate sodium and 7.6 g of anhydrous citric acid in 1800 ml of water, adjust pH to 3.0 with 1 mol/ml sodium hydroxide solution, dilute to 2000 ml with water, mix 1300 ml of the solution with 700 ml of acetonitrile as the mobile phase. Detection wavelength is 280 nm and the number of the theoretical plates of the column is not less than 2500,

calculated with reference to the peak of naphazoline hydrochloride. The resolution factor between the peaks of chlorphenamine maleate and internal standard complies with the related requirements.

Internal standard solution Dissolve a quantity of *p*-aminoisopropyl benzoate with the mobile phase to produce a solution of 5 µg per ml.

Procedure Measure accurately 5 ml of the eye drops to a 10 ml volumetric flask, dilute with the internal standard solution to volume, mix well. Inject 20 µl of the resulting solution into the column, record the peak area correspondingly obtained in the chromatogram. Dissolve a quantity of naphazoline hydrochloride CRS and chlorphenamine maleate CRS with water to produce a solution of 20 µg of naphazoline hydrochloride and 0.2 mg of chlorphenamine maleate per ml. Measure accurately 5 ml of the solution to a 10 ml volumetric flask, dilute with the internal standard solution to volume, mix well. Inject 20 µl of the resulting solution into the column, calculate the content of $C_{14}H_{14}N_2 \cdot HCl$ and $C_{16}H_{19}ClN_2 \cdot C_4H_4O_4$.

Vitamin B₁₂ Measure accurately 2 ml of the eye drops to a 10 ml volumetric flask, dilute with water to volume, mix well as test solution. Dissolve an accurately weighed quantity of vitamin B₁₂ CRS with water to produce a solution of 20 µg of vitamin B₁₂ per ml as reference solution. Measure the absorbance of the resulting solutions at 361 nm (Appendix IV A), calculate the content of $C_{63}H_{88}CoN_{14}O_{14}P$.

Category Ophthalmics.

Strength 10 ml

Storage Preserve in tightly closed containers.

Naphazoline Hydrochloride Eye Drops

Naphazoline Hydrochloride Eye Drops contain not less than 90.0% and not more than 110.0% of naphazoline hydrochloride ($C_{14}H_{14}N_2 \cdot HCl$).

Description A clear, colourless liquid.

Identification (1) Dilute a quantity, equivalent to about 25 mg of naphazoline hydrochloride, with 5 ml of sodium hydroxide TS in a separator, make saturation with sodium chloride, extract with two 25 ml quantities of ether. Combine the ether layers and wash with 5 ml water. Filter and evaporate to dryness. The residue complies with the test for Identification (1) described under Naphazoline Hydrochloride.

(2) The retention time of principal peak of the substance being examined in the chromatogram obtained in the Assay is identical with that of the principal peak in the chromatogram of the reference solution.

pH value 5.5-7.0 (Appendix VI H).

Other requirements Comply with the general requirements for eye preparations (Appendix I G).

Assay Carry out the method for high performance liquid chromatography (Appendix V D), using a column packed with octadecylsilane bonded silica gel and a mixture of methanol-water-triethylamine-phosphoric acid (50:50:0.25:0.075) as the mobile phase. Detection wavelength is 280 nm and the number of the theoretical plates of the column is not less than 400, calculated with reference to the peak of naphazoline hydrochloride.

Procedure Measure accurately 5 ml (for strength 0.1%) or 10 ml (for strength 0.05%) to a 50 ml volumetric flask,

dilute with water to volume and mix well as the test solution. Inject 20 µl into the column and record the chromatogram. Dissolve about 25 mg of naphazoline hydrochloride CRS, accurately weighed, in water in a 50 ml volumetric flask, dilute to volume and mix well, measure accurately 5 ml to a 25 ml volumetric flask and mix well as the reference solution. Repeat the operation using the reference solution instead of the test solution. Calculate the content of $C_{14}H_{14}N_2 \cdot HCl$ with respect to the peak area obtained in the chromatogram by the external standard method.

Category As described under Naphazoline Hydrochloride.

Strength (1) 0.05% (2) 0.1%

Storage Preserve in tightly closed containers, protected from light.

Naphazoline Hydrochloride Nasal Drops

Naphazoline Hydrochloride Nasal Drops contain not less than 90.0% and not more than 110.0% of the labelled amount of naphazoline hydrochloride ($C_{14}H_{14}N_2 \cdot HCl$).

Description A clear, colourless liquid.

Identification (1) Transfer a quantity of nasal drops equivalent to about 25 mg of naphazoline hydrochloride to a separator, add 5 ml of sodium hydroxide TS, saturate with sodium chloride, and extract twice with 25 ml each of ether. Wash the combined ether extract with 5 ml of water, filter, evaporate the filtrate to dryness. The residue complies with test (1) for Identification described under Naphazoline Hydrochloride.

(2) The retention time of principal peak of the substance being examined is identical with that of principal peak of the reference solution in the chromatogram obtained in Assay.

pH value 5.5-7.0 (Appendix VI H).

Other requirements Comply with the general requirements for nasal preparations (Appendix I R).

Assay Carry out the method for high performance liquid chromatography (Appendix V D), using a column packed with octadecylsilane bonded silica gel and a mixture of methanol-water-triethylamine-phosphoric acid (50:50:0.25:0.075) as the mobile phase. Detection Wavelength is 280 nm. The number of the theoretical plates of the column is not less than 400, calculated with reference to the peak of naphazoline hydrochloride.

Procedure Transfer accurately 5 ml (for strength 0.1%) or 10 ml (for strength 0.05%) of the substance being examined to a 50 ml volumetric flask, dilute with methanol to volume, mix well as the test solution. Inject 20 µl of the test solution into the column and record the chromatogram. Dissolve about 25 mg of naphazoline hydrochloride CRS, weighed accurately, with methanol in a 50 ml volumetric flask, dilute with methanol to volume, mix well. Measure accurately 5 ml into a 25 ml volumetric flask and dilute with water to volume, mix well as the reference solution. Repeat the operation instead of the test solution, calculate the content of $C_{14}H_{14}N_2 \cdot HCl$ with respect to the peak area obtained in the chromatogram by the external standard method.

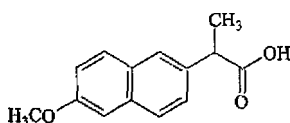
Category As described under Naphazoline Hydrochloride.

Strength (1) 0.05% (2) 0.1%

Storage Preserve in tightly closed containers, protected

from light.

Naproxen



$C_{14}H_{14}O_3$ 230.26

[22204-53-1]

Naproxen is (+)-6-methoxy- α -methyl-2-naphthylpropanoic acid. It contains not less than 98.5% of $C_{14}H_{14}O_3$, calculated on the dried basis.

Description A white or almost white crystalline powder; odourless or almost odourless. Soluble in methanol, ethanol or chloroform; sparingly soluble in ether; practically insoluble in water.

Melting range 153-158°C (Appendix VI C).

Specific optical rotation +63.0° to +68.5° in a solution of 10 mg per ml in chloroform (Appendix VI E).

Identification (1) The light absorption of a 30 μ g per ml solution in methanol exhibits four maxima at 262 nm, 271 nm, 317 nm and 331 nm (Appendix IV A).

(2) The infrared absorption spectrum (Appendix IV C) is concordant with the reference spectrum of naproxen (Appendix XVI).

Chloride To 0.50 g add 50 ml of water, shake for 10 minutes, filter (moisten the filter Paper previously with dilute nitric acid). Discard the initial filtrate, carry out the limit test for chlorides (Appendix VIII A), using 25 ml of the successive filtrate. Any opalescence produced is not more pronounced than that of a reference using 7.5 ml of sodium chloride standard solution (0.030%).

Related substances Protect from light throughout the procedure. Carry out the method for high performance liquid chromatography (Appendix V D), using a column packed with octadecylsilane bonded silica gel and a mixture of methanol-0.01 mol/L potassium dihydrogen phosphate solution (75:25) (adjust with phosphoric acid to pH 3.0) as the mobile phase. Detection wavelength is 240 nm and the number of theoretical plates of the column is not less than 5000, calculated with reference to the peak of naproxen, the resolution factor between the peaks of naproxen and the impurity complies with the related requirements. Dissolve a quantity in the mobile phase, shake thoroughly to dissolve naproxen and dilute to produce a solution of 0.5 mg per ml as the solution (1). Dissolve a quantity of 6-methoxy-2-acetonaphthone CRS in the mobile phase and dilute to produce the solution (2) of 50 μ g per ml. Transfer 1 ml of solution (1) and 2 ml of solution (2) respectively, accurately measured, to a 200 ml volumetric flask and dilute with the mobile phase to the volume, mix well, as the solution (3). Inject 20 μ l of the solution (3) into the column, adjust the attenuation so that the principal peak height in the chromatogram is 10%-20% of the full scale of the chart. Inject separately 10 μ l each of the solution (1) and (3), both accurately measured, into the column and record the chromatogram for 2.5 times of the retention time of the principal peak. The area of the peak with the same retention time as 6-methoxy-2-acetonaphthone, obtained with solution (1), is not greater than that of 6-methoxy-2-acetonaphthone obtained with solution (3) (0.1%). The area of the largest impurity except 6-methoxy-2-acetonaphthone

is not greater than twice of the area of 6-methoxy-2-acetonaphthone in solution (3) (0.2%). The sum of the areas of all peaks other than the naproxen peak obtained with solution (1) is not greater than the area of the naproxen peak obtained with solution (3) in the chromatogram (0.5%).

Loss on drying When dried at 105°C for 3 hours, loses no more than 0.5% of its weight (Appendix VIII L).

Residue on ignition Not more than 0.1% (Appendix VII N), using 1.0 g.

Heavy metals Carry out the limit test for heavy metals (Appendix VII H, method 2), using the residue obtained in the test for Residue on ignition, not more than 0.002%.

Assay Dissolve about 0.5 g, accurately weighed, in 45 ml of methanol, add 15 ml of water and 3 drops of phenolphthalein IS. Titrate with sodium hydroxide (0.1 mol/L) VS. Perform a blank determination and make any necessary correction. Each ml of sodium hydroxide (0.1 mol/L) VS is equivalent to 23.03 mg of $C_{14}H_{14}O_3$.

Category Antipyretic, analgesic, non-steroids anti-inflammatory agent.

Storage Preserve in tightly closed containers, protected from light.

Preparation (1) Naproxen Capsules
(2) Naproxen Granules
(3) Naproxen Injection
(4) Naproxen Suppositories
(5) Naproxen Tablets

Naproxen and Codeine Phosphate Tablets

Naproxen and Codeine Phosphate Tablets contain not less than 93.0% and not more than 107.0% of the labelled amount of naproxen ($C_{14}H_{14}O_3$), and not less than 90.0% and not more than 110.0% of the labelled amount of codeine phosphate ($C_{18}H_{21}NO_3 \cdot H_3PO_4 \cdot 1 \frac{1}{2} H_2O$) in each tablet.

Formula	Naproxen	150 g
	Codeine Phosphate	15 g
	Excipient	a quantity
	to make	1000 tablets

Description White or almost white tablets.

Identification Weigh a quantity of the powdered tablets, equivalent to about 1 g of naproxen and 0.1 g of codeine phosphate, add 15 ml of water and 5 ml of dilute sulfuric acid TS, ultrasonic for 10 minutes and filter, the successive filtrate is used as the test solution (1) for identification; Transfer all the residue to a 50 ml conical flask by 25 ml of anhydrous ethanol, ultrasonic for 10 minutes and filter, the successive filtrate is used as the test solution (2) for identification.

(1) Transfer a quantity of the test solution (1) to a separator, add drops of ammonia TS to make the solution alkaline (pH value is about 10), extract with 15 ml of chloroform, wash the chloroform layer with a small quantity of water, evaporate the chloroform layer in vacuum to dryness. To about 1 mg of the residue on a white porcelain dish, add 0.5 ml of sulfuric acid containing 2.5 mg of selenic

acid, a green colour is produced immediately which turns to blue gradually.

(2) Dissolve about 1 mg of the residue of test (1) for identification in 1 ml of methanol as the test solution. Dissolve an accurately weighed quantity of codeine phosphate CRS in methanol to produce a solution of 1 mg of codeine phosphate per ml as the reference solution. Carry out the method for thin-layer chromatography (Appendix V B), using silica gel G as the coating substance and a mixture of ethyl acetate-methanol-concentrated ammonia solution (85:10:5) as the mobile phase. Apply separately to the plate 10 μ l of each of the above two solutions. After developing and removal of the plate, dry it in air and spray with dilute potassium iodobismuthate TS. The principal spot in the chromatogram obtained with the test solution corresponds in colour and position to the principal spot obtained with the reference solution.

(3) Dilute a quantity of the test solution (2) with anhydrous ethanol to produce a solution of 30 μ g of naproxen per ml. The absorbance of the solution exhibits four maxima at 262 nm, 271 nm, 317 nm and 331 nm (Appendix IV A).

(4) Add drops of sodium hydroxide TS to a small quantity of the test solution (1) to adjust the pH to neutral. The solution yields the reactions characteristic of phosphates (Appendix III).

Related substances Weigh accurately a quantity of the powdered tablets, equivalent to about 1.0 g of naproxen, add 15 ml of water and 5 ml of dilute sulfuric acid TS, ultrasonic for 10 minutes and filter. Transfer all the residue to a 25 ml volumetric flask with a quantity of anhydrous ethanol, ultrasonic for 10 minutes, dilute with anhydrous ethanol to volume, shake thoroughly and filter, the successive filtrate is used as the test solution. Measure accurately a quantity of the test solution, dilute with anhydrous ethanol to produce a solution of 0.20 mg of naproxen per ml as the reference solution (1). Dissolve an accurately weighed quantity of 6-methoxy-2-acetonaphthone CRS in anhydrous ethanol to produce a solution of 40 μ g per ml as the reference solution (2). Carry out the method for thin-layer chromatography (Appendix V B), using silica gel GF₂₅₄ as the coating substance and a mixture of toluene-tetrahydrofuran-glacial acetic acid (90:9:3) as the mobile phase. Apply separately to the plate 10 μ l of each of the above three solutions, after developing and removal of the plate, dry it in air and examine under ultraviolet light (254 nm). Any spot other than the principal spot obtained with the test solution is not more intense than the principal spot obtained with the reference solution (1). Any fluorescence spot obtained with the test solution is not more intense than the principal spot obtained with the reference solution (2).

Content uniformity Comply with the requirements for content uniformity (Appendix X E). To 1 tablet in a 50 ml volumetric flask, add a quantity of 75% methanol solution, carry out the procedure as described under the Assay, beginning at the words "ultrasonic for 10 minutes...". Calculate the content of $C_{14}H_{14}O_3$ and $C_{18}H_{21}NO_3 \cdot H_3PO_4 \cdot 1 \frac{1}{2} H_2O$.

Dissolution Carry out the dissolution test (Appendix X C, method 1), using 900 ml of phosphate BS (pH 7.4) as the dissolution medium, adjust the rotational speed of the basket to 100 rpm. Withdraw 10 ml of the solution after exactly 30 minutes and filter. The successive filtrate is used as the test solution. Measure accurately 5 ml of the reference solution as described under the Assay in a 25 ml volumetric flask, dilute with the dissolution medium to volume and mix well as the reference solution. Measure accurately 100 μ l each of the test solution and the reference solution, carry out the method in the Assay. Calculate the dissolution of $C_{14}H_{14}O_3$

and $C_{18}H_{21}NO_3 \cdot H_3PO_4 \cdot 1 \frac{1}{2} H_2O$ from each tablet. Not

less than 70% of $C_{18}H_{21}NO_3 \cdot H_3PO_4 \cdot 1 \frac{1}{2} H_2O$ of the labelled amount and 80% of $C_{14}H_{14}O_3$ of the labelled amount is dissolved.

Other requirements Comply with the general requirements for tablets (Appendix I A).

Assay Carry out the method for high performance liquid chromatography (Appendix V D), using a column packed with octasilane bonded silica gel and a mixture of 0.05 mol/L potassium dihydrogen phosphate solution-methanol-tetrahydrofuran (4:6:0.04) as the mobile phase. Detection wavelength is 254 nm and the number of the theoretical plates of the column is not less than 1000, calculated with reference to the peak of codeine phosphate. The resolution factor between the peaks of codeine phosphate and naproxen is more than 2.0.

Procedure Weigh accurately and powder 20 tablets. To an accurately weighed quantity of powder, equivalent to about 150 mg of naproxen and 15 mg of codeine phosphate respectively, in a 50 ml volumetric flask, add a quantity of 75% methanol solution, ultrasonic for 10 minutes, dilute with 75% methanol solution to volume, shake thoroughly and filter. Measure accurately 3 ml of the successive filtrate into a 10 ml volumetric flask, dilute with 75% methanol solution to volume and mix well as the test solution. Inject 20 μ l of the test solution into the column, record the chromatogram. Dissolve an accurately weighed quantity of naproxen CRS and codeine phosphate CRS in 75% methanol solution to produce a solution of 0.9 mg of naproxen and 0.09 mg of codeine phosphate per ml as the reference solution. Repeat the operation, using the reference solution instead of the test solution. Calculate the content of $C_{14}H_{14}O_3$ and $C_{18}H_{21}NO_3 \cdot H_3PO_4 \cdot 1 \frac{1}{2} H_2O$ respectively with respect to the peak areas obtained in the chromatogram by the external standard method. The coefficient 1.068 is used in the calculation of the content of codeine phosphate.

Category Analgetic.

Storage Preserve in tightly closed containers, stored in a cold place and protected from light.

Naproxen Capsules

Naproxen Capsules contain not less than 90.0% and not more than 110.0% of the labelled amount of naproxen ($C_{14}H_{14}O_3$).

Identification A quantity of the contents complies with tests for Identification described under Naproxen Tablets.

Related substances Protect from light throughout the procedure. Carry out the method for high performance liquid chromatography (Appendix V D), using a column packed with octadecylsilane bonded silica gel and a mixture of methanol-0.01 mol/L potassium dihydrogen phosphate solution (75:25) (adjust with phosphoric acid to pH 3.0) as the mobile phase. Detection wavelength is 240 nm and the number of theoretical plates of the column is not less than 5000, calculated with reference to the peak of naproxen. The resolution factor between the peaks of naproxen and the impurity complies with the related requirements. Dissolve a quantity of the content, equivalent to 25 mg naproxen, in the mobile phase in a 50 ml volumetric flask, shake thoroughly to dissolve naproxen and dilute to the volume.

mix well and filter. Take the successive filtrate as solution (1). Dissolve a quantity of 6-methoxy-2-acetonaphthone CRS in the mobile phase and dilute to produce the solution (2) of 50 µg per ml. Transfer 1 ml each of solution (1) and solution (2) respectively, accurately measured, to a 100 ml volumetric flask and dilute with the mobile phase to the volume, mix well as the solution (3). Inject 20 µl of the solution (3) into the column, adjust the attenuation so that the principal peak height in the chromatogram is 10%-20% of the full scale of the chart. Inject separately 10 µl each of the solution (1) and (3), both accurately measured, into the column and record the chromatogram for 2.5 times of the retention time of the principal peak. The area of the peak with the same retention time as 6-methoxy-2-acetonaphthone, obtained with solution (1), is not greater than that of 6-methoxy-2-acetonaphthone obtained with solution (3) (0.1%). The area of the largest impurity except 6-methoxy-2-acetonaphthone is not greater than twice of the area of 6-methoxy-2-acetonaphthone in solution (3) (0.2%). The sum of the areas of all peaks other than the naproxen peak obtained with the solution (1) is not greater than the area of the naproxen peak obtained with the solution (3) in the chromatogram.

Dissolution Comply with the requirements for dissolution test (Appendix X C, method 1), using 900 ml of phosphate BS (pH 7.4) (Dissolve 2.28 g of sodium Dihydrogen phosphate and 11.50 g of disodium hydrogen phosphate with water and dilute to 1000 ml) as the dissolution medium, adjust the rotational speed of the basket to 100 rpm. Withdraw 10 ml of the solution after exactly 45 minutes and filter. Dissolve naproxen CRS, accurately weighed, with the dissolution medium and dilute to produce a solution of 100 µg per ml. Measure the absorbances of the resulting solutions at 331 nm (Appendix IV A). Calculate the dissolution of $C_{14}H_{14}O_3$ from each tablet, not less than 80% of the labelled amount is dissolved.

Other requirements Comply with the general requirements for capsules (Appendix I E).

Assay Mix the contents obtained in the test for weight variation for contents. Dissolve an accurately weighed quantity equivalent to about 0.5 g of naproxen in 45 ml of methanol, complete the Assay described under Naproxen, beginning at the words "add 15 ml of water...". Each ml of sodium hydroxide (0.1 mol/L) VS is equivalent to 23.03 mg of $C_{14}H_{14}O_3$.

Category As described under Naproxen.

Strength (1) 0.125 g (2) 0.2 g (3) 0.25 g

Storage Preserve in tightly closed containers, protected from light.

Naproxen Granules

Naproxen Granules contain not less than 90.0% and not more than 110.0% of the labelled amount of naproxen ($C_{14}H_{14}O_3$).

Description Granules with colour.

Identification (1) Dissolve a quantity, equivalent to about 5 mg of naproxen, in 5 ml of dehydrated ethanol and filter to a tube. To the filtrate add 2 ml of sulfuric acid along with the wall of the tube; The sulfuric acid layer turns to yellow, allow to stand and examine under ultra-violet light, the interface of two layers exhibits a yellowish-green fluorescence.

(2) Dissolve a quantity, equivalent to about 8 mg of

naproxen, in dehydrated ethanol in a 100 ml volumetric flask by shaking, dilute to volume, mix well and filter. The light absorption of the filtrate exhibits maxima at 262 nm, 271 nm, 317 nm and 331 nm (Appendix IV A).

Related substances Protect from light throughout the procedure. Carry out the method for high performance liquid chromatography (Appendix V D), using a column packed with octadecylsilane bonded silica gel and a mixture of methanol-0.01 mol/L potassium dihydrogen phosphate solution (75:25) (adjust with phosphoric acid to pH 3.0) as the mobile phase. Detection wavelength is 240 nm and the number of theoretical plates of the column is not less than 5000, calculated with reference to the peak of naproxen, the resolution factor between the peaks of naproxen and the impurity complies with the related requirements. Dissolve a quantity of powdered granules, equivalent to 25 mg naproxen in the mobile phase, in 50 ml volumetric flask, shake thoroughly to dissolve naproxen and dilute to the volume, mix well and filter. Take the successive filtrate as solution (1). Dissolve a quantity of 6-methoxy-2-acetonaphthone CRS in the mobile phase and dilute to produce the solution (2) of 50 µg per ml. Transfer 1 ml each of solution (1) and solution (2) respectively, accurately measured, to a 100 ml volumetric flask and dilute with the mobile phase to the volume, mix well as the solution (3). Inject 20 µl of the solution (3) into the column, adjust the attenuation so that the principal peak height in the chromatogram is 10%-20% of the full scale of the chart. Inject separately 10 µl each of the solution (1) and (3), both accurately measured, into the column and record the chromatogram for 2.5 times of the retention time of the principal peak. The area of the peak with the same retention time as 6-methoxy-2-acetonaphthone, obtained with solution (1), is not greater than that of 6-methoxy-2-acetonaphthone obtained with solution (3) (0.1%). The area of the largest impurity except 6-methoxy-2-acetonaphthone is not greater than twice of the area of 6-methoxy-2-acetonaphthone in solution (3) (0.2%). The sum of the areas of all peaks other than the naproxen peak obtained with the solution (1) is not greater than the area of the naproxen peak obtained with the solution (3) in the chromatogram.

Other requirements Comply with the general requirements for granules except dispersing capacity (Appendix I N).

Assay Dissolve an accurately weighed quantity of the powdered contents obtained in the test for weight variation of contents, equivalent to about 0.4 g of naproxen, in 25 ml of water in a separator, extract with chloroform for 4 times, first time 20 ml, the following three times each 10 ml, respectively. Combine the chloroform layers, wash with two 10 ml portions of water, combine the chloroform layers into a vonical flask, evaporate to dryness on a water bath. Dissolve the residue in 30 ml of neutral ethanol (neutral to phenolphthalein IS), add 1 drop of phenolphthalein IS, titrate with sodium hydroxide (0.1 mol/L) VS. Each ml of sodium hydroxide (0.1 mol/L) VS is equivalent to 23.03 mg of $C_{14}H_{14}O_3$.

Category As described under Naproxen.

Strength 10 g : 0.25 g

Storage Preserve in well closed containers, protected from light.

Naproxen Injection

Naproxen Injection is a sterile solution of naproxen

in Water for Injection with suitable vehicle. It contains not less than 90.0% and not more than 110.0% of the labelled amount of naproxen ($C_{14}H_{14}O_3$).

Description A clear, almost colourless or pale yellow liquid.

Identification The light absorption of the solution obtained for Assay exhibits maxima at 262 nm, 271 nm, 318 nm and 330 nm (Appendix IV A).

pH value 7.5-9.0 (Appendix VI H).

Other requirements Complies with the general requirements for injections (Appendix I B).

Assay Dissolve a quantity, accurately measured, in sodium hydroxide (0.1 mol/L) VS, to produce a solution of 40 µg per ml. Measure the absorbance at 330 nm (Appendix IV A), then repeat the operation with Naproxen CRS instead of the substance being examined. Calculate the content of $C_{14}H_{14}O_3$.

Category As described under Naproxen.

Strength (1) 2 ml : 100 mg (2) 2 ml : 200 mg

Storage Preserve in well closed containers, protected from light.

Naproxen Suppositories

Naproxen Suppositories contain not less than 90.0% and not more than 110.0% of the labelled amount of naproxen ($C_{14}H_{14}O_3$).

Description Creamy-white or faintly yellow suppositories.

Identification Dilute the solution obtained in the Assay with methanol to make a solution containing 30 µg per ml of naproxen. The light absorption of the solution exhibits maxima at 262 nm, 271 nm, 317 nm and 330 nm (Appendix IV A).

Related substances Protect from light throughout the procedure. Carry out the method for high performance liquid chromatography (Appendix V D), using a column packed with octadecylsilane bonded silica gel and a mixture of methanol-0.01 mol/L potassium dihydrogen phosphate solution (75:25) (adjust with phosphoric acid to pH 3.0) as the mobile phase. Detection wavelength is 240 nm and the number of theoretical plates of the column is not less than 5000, calculated with reference to the peak of naproxen, the resolution factor between the peaks of naproxen and the impurity complies with the related requirements. Weigh accurately a quantity, melt by warming on a water bath, then cool to room temperature, equivalent to about 50 mg of naproxen, in 50 ml volumetric flask, dilute with methanol to the volume and heat on a water bath at 50-60°C and shake well. Allow to stand for 10 minutes and cool to room temperature. After freezing in refrigerator for 1 hour, filter immediately, and cool to room temperature. Measure accurately 25 ml of the successive filtrate in a 50 ml volumetric flask, dilute with the mobile phase to the volume, mix well. Filter with the membrane (0.45 µm) and take the successive filtrate as the solution (1). Dissolve a quantity of 6-methoxy-2-acetonaphthone CRS in the mobile phase and dilute to produce the solution (2) of 50 µg per ml. Transfer 1 ml each of solution (1) and solution (2) respectively, accurately measured, to a 100 ml volumetric flask and dilute with the mobile phase to the volume, mix well as the solution (3). Inject 20 µl of the solution (3)

into the column, adjust the attenuation so that the principal peak height in the chromatogram is 10%-20% of the full scale of the chart. Inject separately 10 µl each of the solution (1) and (3), both accurately measured, into the column and record the chromatogram for 2.5 times of the retention time of the principal peak. The area of the peak with the same retention time as 6-methoxy-2-acetonaphthone, obtained with solution (1), is not greater than that of 6-methoxy-2-acetonaphthone obtained with solution (3) (0.1%). The area of the largest impurity except 6-methoxy-2-acetonaphthone is not greater than twice of the area of 6-methoxy-2-acetonaphthone in solution (3) (0.2%). The sum of the areas of all peaks other than the naproxen peak obtained with the solution (1) is not greater than the area of the naproxen peak obtained with the solution (3) in the chromatogram.

Other requirements Comply with the general requirements for suppositories (Appendix I D).

Assay Reference solution preparation Weigh accurately about 50 mg of naproxen CRS in a 100 ml volumetric flask, add 70 ml of methanol, heat on a water bath at 50-60°C and shake well. Cool to temperature, dilute with methanol to volume, mix well. Transfer accurately 5 ml of the solution to a 50 ml volumetric flask, dilute with methanol to volume and mix well.

Test solution preparation Weigh accurately 10 suppositories, melt by warming on a water bath, cool to room temperature with constant stirring. To a quantity equivalent to about 50 mg of naproxen, accurately weighed, in a 100 ml volumetric flask, add 70 ml of methanol, heat on a water bath at 50-60°C and shake well. Heat for 10 minutes more and cool on a cold water bath for 1.5 hours. Allow to cool to room temperature, dilute with methanol to volume, mix well, filter. Transfer accurately 5 ml of the successive filtrate to a 50 ml volumetric flask, dilute with methanol to volume and mix well.

Procedure Measure the absorbance of the solution at 331 nm (Appendix IV A). Calculate the content of $C_{14}H_{14}O_3$.

Category As described under Naproxen.

Strength 0.25 g

Storage Preserve in well closed containers, protected from light, stored at a temperature below 30°C.

Naproxen Tablets

Naproxen Tablets contain not less than 93.0% and not more than 107.0% of the labelled amount of naproxen ($C_{14}H_{14}O_3$).

Description White or almost white tablets.

Identification Extract a quantity of the powdered tablets with methanol to produce a 30 µg per ml solution of naproxen, filter. The light absorption of the filtrate exhibits four maxima at 262 nm, 271 nm, 317 nm and 331 nm (Appendix IV A).

Related substances Protect from light throughout the procedure. Carry out the method for high performance liquid chromatography (Appendix V D), using a column packed with octadecylsilane bonded silica gel and a mixture of methanol-0.01 mol/L potassium dihydrogen phosphate solution (75:25) (adjust with phosphoric acid to pH 3.0) as the mobile phase. Detection wavelength is 240 nm and the number of theoretical plates of the column is not less than 5000, calculated with reference to the peak of naproxen, the

resolution factor between the peaks of naproxen and the impurity complies with the related requirements. Dissolve a quantity of powdered tablets, equivalent to 25 mg naproxen, in the mobile phase in a 50 ml volumetric flask, shake thoroughly to dissolve naproxen and dilute to the volume, mix well and filter. Take the successive filtrate as solution (1). Dissolve a quantity of 6-methoxy-2-acetonaphthone CRS in the mobile phase and dilute to produce the solution (2) of 50 µg per ml. Transfer 1 ml each of solution (1) and solution (2) respectively, accurately measured, to a 100 ml volumetric flask and dilute with the mobile phase to the volume, mix well as the solution (3). Inject 20 µl of the solution (3) into the column, adjust the attenuation so that the principal peak height in the chromatogram is 10%-20% of the full scale of the chart. Inject separately 10 µl each of the solution (1) and (3), both accurately measured, into the column and record the chromatogram for 2.5 times of the retention time of the principal peak. The area of the peak with the same retention time as 6-methoxy-2-acetonaphthone, obtained with solution (1), is not greater than that of 6-methoxy-2-acetonaphthone obtained with solution (3) (0.1%). The area of the largest impurity except 6-methoxy-2-acetonaphthone is not greater than twice of the area of 6-methoxy-2-acetonaphthone in solution (2) (0.2%). The sum of the areas of all peaks other than the naproxen peak obtained with the solution (1) is not greater than the area of the naproxen peak obtained with the solution (3) in the chromatogram.

Dissolution Carry out the dissolution test (Appendix X C, method 1), using 900 ml of phosphate BS (pH 7.4) (dissolve 2.28 g of sodium dihydrogen phosphate and 11.50 g of disodium hydrogen phosphate with water, and dilute to 1000 ml) as dissolution medium. The rotational speed of the basket to 100 rpm. Withdraw 10 ml of the solution after exactly 45 minutes and filter, take the successive filtrate as test solution. Weigh accurately a quantity of naproxen CRS, and dissolve with the dissolution medium to produce solutions of 100 µg (for strength 0.1 g) or 125 µg (for strength 0.125 g) or 250 µg (for strength 0.25 g) per ml as the reference solution. Measure the absorbances of the resulting solutions at 331 nm (Appendix IV A). Calculate the dissolution of $C_{14}H_{13}NaO_3$ from each tablets, not less than 80% of the labelled amount is dissolved.

Other requirements Comply with the general requirements for tablets (Appendix I A).

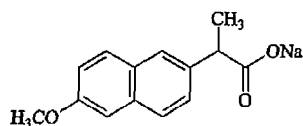
Assay Weigh accurately and powder 20 tablets. Dissolve an accurately weighed quantity, equivalent to about 0.5 g of naproxen in 45 ml of methanol. Complete the Assay described under Naproxen, beginning at the words "add 15 ml of water...". Each ml of sodium hydroxide (0.1 mol/L) VS is equivalent to 23.03 mg of $C_{14}H_{13}NaO_3$.

Category As described under Naproxen.

Strength (1) 0.1 g (2) 0.125 g (3) 0.25 g

Storage Preserve in tightly closed containers, protected from light.

Naproxen Sodium



$C_{14}H_{13}NaO_3$ 252.25

[26159-34-2]

Naproxen sodium is (S)-(-)-sodium (S)-6-methoxy- α -methyl-2-naphthaleneacetate. It contains not less than 98.0% and not more than 102.0% of $C_{14}H_{13}NaO_3$, calculated on the dried basis.

Description A white or almost white crystalline powder; odourless; slightly hygroscopic.

Freely soluble in water; soluble in methanol; sparingly soluble in ethanol; very slightly soluble in acetone; practically insoluble in chloroform or toluene.

Specific optical rotation To 0.5 g add 6 ml of water. Add 2.4 ml of 1 mol/L hydrochloric acid solution dropwise with shaking until a precipitate is produced. Wash the precipitate with water until the washing is neutral, dry to constant at 105°C and weigh accurately. Dissolve the precipitate in chloroform to produce a solution of 10 mg per ml, the specific optical rotation of the resulting solution is +63° to +69° (Appendix VI E).

Identification (1) Dissolve about 0.1 g in 2 ml of water, add a few drops of dilute hydrochloric acid; a white precipitate is produced. Filter, the filtrate yields the reactions characteristic of sodium salts (Appendix III).

(2) The infrared absorption spectrum of the substance being examined, dried at 105°C for 3 hours, is concordant with the reference spectrum of naproxen sodium (Appendix XVI).

Related substances Carry out the method for thin-layer chromatography (Appendix V B), using silica GF₂₅₄ as the coating substance and a mixture of toluene-tetrahydrofuran-glacial acetic acid (30:3:1) as the mobile phase. Apply separately to the plate 10 µl each of two solutions in methanol containing (1) 20 mg per ml, (2) 0.1 mg per ml of the substance being examined. After developing and removal of the plate, dry it in air and examine under ultraviolet light (254 nm). Any spot in the chromatogram other than the principal spot obtained with solution (1) is not more intense than the principal spot obtained with solution (2).

Free naproxen Dissolve 5.0 g, accurately weighed, in 25 ml of water in a separator, extract the solution with three 15 ml portions of chloroform, and evaporate the combined chloroform extracts to dryness on a water bath. Dissolve the residue in 50 ml of 75% neutral methanol (neutral to phenolphthalein IS), add 3 drops of phenolphthalein IS, titrate with sodium hydroxide (0.1 mol/L) VS; the volume of sodium hydroxide (0.1 mol/L) VS consumed is not more than 2.2 ml (1.0%).

Loss on drying When dried to constant weight at 105°C, loses not more than 1.0% of its weight (Appendix VIII L).

Heavy metals Dissolve naproxen sodium in 20 ml of water in a separator, add 5 ml of 1 mol/L hydrochloric acid solution. Extract with 20 ml, 20 ml and 10 ml of dichloromethane separately and discard the dichloromethane layer. Carry out the limit test for heavy metals (Appendix VIII H, method 1), using the aqueous layer extracts: not more than 0.002%.

Assay Dissolve about 0.2 g, accurately weighed, in 30 ml of glacial acetic acid, add 1 drop of crystal violet TS, titrate with perchloric acid (0.1 mol/L) VS until the colour of solution changes to bluish-green. Perform a blank determination and make any necessary correction. Each ml of perchloric acid (0.1 mol/L) VS is equivalent to 25.22 mg of $C_{14}H_{13}NaO_3$.

Category A non-inflammatory analgesic, antipyretic.

Storage Preserve in tightly closed containers, stored in a dry place and protected from light.

Preparation Naproxen Sodium Tablets**Naproxen Sodium Tablets**

Naproxen Sodium Tablets contain not less than 93.0% and not more than 107.0% of the labelled amount of naproxen sodium ($C_{14}H_{13}NaO_3$).

Description White or almost white tablets.

Identification (1) Shake a quantity of powdered tablets equivalent to about 250 mg of naproxen sodium with 12 ml of water, add 1 ml of hydrochloric acid; a white precipitate is produced. Filter, the filtrate yields the reactions characteristic of sodium (Appendix III).

(2) Shake the precipitate obtained in Identification test (1) with 10 ml of chloroform, filter, and dilute 1 ml of the filtrate to 50 ml with chloroform. The light absorption of the resulting solution exhibits maxima and minima in the range of 200-400 nm (Appendix IV A).

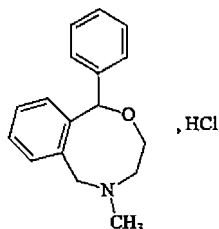
Other requirements Comply with the general requirements for tablets (Appendix I A).

Assay Weigh accurately and powder 10 tablets. To an accurately weighed quantity of the powder, equivalent to about 275 mg of naproxen sodium, in a 100 ml volumetric flask, add about 70 ml of methanol, shake thoroughly for 30 minutes to dissolve naproxen sodium, dilute with methanol to volume, mix well and filter. Transfer 2 ml of the successive filtrate, accurately measured, to a 100 ml volumetric flask, dilute with methanol to volume and shake well. Measure the absorbance of the resulting solution at 332 nm (Appendix IV A). Repeat the operation, using a solution containing 55 μ g of naproxen sodium CRS per ml, in methanol in the same manner. Calculate the content of $C_{14}H_{13}NaO_3$.

Category As described under Naproxen Sodium.

Strength (1) 0.1 g (equivalent to 91 mg of naproxen)
(2) 0.275 g (equivalent to 250 mg of naproxen)

Storage Preserve in tightly closed containers, stored in a dry place and protected from light.

Nefopam Hydrochloride

$C_{17}H_{19}NO \cdot HCl$ 289.20

[23327-57-3]

Nefopam Hydrochloride is 5-methyl-1-phenyl-3,4,5,6-tetrahydro-1H-2,5-benzoxazocine hydrochloride. It contains not less than 98.5% of $C_{17}H_{19}NO \cdot HCl$, calculated on the dried basis.

Description White crystalline powder; odourless; taste, slightly bitter.

Sparingly soluble in water, slightly soluble in ethanol, insoluble in benzene.

Identification (1) To about 10 mg, add 1 ml of sulfuric acid; the solution becomes orange red, and changes to purplish red on adding 1 drop of nitric acid; To another portion of about 10 mg, add 1 ml of sulfuric acid and 1 drop of formaldehyde, a brown colour is produced.

(2) The light absorption of the solution of 0.15 mg per ml in dehydrated ethanol exhibits maximum at 266 nm and 274 nm (Appendix IV A).

(3) The aqueous solution yields the reactions characteristic of chlorides (Appendix III).

(4) The infrared absorption spectrum (Appendix IV C) is concordant with the reference spectrum of nefopam hydrochloride (Appendix XVI).

Loss on drying When dried to constant weight at 105°C, loses not more than 0.5% (Appendix VIII L).

Residue on ignition Not more than 0.1% (Appendix VII N), using 1.0 g.

Heavy metals Carry out the limit test for heavy metals (Appendix VII H, method 2), using the residue obtained in test for residue on ignition, not more than 0.002%.

Assay Dissolve about 0.15 g, accurately weighed, with 10 ml of glacial acetic acid, on warming, cool, add 5 ml of 5% mercuric acetate solution and 1 drop of crystal violet IS, titrate with perchloric acid (0.1 mol/L) VS until the colour changes to blue. Perform a blank determination and make any necessary correction. Each ml of perchloric acid (0.1 mol/L) VS is equivalent to 28.98 mg of $C_{17}H_{19}NO \cdot HCl$.

Category Analgesic agent.

Storage Preserve in tightly closed containers, stored in dry place.

Preparation (1) Nefopam Hydrochloride Injection
(2) Nefopam Hydrochloride Tablets

Nefopam Hydrochloride Injection

Nefopam Hydrochloride Injection is a sterile solution of Nefopam hydrochloride in water for Injection. It contains not less than 90.0% and not more than 110.0% of the labelled amount of nefopam hydrochloride ($C_{17}H_{19}NO \cdot HCl$).

Description A clear, colourless liquid.

Identification (1) To 0.5 ml, add 1 drop of Potassium iodide TS or mercuric chloride TS, a white precipitate is produced.

(2) Yields the reactions characteristic of chlorides (Appendix III).

pH value 4.0-6.0 (Appendix VI H).

Other requirements Complies with the general requirements for injections (Appendix I B).

Assay Measure accurately a quantity, equivalent to about 20 mg of nefopam hydrochloride, to a 100 ml volumetric flask, dilute with dehydrated ethanol to a volume and mix well. Measure the absorbance at 267 nm (Appendix VI A), then weigh accurately 20 mg of the nefopam hydrochloride CRS proceed in the same manner. Calculate the content of $C_{17}H_{19}NO \cdot HCl$.

Category As described under Nefopam Hydrochloride.

Strength 1 ml:20 mg

Storage Preserve in well closed containers, protected from light.

Nefopam Hydrochloride Tablets

Nefopam Hydrochloride Tablets contain not less than 90.0% and not more than 110.0% of the labelled amount of nefopam hydrochloride ($C_{17}H_{19}NO \cdot HCl$).

Description White tablets.

Identification (1) To a quantity of the powdered tablets, equivalent to about 10 mg of nefopam hydrochloride, add 1 ml of sulfuric acid, a yellow colour is produced, then add 1 drop of nitric acid, the colour changes to red.

(2) To a quantity of the powdered tablets, equivalent to about 10 mg of nefopam hydrochloride, add 1 ml of sulfuric acid and 1 drop of formaldehyde solution, a brown colour is produced.

(3) Dissolve a quantity of the powdered tablets with ethanol to produce a solution of 0.15 mg per ml and filter. The light absorption of the successive filtrate exhibits maxima at 266 nm and 274 nm (Appendix IV A).

(4) The aqueous solution yields the reactions characteristic of chlorides (Appendix III).

Dissolution Comply with the dissolution test (Appendix X C, method 2), using 1000 ml water as the dissolution medium, adjust the rotational speed of the paddle to 50 rpm. Withdraw a quantity of solution after exactly 45 minutes and filter. Take the successive filtrate as test solution. Carry out the method for high performance liquid chromatography (Appendix V D), using a column packed with octadecylsilane bonded silica gel and a mixture of 0.01 mol/L heptane sulfonate solution (adjust with dilute phosphoric acid to pH 3.0)-acetonitrile (67:33) as the mobile phase. Detection wavelength is 215 nm and the number of theoretical plates of the column is not less than 2000. Inject 20 μ l of the test solution into the column, accurately measured, record the chromatogram. Repeat the operation, dissolve a quantity of nefopam hydrochloride CRS, weighed accurately, in water to produce a solution of 0.02 mg per ml. Calculate the dissolution of $C_{17}H_{19}NO \cdot HCl$ from each tablet, with respect to the peak area obtained in the chromatogram by the external standard method. Not less than 75% of the labelled amount is dissolved.

Other requirements Comply with the general requirements for tablets (Appendix I A).

Assay Weigh and powder 20 tablets. Dissolve a quantity of the powdered tablets equivalent to about 0.12 g of nefopam hydrochloride, accurately weighed, with 20 ml of glacial acetic acid, on warming. Cool, add 5 ml of mercuric acetate TS and 1 drop of crystal violet IS, titrate with perchloric acid (0.1 mol/L) VS until the colour changes to pure blue. Perform a blank determination and make any necessary correction. Each ml of perchloric acid (0.1 mol/L) VS is equivalent to 28.95 mg of $C_{17}H_{19}NO \cdot HCl$.

Category As described under Nefopam Hydrochloride.

strength 20 mg

storage Preserve in tightly closed containers, protected from light.

Neomycin Sulfate

Neomycin Sulfate has a potency of not less than 650 neomycin Units per mg, calculated on the dried basis.

Description A white, or almost white powder; odourless; hygroscopic. The aqueous solution is dextro-rotatory. Very soluble in water; practically insoluble in ethanol, ether, acetone or chloroform.

Identification (1) Dissolve 10 mg in 1 ml of water, add 2 ml of hydrochloric acid solution (9→100), heat in a water bath for 10 minutes, add 2 ml of 8% sodium hydroxide solution and 1 ml of a 2% solution of acetylacetone in water, heat in a water bath for further 5 minutes. Allow to cool, add 1 ml of p-dimethylaminobenzaldehyde TS; a cherry red colour is produced.

(2) Carry out the method for thin layer chromatography (Appendix V B), using silica gel H as the coating substance (prepared by mixing 1.5 g of silica gel H with 6 ml of a 0.25% solution of carboxymethylcellulose sodium), and a mixture of methanol-ethyl acetate-acetone-8.8% ammonium acetate solution (25:15:10:40) as the mobile phase. Apply separately to the plate 1 μ l each of two solutions in water containing (1) 20 mg per ml of the substance being examined and (2) 20 mg per ml of neomycin sulfate RS. After developing and removal of the plate, allow it to dry in air and then heat at 110°C for 20 minutes, spray the hot plate with a 10% solution of sodium hypochlorite, dry in a current of cold air and again spray with starch-potassium iodide solution (100 ml of a 0.5% starch solution containing 0.5 g of potassium iodide) and examine immediately. The colour and position of the principal spot in the chromatogram obtained with solution (1) correspond to that of the principal spot obtained with solution (2).

(3) The infrared absorption spectrum (Appendix IV C) is concordant with the spectrum of neomycin CRS.

(4) The aqueous solution yields the reactions characteristic of sulfates (Appendix III).

Acidity An aqueous solution of 0.1 g per ml, pH 5.0-7.0 (Appendix VI H).

Sulfate Dissolve 0.16 g, accurately weighed, in 100 ml of water, and adjust pH value to 11 using concentrated ammonia solution. Add 10.0 ml of barium chloride (0.1 mol/L) VS and 5 drops of phthalein purple IS. Titrate with disodium edetate (0.05 mol/L) VS, make sure to keep pH value 11 during the period of titration. Add 50 ml of ethanol when the colour of the solution begins to change and continue the titration until the blue purple colour disappears. Perform a blank determination and make any necessary correction. Each ml of barium chloride (0.1 mol/L) VS is equivalent to 9.606 mg of sulfate (SO_4). The content of sulfate is 27.0%-31.0%, calculated on the dried basis.

Neamine Carry out the method for thin layer chromatography described under the test (2) for Identification, Applying two solutions in water containing (1) 20 mg per ml of the substance being examined and (2) 0.4 mg of neamine RS per ml. Any spot other than the principal spot in the chromatogram obtained with solution (1) is not more intense than the principal spot obtained with solution (2).

Loss on drying When dried in vacuum over phosphorus pentoxide to constant weight at 60°C, loses not more than 6.0% of its weight (Appendix VII L).

Residue on ignition Not more than 1.0% (Appendix VIII N).

Assay Dissolve an accurately weighed quantity in sterile water to produce a solution of 1000 Units per ml and carry out the Microbiological Assay of Antibiotics (Appendix XI A). 1000 Neomycin Units are equivalent to 1 mg of

Neomycin.

Category Aminoglycosides.

Storage Preserve in tightly closed containers, stored in a dry place.

Preparation (1) Neomycin Sulfate Eye Drops
(2) Neomycin Sulfate Tablets
(3) Compound Neomycin Ointment

Neomycin Sulfate Eye Drops

Neomycin Sulfate Eye Drops contain not less than 90.0% and not more than 110.0% of the labelled amount of neomycin.

Description A clear, colourless to pale yellow liquid.

Identification Comply with the tests (1), (2) and (4) for Identification described under Neomycin Sulfate.

pH value 6.0-7.0 (Appendix VI H).

Colour The solution is colourless; any colour produced is not more intense than that of the reference solution Y₃ (Appendix IX A, Method 1).

Other requirements Comply with the general requirements for eye preparations (Appendix I G).

Assay Measure accurately a quantity, carry out the method described under Neomycin Sulfate.

Category As described under Neomycin Sulfate.

Strength 8 ml (40000 Units)

Storage Preserve in tightly closed containers, stored in a cool place and protected from light.

Neomycin Sulfate Tablets

Neomycin Sulfate Tablets contain not less than 93.0% and not more than 107.0% of the labelled potency of neomycin.

Description White tablets.

Identification To a quantity of powdered tablets add water to produce a suspension containing 20 mg of neomycin per ml and filter. The filtrate complies with the tests (1), (2) and (4) for Identification described under Neomycin Sulfate.

Other requirements Comply with the general requirements for tablets (Appendix I A).

Assay Weigh accurately and powder 10 tablets. Dissolve an accurately weighed quantity of the powder equivalent to about 0.25 g of neomycin in sterile water to produce a suspension of 1000 Units per ml and shake thoroughly. Allow to stand, measure accurately a quantity of the suspension liquid and carry out the Assay described under Neomycin Sulfate.

Category As described under Neomycin Sulfate.

Strength (1) 0.1 g (100000 Units)
(2) 0.25 g (250000 Units)

Storage Preserve in tightly closed containers, stored in a dry place.

Compound Neomycin Ointment

Compound Neomycin Ointment contains not less than 90.0% and not more than 120.0% of the labelled potency of neomycin sulfate and bacitracin.

Formula	Neomycin Sulfate	2000000 Units
	Bacitracin	250000 Units
	Liquid Paraffin	a sufficient quantity
	Vaseline	a sufficient quantity

to produce 1000 g

Description A pale yellow to yellow ointment.

Identification Dissolve about 1 g of the ointment with 20 ml of ether by shaking and extract with 2 ml of water in a separator. Take the aqueous layer as solution (1). Dissolve a quantity of neomycin RS and bacitracin RS, respectively, with water to produce solution (2) 1000 Units of neomycin per ml and (3) 125 Units of bacitracin. Carry out the method for thin-layer chromatography (Appendix V B), using silica gel G as the coating substance and a mixture of methanol-ethyl acetate-acetone-8.8% ammonium acetate solution (25 : 15 : 10 : 40) as the mobile phase. Apply separately to the plate 5 µl each of above three solutions, after developing and removal of the plate, dry it in air, spray with *n*-butanol-pyridine (99 : 1) containing 1% of ninhydrin. The colour and position of the two principal spots in the chromatogram obtained with solution (1) correspond to the principal spots obtained with solution (2) and (3).

Other requirements Comply with the general requirements for ointments (Appendix I F).

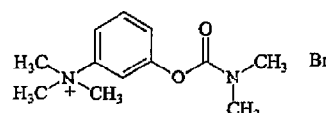
Assay Neomycin Weigh accurately about 2 g, shake in a separator with 50 ml of ether and extract with four quantities of 20 ml of phosphate BS (pH 7.8) containing 3% of sodium chloride. Dilute the combined extracts to 100 ml with the buffer solution, mix well, and carry out the Microbiological Assay of Antibiotics (Appendix XI A). It is necessary to add bacitracin RS according to the formula when prepare the neomycin reference solution.

Bacitracin Weigh accurately about 2 g, shake in a separator with 50 ml of ether and extract with four quantities of 20 ml of phosphate BS (pH 6.0). Dilute the combined extracts to 100 ml with the buffer solution, mix well and carry out the Microbiological Assay of Antibiotics (Appendix XI A).

Category Antibiotic.

Storage Preserve in well closed containers, stored in a dry and cool place.

Neostigmine Bromide



C₁₂H₁₉BrN₂O₂ 303.20

[114-80-7]

Neostigmine Bromide is 3-[(dimethylamino)-carbonyl]oxy-N,N,N-trimethyl benzenaminium bromide. It contains not less than 98.0% of

$C_{12}H_{19}BrN_2O_2$, calculated on the dried basis.

Description A white crystalline powder; odourless; taste bitter.

Very soluble in water; freely soluble in ethanol or chloroform; practically insoluble in ether.

Melting range 171-176°C, with decomposition (Appendix VI C).

Identification (1) To about 1 mg in an evaporating dish, add 1 ml of 20% sodium hydroxide solution and 2 ml of water, then evaporate to dryness on a water bath. Dissolve the residue in 1 ml of water, cool and add 1 ml of diazotized sulfanilic acid TS; a red colour is produced.

(2) The infrared absorption spectrum (Appendix IV C) is concordant with the reference spectrum of neostigmine bromide (Appendix XVI).

(3) The aqueous solution yields the reactions characteristic of bromides (Appendix III).

Sulfate Dissolve 0.25 g in 10 ml of water, add 1 ml of dilute hydrochloric acid and 2 ml of barium chloride TS; no turbidity is produced.

Extraneous absorbance Measure the absorbance of a solution of 5.0 mg per ml in 1.0% sodium carbonate solution at 294 nm (Appendix IV A), the absorbance is not greater than 0.25.

Loss on drying When dried to constant weight at 105°C loses not more than 1.0% of its weight (Appendix VIII L).

Residue on ignition Not more than 0.1% (Appendix VIII N).

Assay Dissolve about 0.2 g, accurately weighed, in 20 ml of glacial acetic acid and 5 ml of mercuric acetate TS, add 1 drop of crystal violet IS, titrate with perchloric acid (0.1 mol/L) VS until the colour changes to blue. Perform a blank determination and make any necessary correction. Each ml of perchloric acid (0.1 mol/L) VS is equivalent to 30.32 mg of $C_{12}H_{19}BrN_2O_2$.

Category Anticholinesterase agent.

Storage Preserve in tightly closed containers.

Preparation Neostigmine Bromide Tablets

Neostigmine Bromide Tablets

Neostigmine Bromide Tablets contain not less than 93.0% and not more than 107.0% of the labelled amount of neostigmine bromide ($C_{12}H_{19}BrN_2O_2$).

Description White tablets.

Identification Macerate a quantity of the powdered tablets equivalent to about 0.1 g neostigmine bromide with successive quantities 10 ml each of ethanol and filter the combined ethanol extracts. Evaporate the filtrate to dryness on a water bath. The residue complies with tests (1) and (3) for Identification described under Neostigmine Bromide.

Other requirements Comply with the general requirements for tablets (Appendix I A).

Assay Weigh accurately and powder 40 tablets. Dissolve an accurately weighed quantity of the powder, equivalent to about 0.2 g of neostigmine bromide, in a 100 ml volumetric flask with a quantity of water on shaking, add sufficient water to volume and mix well. Filter, discard the initial filtrate and transfer 50 ml, measured accurately, of the successive filtrate to a Kjeldahl flask. Add 40 ml of water,

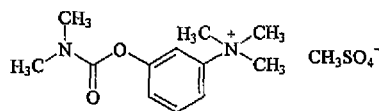
100 ml of sodium hydroxide TS and distil. Collect the distillate in 50 ml of 2% boric acid solution until the volume is about 150 ml. Add 6 drops of methyl red-bromocresol green IS, titrate with sulfuric acid (0.01 mol/L) VS. Perform a blank determination and make any necessary correction. Each ml of sulfuric acid (0.01 mol/L) VS is equivalent to 6.064 mg of $C_{12}H_{19}BrN_2O_2$.

Category As described under Neostigmine Bromide.

Strength 15 mg

Storage Preserve in tightly closed containers.

Neostigmine Methylsulfate



$C_{13}H_{22}N_2O_6S$ 334.39

[51-60-5]

Neostigmine Methylsulfate is 3-(dimethylcarbamoyloxy-*N,N,N*-trimethylanilinium methylsulfate. It contains not less than 98.0% of $C_{13}H_{22}N_2O_6S$, calculated on the dried basis.

Description A white crystalline powder; odourless; taste, bitter; hygroscopic.

Very soluble in water; freely soluble in ethanol.

Melting range 143-149°C (Appendix VI C).

Identification (1) To about 1 mg in an evaporating dish add 1 ml of 20% sodium hydroxide solution and 2 ml of water, evaporate to dryness on a water bath and heat at 250°C for about half minute. Dissolve the residue in 1 ml of water cool and add 1 ml of diazotized sulfanilic acid TS; a red colour is produced.

(2) The infrared absorption spectrum (Appendix IV C) is concordant with the reference spectrum of neostigmine methylsulfate (Appendix XVI).

(3) To about 20 mg add 1 ml of 20% sodium hydroxide solution and 10 drops of strong hydrogen peroxide solution, heat to boil. Cool, acidify the solution with dilute hydrochloric acid and add barium chloride TS; a white precipitate is produced.

Acidity or alkalinity Dissolve 0.10 g in 10 ml of water, add 2 drops of phenolphthalein IS, no pink colour is produced; add 0.20 ml of sodium hydroxide (0.02 mol/L) VS, a pink colour is produced.

Chloride Dissolve 0.2 g in 10 ml of water, add 1 ml of dilute nitric acid and 3 ml of silver nitrate TS, no turbidity is immediately produced.

Sulfate Carry out the limit test for sulfates (Appendix VII B), using 0.5 g. Any opalescence produced is not more pronounced than that of a reference using 3.0 ml of potassium sulfate standard solution (0.06%).

Light absorption of impurity Dissolve an accurately weighed quantity in 1.0% sodium carbonate solution to produce a solution of 5.0 mg per ml. Measure the absorbance of the resulting solution at 294 nm (Appendix IV A); not greater than 0.15.

Readily oxidizable substances Dissolve 0.1 g in 1.0 ml of freshly boiled and cooled water, add 0.5 ml of potassium permanganate (0.001 mol/L) VS, the colour remains unfaded for 30 seconds.

Loss on drying When dried to constant weight at 105°C, loses not more than 1.0% of its weight (Appendix VII L).

Residue on ignition Not more than 0.1% (Appendix VII N).

Assay Dissolve about 0.15 g, accurately weighed, in 9 ml of water in a Kjeldahl flask, add 100 ml of sodium hydroxide TS and distil. Collect the distillate in 50 ml of 2% boric acid solution until the total volume reaches 150 ml. To the solution add 6 drops of a mixture of methyl red and bromocresol green IS, titrate with sulfuric acid (0.01 mol/L) VS until the solution changes from bluish green to greyish violet. Perform a blank determination and make any necessary correction. Each ml of sulfuric acid (0.01 mol/L) VS is equivalent to 6.688 mg of $C_{13}H_{22}N_2O_6S$.

Category Antinergic.

Storage Preserve in tightly closed containers, protected from light.

Preparation Neostigmine Methylsulfate Injection

Neostigmine Methylsulfate Injection

Neostigmine Methylsulfate Injection is a sterile solution of Neostigmine Methylsulfate in Water for Injection. It contains not less than 90.0% and not more than 110.0% of the labelled amount of neostigmine methylsulfate ($C_{13}H_{22}N_2O_6S$).

Description A clear, colourless liquid.

Identification (1) Complies with test (1) for Identification described under Neostigmine Methylsulfate, using 2 ml.

(2) Evaporate 20 ml to dryness, the residue complies with test (3) for Identification described under Neostigmine Methylsulfate.

pH value 5.0-7.0 (Appendix VI H).

Other requirements Complies with the general requirements for injections (Appendix I B).

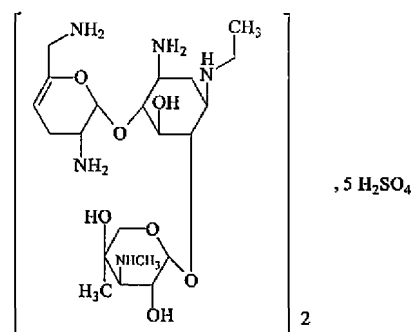
Assay Measure accurately a quantity equivalent to about 10 mg of neostigmine methylsulfate, carry out the method for determination of nitrogen (Appendix VII D, method II). Transfer the injection to the semi-micro Kjeldahl apparatus, add 5 ml of 40% sodium hydroxide solution and distil slowly. Collect the distillate in 5 ml of 2% boric acid solution until the total volume reaches about 70 ml. Titrate with sulfuric acid (0.005 mol/L) VS on adding 6 drops of methylred-bromocresol green IS, until the solution becomes greyish-violet. Perform a blank determination and make any necessary correction. Each ml of sulfuric acid (0.005 mol/L) VS is equivalent to 3.344 mg of $C_{13}H_{22}N_2O_6S$.

Category As described under Neostigmine Methylsulfate.

Strength 1 ml; 0.5 mg

Storage Preserve in well closed containers, protected from light.

Netilmicin Sulfate



$(C_{21}H_{41}N_5O_7)_2 \cdot 5H_2SO_4$ 1441.54 [56391-57-2]

Netilmicin Sulfate is *O*-3-Deoxy-4-*C*-methyl-3-(methylamino)- β -L-arabinopyranosyl-(1 \rightarrow 4)-*O*-[2,6-diamino-2,3,4,6-tetradeoxy- α -D-glycero-hex-4-enopyranosyl-(1 \rightarrow 6)]-2-deoxy-*N*³-ethyl-L-streptamine sulfate (2:5) (salt). It has a potency of not less than 610 netilmicin Units per mg, calculated on the anhydrous basis.

Description A white or almost white powder or loose mass; odourless; taste, slightly bitter; hygroscopic. Freely soluble in water; insoluble in ethanol, chloroform or ether.

Specific optical rotation +88° to +96°, in a solution of 10 mg per ml in water (Appendix VI E).

Identification (1) Carry out the method for thin-layer chromatography (Appendix V B) described under Related substances. Apply separately to the plate 2 μ l each of three solutions in water containing (1) 3 mg per ml of the substance being examined, (2) 3 mg per ml of netilmicin RS, and (3) 1.5 mg per ml of each of the substance being examined and netilmicin RS. The colour and position of the principal spot in the chromatogram obtained with solution (1) correspond to that in the chromatogram obtained with solution (2), and the solution (3) shows only one principal spot.

(2) The aqueous solution yields the reactions characteristic of sulfates (Appendix III).

Acidity Dissolve a quantity in water to produce a solution containing 40 mg per ml, pH 3.5-5.5 (Appendix VI H).

Clarity and colour of solution Dissolve 700 mg each of 5 portions in 5 ml water respectively, the solutions are clear and colourless; any opalescence produced is not more pronounced than that of reference suspension 1 (Appendix IX B); any colour produced is not more intense than that of reference solution Y₂ or YG₂ (Appendix IX A, method 1).

Sulfate Dissolve about 0.12 g, accurately weighed, in 100 ml of water, adjust pH value to 11 with concentrated ammonia solution, add accurately 10 ml of barium chloride (0.1 mol/L) VS and 5 drops of phthalein purple IS. Titrate with disodium edetate (0.05 mol/L) VS, keep pH 11 during the period of titration. When the purple colour of the solution begins to discolour slightly add 50 ml of ethanol and continue titration until the purple colour disappears. Perform a blank determination and make any necessary correction. Each ml of barium chloride (0.1 mol/L) VS is equivalent to 9.606 mg of sulfate (SO_4). The content of sulfate is not less than 31.5% and not more than 35.0%, calculated on the

anhydrous basis.

Related substances Carry out the method for thin layer chromatography (Appendix V B), using silica gel G as the coating substance and a mixture of dichloromethane-methanol-concentrate ammonia solution (4 : 4 : 2) as the mobile phase. Apply separately to the plate 2 μ l each of four solutions in water containing (1) 150 mg per ml of the substance being examined, (2) 1.5 mg per ml of netilmicin RS, (3) 3 mg per ml of netilmicin RS, and (4) 1.44 mg per ml of sisomicin RS. After developing and removal of the plate, allow it to dry in air and spray with a 0.2% solution of ninhydrin in *n*-butanol saturated with water, heat at 110°C for 20 minutes. The sisomicin spot in the chromatogram obtained with solution (1) are not more intense than the principal spot obtained with solution (4) (1%). Any other secondary spot in the chromatogram obtained with solution (1) is not more intense than the principal spot obtained with solution (2) (1%) and not more than one such spot may be more intense than the principal spots obtained with solution (3) (2%).

Water Not more than 15.0% (Appendix VIII M, method 1).

Residue on ignition Not more than 1.0% (Appendix VIII N), using 1.0 g.

Heavy metals Carry out the limit test for heavy metals (Appendix VIII H, method 2), using the residue obtained in the test for Residue on ignition; not more than 0.002%.

Bacterial endotoxin Carry out the test for bacterial endotoxin (Appendix XI E); less than 1.25 EU per 1000 Netilmicin Units.

Assay Carry out the Microbiological assay of antibiotics (Appendix XI A), using a solution of about 1000 Units per ml in phosphate BS (pH 7.8). The fiducial limit is not more than 7%. 1000 Netilmicin Units is equivalent to 1 mg of $C_{21}H_{41}N_5O_7$.

Category Aminoglycosides antibiotic.

Storage Preserve in tightly closed containers, stored at a temperature below -6°C.

Preparation Netilmicin Sulfate Injection

Netilmicin Sulfate Injection

Netilmicin Sulfate Injection is a sterile solution of netilmicin sulfate in Water for Injection. It contains not less than 90.0% and not more than 110.0% of the labelled amount of netilmicin ($C_{21}H_{41}N_5O_7$).

Description A clear, colourless or almost colourless liquid.

Identification Complies with the tests for Identification described under Netilmicin Sulfate.

pH value 5.0-7.0 (Appendix VI H).

Colour The solution is colourless; any colour produced is not more intense than that of reference solution Y₂ or YG₂ (Appendix IX A, method 1).

Sterility Dilute each vial with not less than 500 ml of 0.9% sterile Sodium Chloride Injection, the solution complies with the test for sterility (Appendix XI H, membrane filtration method).

Bacterial endotoxin Complies with the corresponding requirements described under Netilmicin Sulfate.

Other requirements Complies with the general requirements

for injection (Appendix I B).

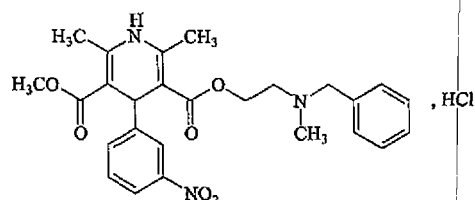
Assay Measure accurately a quantity and carry out the Assay described under Netilmicin Sulfate.

Category As described under Netilmicin Sulfate.

Strength (1) 1 ml : 50000 Units
(2) 2 ml : 100000 Units

Storage Preserve in well closed containers, stored in a cool place.

Nicardipine Hydrochloride



$C_{26}H_{29}N_3O_6 \cdot HCl$ 515.99

[54527-84-3]

Nicardipine Hydrochloride is 2,6-dimethyl-4-(3-nitro-phenyl)-1,4-dihydropyridine-3,5-dicarboxylic acid, 3-[β -(*N*-benzyl-*N*-methylamino)]ethyl ester-5-methyl ester hydrochloride. It contains not less than 98.5% of $C_{26}H_{29}N_3O_6 \cdot HCl$, calculated on the dried basis.

Description A pale yellow powder or yellow crystalline powder; odourless; almost tasteless. Soluble in methanol; sparingly soluble in ethanol or chloroform; practically insoluble in water or ether; soluble in glacial acetic acid.

Melting range 179-185°C, with decomposition (Appendix VI C).

Specific absorbance Measure the absorbance of a solution of 8 μ g per ml in methanol at 236 nm (Appendix IV A), the value of *A* (1%, 1 cm) is 507-539.

Identification (1) Dissolve about 10 mg in 3 ml of methanol, add a few drops of ammonium reineckate TS, a pink precipitate is produced.

(2) The light absorption of the solution obtained in the Specific absorbance exhibits a maximum at 236 nm and a minimum at 219 nm (Appendix IV A).

(3) The infrared absorption spectrum (Appendix IV C) is concordant with the reference spectrum of nicardipine hydrochloride (Appendix XVI).

(4) Dissolve about 10 mg in 4 ml of methanol, the solution yields the reactions characteristic of chlorides (Appendix III).

Related substances Carry out the method for thin-layer chromatography (Appendix V B), using silica gel GF₂₅₄ as the coating substance and a mixture of chloroform-benzene-methanol (5:4:1) as the mobile phase. Apply separately to the plate 10 μ l each of two solutions of the substance being examined in methanol containing (1) 6.5 mg per ml, (2) 0.065 mg per ml. After developing and removal of the plate, dry it in air and examine under ultra-violet light (254 nm). Any spot other than the principal spot in the chromatogram obtained with solution (1) is not more intense than the principal spot obtained with solution (2).

Loss on drying When dried to constant weight at 105°C, loses not more than 0.5% of its weight (Appendix VII L).

Residue on ignition Not more than 0.1% (Appendix VII N), using 1.0 g.

Heavy metals Carry out the limit test for heavy metals (Appendix VIII H, method 2), using the residue obtained in the test for Residue on ignition; not more than 0.002%.

Assay Dissolve 0.4 g, accurately weighed, in 20 ml of glacial acetic acid and 6 ml of mercuric acetate TS by warming, allow to cool, add 1 drop of crystal violet IS, titrate with perchloric acid (0.1 mol/L) VS until the colour changes to blue. Perform a blank determination and make any necessary correction, each ml of perchloric acid (0.1 mol/L) VS is equivalent to 51.60 mg of $C_{26}H_{29}N_3O_6 \cdot HCl$.

Category Vasodilator.

Storage Preserve in tightly closed containers, protected from light.

Preparation (1) Nicardipine Hydrochloride and Glucose Injection
(2) Nicardipine Hydrochloride Injection
(3) Nicardipine Hydrochloride Tablets

Nicardipine Hydrochloride and Glucose Injection

Nicardipine Hydrochloride and Glucose Injection is a sterile solution of Nicardipine Hydrochloride and Glucose in Water for Injections. It contains not less than 90.0% and not more than 110.0% of the labelled amount of nicardipine hydrochloride ($C_{26}H_{29}N_3O_6 \cdot HCl$); and not less than 95.0% and not more than 105.0% of the labelled amount of glucose ($C_6H_{12}O_6 \cdot H_2O$).

Description A clear, colourless or slightly yellowish-green liquid.

Identification (1) To a quantity, add dropwise hot alkaline cupric tartrate TS, a red precipitate of cuprous oxide is produced.
(2) The retention time of principal peak of the substance being examined in the chromatogram obtained in the Assay is identical with that of the reference solution.

pH value 3.2-5.0 (Appendix VI H).

Colour The colour of the injection is not more intense than that of reference solution YG₄ (Appendix IX A, method 1).

Related substances Protect from light throughout the procedure. Carry out the method as described under Assay. Dissolve a quantity of the injection, accurately measured, in mobile phase to produce the test solution containing nicardipine hydrochloride of 50 µg per ml and the reference solution of 2 µg per ml. Inject 20 µl of the reference solution into the column, adjust the attenuation so that the principal peak height in the chromatogram is about 20% of the full scale of the chart. Inject separately 20 µl of the test solution and the reference solution into the column, record the chromatogram for 4 times of the retention time of the principal peak. The area of single peak other than the principal peak in the chromatogram obtained with the test solution is not greater than 1/2 of the area of the principal peak in the chromatogram obtained with the reference solution. The sum of the areas of all peaks other than the principal peak in the chromatogram obtained with the test solution is not greater than the area of the principal peak in the chromatogram obtained with the reference solution.

Heavy metals Measure a quantity of the injection (equivalent to about 3 g of glucose), evaporate to about 20 ml and cool. Add 2 ml of acetate BS (pH 3.5) and a quantity of water to 25 ml. Carry out the limit test for heavy metals (Appendix VIII H, method 1); not more than 0.0005%, calculated with reference to the contents of glucose.

Pyrogens Complies with the test for pyrogens (Appendix XI D), using 10 ml per kg of rabbit's weight, inject slowly.

Other requirements Complies with the general requirements for injections (Appendix I B).

Assay Nicardipine hydrochloride Carry out the method for high performance liquid chromatography (Appendix V D), using a column packed with octadecylsilane bonded silica gel and a mixture of methanol-0.01 mol/L potassium dihydrogen phosphate solution (72:28) as the mobile phase. Detection wavelength is 236 nm and the number of theoretical plates of the column is not less than 1500, calculated with reference to the peak of nicardipine hydrochloride.

Procedure Protect from light throughout the procedure. Transfer an accurately measured quantity of the injection, dilute with the mobile phase to produce a solution of 50 µg of nicardipine hydrochloride per ml. Inject 20 µl of the resulting solution into the column and record the chromatogram. Dissolve about 50 mg of nicardipine hydrochloride CRS, accurately weighed, with 3 ml of methanol in a 100 ml volumetric flask and dilute with water to volume, mix well. Transfer 10 ml of the solution into a 100 ml volumetric flask, accurately measured, dilute with the mobile phase to volume, mix well, repeat the operation. Calculate the content of $C_{26}H_{29}N_3O_6 \cdot HCl$.

Glucose Measure a quantity of the injection, carry out the determination of optical rotation (Appendix VI E), the observed rotation in degree multiplied by 2.0852, represents the weight in g of $C_6H_{12}O_6 \cdot H_2O$ in the volume taken for Assay.

Category Calcium channel blocker.

Strength 100 ml: 10 mg of nicardipine hydrochloride and 5.5 g of glucose

Storage Stored in cool place, protected from light.

Nicardipine Hydrochloride Injection

Nicardipine Hydrochloride Injection is a sterile solution of Nicardipine Hydrochloride in Water for Injections. It contains not less than 90.0% and not more than 110.0% of the labelled amount of nicardipine hydrochloride ($C_{26}H_{29}N_3O_6 \cdot HCl$).

Description A clear, pale yellowish-green liquid.

Identification (1) To 4 ml, add drops of ammonium reineckate TS, a pink precipitate is produced.
(2) The light absorption of the solution obtained in the Assay exhibits a maximum at 236 nm, and a minimum at 219 nm (Appendix IV A).
(3) The retention time of principal peak of the substance being examined in the chromatogram obtained in the Assay is identical with that of the reference solution.
(4) Yield the reactions characteristic of chlorides (Appendix III).

pH value 3.5-5.0 (Appendix VI H).

Colour The colour of the injection is not more intense than

that of reference solution YG₃ (Appendix IX A, method 1).

Related substances Protect from light throughout the procedure. Carry out the method as described under Assay. Dissolve a quantity of the substance being examined, accurately measured, in mobile phase to produce a solution of 50 µg of nicardipine hydrochloride per ml as test solution and a solution of 2 µg of nicardipine hydrochloride per ml as reference solution. Inject 20 µl of the reference solution into the column, adjust the attenuation so that the principal peak height in the chromatogram is about 20% of the full scale of the chart. Inject separately 20 µl of the test solution and the reference solution into the column, record the chromatogram for 4 times of the retention time of the principal peak. The area of single peak other than the principal peak in the chromatogram obtained with the test solution is not greater than 1/2 of the area of the principal peak in the chromatogram obtained with the reference solution. The sum of the areas of all peaks other than the principal peak in the chromatogram obtained with the test solution is not greater than the area of the principal peak in the chromatogram obtained with the reference solution.

Bacterial endotoxin Carry out the test for bacterial endotoxin (Appendix XI E), less than 5 EU per 1 mg of nicardipine hydrochloride.

Other requirements Complies with the general requirements for injections (Appendix I B).

Assay Carry out the method for high performance liquid chromatography (Appendix V D), using a column packed with octadecylsilane bonded silica gel and a mixture of methanol-0.01 mol/L potassium dihydrogen phosphate solution (72:28) as mobile phase. Detection wavelength is 236 nm and the number of theoretical plates of the column is not less than 1500, calculated with reference to the peak of nicardipine hydrochloride. The resolution factor between the peaks of nicardipine hydrochloride and neighboring impurity complies with the related requirements.

Procedure Protect from light throughout the procedure. Transfer an accurately measured quantity of the injection, dilute with the mobile phase to produce a solution of 50 µg of nicardipine hydrochloride per ml. Inject 20 µl of the resulting solution into the column and record the chromatogram; Weigh accurately a quantity of nicardipine hydrochloride CRS, repeat the operation. Calculate the content of C₂₆H₂₉N₃O₆ · HCl.

Category As described under Nicardipine Hydrochloride.

Strength (1) 2 ml:2 mg (2) 5 ml:5 mg
(3) 10 ml:10 mg

Storage Stored in cool place, protected from light.

Nicardipine Hydrochloride Tablets

Nicardipine Hydrochloride Tablets contain not less than 90.0% and not more than 110.0% of the labelled amount of nicardipine hydrochloride (C₂₆H₂₉N₃O₆ · HCl).

Description Pale yellow tablets or sugar coated tablets.

Identification (1) To a quantity of the powdered tablets equivalent to 20 mg of nicardipine hydrochloride add 8 ml of methanol to dissolve nicardipine hydrochloride, filter, the filtrate complies with the test (1) and (4) for Identification described under Nicardipine Hydrochloride.
(2) The light absorption of the solution obtained in the

Assay exhibits a maximum at 236 nm and a minimum at 219 nm (Appendix IV A).

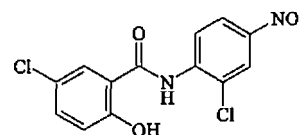
Other requirements Comply with the general requirements for tablets (Appendix I A).

Assay Weigh accurately and powder 10 tablets. To an accurately weighed quantity of the powder equivalent to about 15 mg of nicardipine hydrochloride in a 100 ml volumetric flask add 80 ml of methanol, shake for 30 minutes to dissolve nicardipine hydrochloride, dilute to volume, mix well and filter. Transfer 5 ml of the successive filtrate, accurately measured, to another 100 ml volumetric flask, dilute with methanol to volume and mix well. Measure the absorbance of the resulting solution at 236 nm (Appendix IV A), calculate the content of C₂₆H₂₉N₃O₆ · HCl, taking 523 as the value of A (1%, 1 cm).

Category, Storage As described under Nicardipine Hydrochloride.

Strength 10 mg

Niclosamide



C₁₃H₈Cl₂N₂O₄ 327.12

[50-65-7]

Niclosamide is 5-chloro-N-(2-chloro-4-nitrophenyl)-2-hydroxybenzamide. It contains not less than 98.0% of C₁₃H₈Cl₂N₂O₄, calculated on the dried basis.

Description A pale yellow powder; tasteless. Slightly soluble in ethanol, chloroform or ether; practically insoluble in water.

Melting point 228-232°C (Appendix VI C).

Identification (1) Heat 50 mg with 5 ml of hydrochloric acid solution (9→100) and 0.1 g of zinc powder on a water bath for 10 minutes, cool and filter. To the filtrate add 0.5 ml of sodium nitrite TS, mix, and allow to stand for 10 minutes; add 2 ml of 2% ammonium sulphamate solution, shake, allow to stand for 10 minutes and add 2 ml of 0.5% N-(1-naphthyl) ethylenediamine dihydrochloride solution; a deep red colour is produced.

(2) Heat to decompose a quantity in a test tube with a small flame. Dissolve the sublimate in water, add a few drops of ferric chloride TS; a violet colour is produced.

(3) The infrared absorption spectrum (Appendix IV C) is concordant with the reference spectrum of niclosamide (Appendix XVI).

(4) Carry out the method for oxygen flask combustion with 20 mg (Appendix VII C), using 5 ml of 10% sodium hydroxide solution as the absorbing liquid. The resulting solution yields the reactions characteristic of chlorides (Appendix III).

Chloride Boil 0.50 g with 50 ml of water, cool rapidly and filter. Carry out the limit test for chlorides (Appendix VII A), using 25 ml of filtrate. Any opalescence produced is not more pronounced than that of a reference using 10 ml of sodium chloride standard solution (0.04%).

2-Chloro-4-nitroaniline Boil 0.10 g with 20 ml of methanol for 2 minutes, cool, add sufficient hydrochloric acid solution

(9→100) to produce 50 ml and filter. To 10 ml of filtrate add 5 drops of sodium nitrite TS, mix and allow to stand for 10 minutes; add 1 ml of 2% ammonium sulphamate solution, shake, allow to stand for another 10 minutes and add 1 ml of 0.5% *N*-(1-naphthyl) ethylenediamine hydrochloride solution. The colour produced is not more intense than that of the reference solution prepared in similar manner using 10 µg of 2-chloro-4-nitroaniline CRS dissolved in 4 ml of methanol and sufficient quantity of hydrochloric acid solution (9→100) to produce 10 ml (0.05%).

5-Chlorosalicylic acid Dissolve 0.5 g in 10 ml of water, boil for two minutes, cool and filter. To the filtrate add a few drops of ferric chloride TS; no red or violet colour is produced.

Loss on drying When dried to constant weight at 105°C, loses not more than 0.5% of its weight (Appendix VIII L).

Residue on ignition Not more than 0.1% (Appendix VIII N); using 1.0 g.

Heavy metals Carry out the limit test for heavy metals (Appendix VIII H, method 2), using the residue obtained in the test for Residue on ignition; not more than 0.002%.

Assay Dissolve about 0.3 g, accurately weighed, in 60 ml of dimethylformamide, carry out the method for Potentiometric Titration (Appendix VII A), titrate with sodium methoxide (0.1 mol/L) VS. Perform a blank determination and make any necessary correction. Each ml of sodium methoxide (0.1 mol/L) VS is equivalent to 32.71 mg of $C_{13}H_8Cl_2N_2O_4$.

Category Anthelmintic.

Storage Preserve in tightly closed containers, protected from light.

Preparation Niclosamide Tablets

Niclosamide Tablets

Niclosamide Tablets contain not less than 95.0% and not more than 105.0% of the labelled amount of niclosamide ($C_{13}H_8Cl_2N_2O_4$).

Description Pale yellow tablets.

Identification Boil 1 tablet, finely powdered, with 25 ml of ethanol, cool and filter. Evaporate the filtrate on a water bath to dryness, the residue complies with tests (1), (2) and (4) for the Identification described under Niclosamide.

2-Chloro-4-nitroaniline and 5-chlorosalicylic acid Comply with the tests described under Niclosamide.

Other requirements Comply with the general requirements for tablets (Appendix I A).

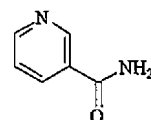
Assay Weigh and finely powder 20 tablets. Carry out the determination of nitrogen (Appendix VII D, method 1), using a quantity, accurately weighed, of powdered tablets equivalent to about 0.3 g of Niclosamide. Each ml of sulphuric acid (0.05 mol/L) VS is equivalent to 16.36 mg of $C_{13}H_8Cl_2N_2O_4$.

Category As described under Niclosamide.

Strength 0.5 g

Storage Preserve in tightly closed containers, protected from light.

Nicotinamide



$C_6H_6N_2O$ 122.13

[98-92-0]

Nicotinamide is 3-pyridinecarboxamide. It contains not less than 98.5% of $C_6H_6N_2O$, calculated on the dried basis.

Description A white crystalline powder; odourless or almost odourless; taste, bitter.

Freely soluble in water or ethanol; soluble in glycerin.

Melting point 128-131°C (Appendix VI C).

Identification (1) Dissolve 0.1 g in 5 ml of water, add 5 ml of sodium hydroxide TS, boil gently, an ammonia odour is evolved (distinction from nicotinic acid); heat continuously until no ammonia odour is evolved, cool, add 1-2 drops of phenolphthalein IS, neutralize with dilute sulfuric acid, then add 2 ml of cupric sulfate TS; a light blue precipitate is produced. Filter and ignite the precipitate, a pyridine odour is evolved.

(2) The light absorption of a solution of about 20 µg per ml exhibits a maximum at 262 nm and a minimum at 245 nm; the ratio of the absorption at 245 nm to that at 262 nm is 0.63-0.67 (Appendix IV A).

(3) The infrared absorption spectrum (Appendix IV C) is concordant with the reference spectrum of nicotinamide (Appendix XVI).

Related substances Carry out the method for thin-layer chromatography (Appendix V B), using silica GF₂₅₄ as the coating substance and a mixture of chloroform-dehydrated ethanol-water (48 : 45 : 4) as the mobile phase. Apply separately to the plate 5 µl each of two solutions of the substance being examined in ethanol containing (1) 40 mg per ml, (2) 0.2 mg per ml. After developing and removal of the plate, dry it in air and examine under ultra-violet light (254 nm). Any secondary spot in the chromatogram obtained with solution (1) is not more intense than the principal spot obtained with solution (2).

Acidity and alkalinity Dissolve 1.0 g in 10 ml of water, pH 5.5-7.5 (Appendix VI H).

Loss on drying When dried at 105°C for 2 hours, loses not more than 0.5% of its weight (Appendix VIII L).

Residue on ignition Not more than 0.1% (Appendix VIII N).

Heavy metals Dissolve 1.0 g in 10 ml of water, add 6 ml of hydrochloric acid solution (1 mol/L) and sufficient water to 25 ml. Carry out the limit test for heavy metals (Appendix VIII H, method 1); not more than 0.002%.

Assay Dissolve 0.1 g, accurately weighed, in 20 ml of glacial acetic acid, add 5 ml of acetic anhydride and 1 drop of crystal violet IS, titrate with perchloric acid (0.1 mol/L) VS, until a bluish green colour is produced. Perform a blank determination and make any necessary correction. Each ml of perchloric acid (0.1 mol/L) VS is equivalent to 12.21 mg of $C_6H_6N_2O$.

Category Vitamin.

Storage Preserve in tightly closed containers, protected

from light.

Preparation (1) Nicotinamide Injection
(2) Nicotinamide Tablets

Nicotinamide Injection

Nicotinamide Injection is a sterile solution of nicotinamide in Water for Injection. It contains not less than 95.0% and not more than 105.0% of the labelled amount of nicotinamide ($C_6H_6N_2O$).

Description A colourless clear liquid.

Identification A quantity of injection equivalent to 0.2 g of nicotinamide complies with the tests (1) and (2) for Identification described under Nicotinamide.

pH value 5.5-7.5 (Appendix VI H).

Other requirements Complies with the general requirements j (pp - B).

Assay Dilute an accurately measured quantity of injection, with hydrochloric acid solution (9 → 1000) to produce a solution of about 15 µg per ml. Measure the absorbance at 261 nm (Appendix IV A). Calculate the content of nicotinamide, taking 430 as the value of A (1%, 1 cm).

Category As described under Nicotinamide.

Strength (1) 1 ml:50 mg (2) 1 ml:100 mg

Storage Preserve in well closed containers, protected from light.

Nicotinamide Tablets

Nicotinamide Tablets contain not less than 93.0% and not more than 107.0% of the labelled amount of nicotinamide ($C_6H_6N_2O$).

Description White tablets.

Identification (1) Stir a quantity of powdered tablets equivalent to 0.2 g of nicotinamide with 10 ml of water and filter. The filtrate complies with the test (1) for Identification described under Nicotinamide.

(2) The light absorption of the solution obtained in the Assay exhibits a maximum at 261 nm (Appendix IV A).

Related substances Add 15 ml of dehydrated ethanol to a quantity equivalent to 0.1 g of nicotinamide, shake for 15 minutes and filter. Evaporate the filtrate on a water bath to dryness, dissolve the residue with 2.5 ml of ethanol and mix well as solution (1). Dilute 1 ml of solution (1) with dehydrated ethanol to 200 ml as solution (2). Carry out the method for thin-layer chromatography (Appendix V B), using silica GF₂₅₄ as the coating substance and a mixture of chloroform-dehydrated ethanol-water (48 : 45 : 4) as the mobile phase. Apply separately to the plate 5 µl each of solution (1) and solution (2). After developing a distance of 10 cm and removal of the plate, dry it in air and examine under ultra-violet light (254 nm). Any secondary spot in the chromatogram obtained with solution (1) is not more intense than the principle spot obtained with solution (2).

Other requirements Comply with the general requirements for tablets (Appendix I A).

Assay Weigh accurately and powder 20 tablets. To a quantity of the powdered tablets equivalent to 60 mg of

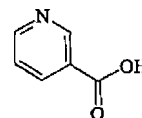
nicotinamide, accurately weighed, in 100 ml volumetric flask add 75 ml of hydrochloric acid solution (9 → 1000), heat on a water bath for 15 minutes and shake constantly to dissolve nicotinamide. Cool to room temperature, dilute with hydrochloric acid solution (9 → 1000) to volume and mix well. Filter and discard the initial filtrate, measure accurately 5 ml of the successive filtrate to 200 ml volumetric flask, dilute with hydrochloric acid solution (9 → 1000) to volume and mix well. Measure the absorbance at 261 nm (Appendix IV A). Calculate the content of nicotinamide, taking 430 as the value of A (1%, 1 cm).

Category As described under Nicotinamide.

Strength (1) 50 mg (2) 100 mg

Storage Preserve in tightly closed containers, protected from light.

Nicotinic Acid



$C_6H_5NO_2$ 123.11

[59-67-6]

Nicotinic Acid is 3-pyridinecarboxylic acid. It contains not less than 99.0% of $C_6H_5NO_2$, calculated on the dried basis.

Description A white crystal or crystalline powder; odourless or with a slight odour; taste, feebly acid; aqueous solution yields an acid reaction.

Soluble in boiling water or boiling ethanol; sparingly soluble in water; slightly soluble in ethanol; practically insoluble in ether; freely soluble in solutions of alkali carbonates and hydroxides.

Melting range 234-238°C (Appendix VI C).

Identification (1) Triturate 4 mg with 8 mg of 2,4-dinitrochlorobenzene, transfer the mixture into a test tube, heat gently to molten and continue the heating for a few seconds. Allow to cool, add 3 ml of ethanolic potassium hydroxide TS; a violet-red colour is produced.

(2) Dissolve 50 mg in 20 ml of water, add 0.4% sodium hydroxide solution dropwise, until the solution is neutral to litmus paper add 3 ml of cupric sulfate TS; a blue precipitate is produced slowly.

(3) The light absorption of a solution of 20 µg per ml exhibits a maximum at 262 nm and a minimum at 237 nm; the ratio of the absorbance at 237 nm to that at 262 nm is 0.35-0.39 (Appendix IV A).

(4) The infrared absorption spectrum (Appendix IV C) is concordant with the reference spectrum of nicotinic acid (Appendix XVI).

Colour of solution Dissolve 1.0 g in 10 ml of sodium hydroxide TS, the solution is not more intensely coloured than an equal volume of a reference solution prepared by mixing 0.15 ml of cobaltous chloride CS, 1.7 ml of potassium dichromate CS, 0.15 ml of cupric sulfate CS, and dilute with water to 100 ml.

Chloride Carry out the limit test for chlorides (Appendix VIII A), using 0.25 g. Any opalescence produced is not more pronounced than that of a reference using 5.0 ml of sodium chloride standard solution (0.02%).

Sulfate Carry out the limit test for sulfate (Appendix VIII

B), using 0.50 g. Any opalescence produced is not more pronounced than that of a reference using 1.0 ml of potassium sulfate standard solution (0.02%).

Loss on drying When dried at 105°C for 1 hour, loses not more than 0.5% of its weight (Appendix VII L).

Residue on ignition Not more than 0.1% (Appendix VII N).

Heavy metals To 1.0 g add 1.5 ml of dilute hydrochloric acid and sufficient water to 25 ml, heat gently to dissolve and cool to room temperature. Carry out the limit test for heavy metals (Appendix VIII H, method 1); not more than 0.002%.

Assay Dissolve 0.3 g, accurately weighed, in 50 ml of freshly boiled and cooled water, add 3 drops of phenolphthalein IS, titrate with sodium hydroxide (0.1 mol/L) VS. Each ml of sodium hydroxide (0.1 mol/L) VS is equivalent to 12.31 mg of $C_6H_5NO_2$.

Category Vitamin.

Storage Preserve in tightly closed containers.

Preparation (1) Nicotinic Acid Injection
(2) Nicotinic Acid Tablets

Nicotinic Acid Injection

Nicotinic Acid Injection contains not less than 95.0% and not more than 105.0% of the labelled amount of nicotinic acid ($C_6H_5NO_2$).

Description A clear, colourless liquid.

Identification (1) To a quantity, equivalent to 4 mg of nicotinic acid, add 8 mg of 2,4-dinitrochlorobenzene, heat gently for a few minutes, cool and add ethanolic potassium hydroxide TS, a violet-red colour is produced.

(2) The light absorption (Appendix IV A) of the solution obtained in Assay exhibits a maximum at 263 nm.

pH value 4.0-6.0 (Appendix VI H).

Other requirements Comply with the general requirements for injections (Appendix I B).

Assay Measure accurately 5 ml of the injection to a 100 ml volumetric flask, dilute with potassium hydroxide solution (0.1 mol/L) to volume, mix well. Measure accurately 5 ml of the solution to a 100 ml volumetric flask, dilute with potassium hydroxide solution (0.1 mol/L) to volume, mix well. Measure the absorbance of the resulting solution at 263 nm (Appendix IV A). Calculate the content of $C_6H_5NO_2$, taking 263 as the value of A (1%, 1 cm).

Category As described under Nicotinic Acid.

Strength (1) 2 ml:20 mg (2) 2 ml:100 mg
(3) 5 ml:50 mg

Storage Preserve in well closed containers, protected from light.

Nicotinic Acid Tablets

Nicotinic Acid Tablets contain not less than 95.0% and not more than 105.0% of the labelled amount of nicotinic acid ($C_6H_5NO_2$).

Description White tablets.

Identification (1) Dissolve a quantity of powdered tablets equivalent to 0.25 g of nicotinic acid in 100 ml of water and filter; the filtrate complies with test (2) for Identification described under Nicotinic Acid.

(2) Dilute the filtrate obtained in the above test with water to produce a solution of 20 µg per ml. The light absorption of the solution exhibits a maximum at 262 nm (Appendix IV A).

Dissolution Carry out the dissolution test (Appendix X C, method 1), using 900 ml of water as the dissolution medium, adjust the rotational speed of the basket to 100 rpm. Withdraw a quantity of the solution after exactly 20 minutes and filter. Measure accurately 5 ml (for strength 100 mg) or 10 ml (for strength 50 mg) of the successive filtrate into a 25 ml volumetric flask and dilute with water to volume, mix well as the test solution. Measure the absorbance of the test solution at 262 nm (Appendix IV A). Dissolve a quantity of nicotinic acid CRS, weighed accurately, with water to produce a solution of about 20 µg per ml as the reference solution, repeat the operation instead of the test solution. Calculate the dissolution of $C_6H_5NO_2$ from each tablet. Not less than 80% of the labelled amount is dissolved.

Other requirements Comply with the general requirements for tablets (Appendix I A).

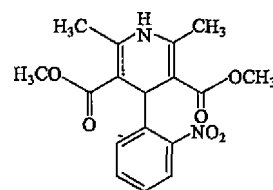
Assay Weigh accurately and powder 10 tablets. To a quantity of the powdered tablets equivalent to 0.2 g of nicotinic acid, accurately weighed, add 50 ml of freshly boiled and cooled water, heat on a water bath and shake constantly. Cool to room temperature, add 3 drops of phenolphthalein IS, titrate with sodium hydroxide (0.1 mol/L) VS. Each ml of sodium hydroxide (0.1 mol/L) VS is equivalent to 12.31 mg of $C_6H_5NO_2$.

Category As described under Nicotinic Acid.

Strength (1) 50 mg (2) 100 mg

Storage Preserve in tightly closed containers.

Nifedipine



$C_{17}H_{18}N_2O_6$ 346.34

[21829-25-4]

Nifedipine is 2,6-dimethyl-4-(2-nitrophenyl)-1,4-dihydro-3,5-pyridinedicarboxylic acid dimethyl ester. It contains not less than 98.0% and not more than 102.0% of $C_{17}H_{18}N_2O_6$, calculated on the dried basis.

Description A yellow, crystalline powder; odourless; tasteless; unstable on exposure to light. Freely soluble in acetone or chloroform; sparingly soluble in ethanol; practically insoluble in water.

Melting range 171-175°C (Appendix VI C).

Identification (1) Dissolve about 25 mg in 1 ml of acetone, add 3-5 drops of 20% sodium hydroxide solution and shake, an orange-red colour is produced.

(2) Dissolve a quantity with 2 ml of chloroform, add dehydrated ethanol to make a solution of 15 µg per ml. The

light absorption of the resulting solution exhibits maxima at 237 nm and wide absorption from 320-355 nm (Appendix IV A).

(3) The infrared absorption spectrum (Appendix IV C) is concordant with the reference spectrum of nifedipine (Appendix XVI).

Related substances Protect from light throughout the procedure. Carry out the method for high performance liquid chromatography (Appendix V D), using a column packed with octadecylsilane bonded silica gel and a mixture of methanol-water (3 : 2) as the mobile phase. Detection wavelength is 235 nm. Dissolve a quantity, accurately weighed, with methanol to produce solutions of the substance being examined containing (1) 1 mg per ml, (2) 0.2 mg per ml. Dissolve 10 mg each of nifedipine related substance A CRS and B CRS, accurately weighed, with methanol in a 50 ml volumetric flask and dilute to the volume as solution (3). Transfer 1 ml each of solution (2) and (3), accurately measured, to a 100 ml volumetric flask and dilute with the mobile phase to the volume as solution (4). Inject 20 μ l of solution (4) into the column. Adjust the attenuation so that the peak heights of substance A and B in the chromatogram are 20% of full scale of the chart. The resolution factors among peaks of substance A, B and nifedipine comply with related requirements. And then, inject 20 μ l each of solution (1) and (4) into the column, and record the chromatogram for twice the retention time of the principal peak. Each peak area of substance A and B in the chromatogram obtained with solution (1) is not greater than that of substance A and B obtained with solution (4) respectively; each peak area of the peak other than the substance A or B is not greater than the peak area of nifedipine obtained with solution (4); and the sum of them are not greater than 0.5% of the peak area of nifedipine. Any peak area obtained with solution (1) less than 10% of the peak area of nifedipine obtained with solution (4) can be omitted.

Loss on drying When dried to constant weight at 105°C, loses not more than 0.5% of its weight (Appendix VIII L).

Residue on ignition Not more than 0.1% (Appendix VIII N); using 1.0 g.

Heavy metals Carry out the limit test for heavy metals (Appendix VIII H, method 2), using the residue obtained in Residue on ignition; not more than 0.001%.

Assay Dissolve 0.4 g, accurately weighed, in 50 ml of dehydrated ethanol by gently heating, add 50 ml of perchloric acid solution (dilute 8.5 ml of 70% perchloric acid with water to 100 ml), 3 drops of o-phenanthroline IS, titrate with cerium sulfate (0.1 mol/L) VS immediately until the reddish orange colour disappeared, heating on water bath to about 50°C when near to the end point. Perform a blank determination and make any necessary correction. Each ml of cerium sulfate (0.1 mol/L) VS is equivalent to 17.32 mg of $C_{17}H_{18}N_2O_6$.

Category Calcium channel blocker.

Storage Preserve in tightly closed containers, protected from light.

Preparation (1) Nifedipine Capsules
(2) Nifedipine Soft Capsules
(3) Nifedipine Tablets

Nifedipine Capsules

Nifedipine Capsules contain not less than 90.0%

and not more than 110.0% of the labelled amount of nifedipine ($C_{17}H_{18}N_2O_6$).

Identification (1) Extract a quantity of the contents, equivalent to about 50 mg of nifedipine, with 3 ml of acetone, allow to stand, to 1 ml of the supernatant liquid add 3-5 drops of 20% sodium hydroxide solution, an orange red colour is produced with shaking.

(2) Dilute the solution obtained in Assay with the equal volume of dehydrated ethanol, the solution complies with the test (2) for Identification described under Nifedipine.

Related substances Protect from light throughout the procedure. Shake a quantity of the mixed contents obtained in the test for weight variation of content with acetone to dissolve nifedipine and produce a suspension containing 10 mg of nifedipine per ml, allow to stand, use the supernatant liquid as test solution. Measure accurately a quantity of the test solution, dilute with acetone to produce a solution of 0.2 mg per ml as reference solution. Carry out the method for thin-layer chromatography (Appendix V B), using silica gel GF₂₅₄ as the coating substance and a mixture of benzene-chloroform-dehydrated ethanol (3 : 1 : 0.2) as the mobile phase. Apply separately to the plate 10 μ l each of the above two solutions. After developing and removal of the plate, dry it in air and examine under ultra-violet light (254 nm). Any secondary spot in the chromatogram obtained with the test solution is not more intense than the principal spot obtained with the reference solution.

Content uniformity Protect from light in the procedure. Comply with the requirements (Appendix X E). Place the content of one capsule in a mortar, wash the shell with 2 ml of chloroform in portions, triturate and transfer to a 50 ml volumetric flask with dehydrated ethanol in portions, dilute with dehydrated ethanol to volume and mix well. Filter with a dry filter paper, measure accurately 5 ml (10 mg) or 10 ml (5 mg) of the successive filtrate into a 25 ml volumetric flask, dilute to volume and mix well. Measure the absorbance of the resulting solution at 333 nm (Appendix IV A), calculate the content of $C_{17}H_{18}N_2O_6$, taking 140 as the value of A (1%, 1 cm).

Other requirements Comply with the general requirements for capsules (Appendix I E).

Assay Protect from light throughout the procedure. Weigh accurately a quantity of the mixed contents obtained in the test for weight variation of content equivalent to about 30 mg of nifedipine, triturate with 2 ml of chloroform, transfer to a 100 ml volumetric flask with dehydrated ethanol in portions, dilute with dehydrated ethanol to volume and mix well. Measure accurately 5 ml of the successive filtrate into a 50 ml volumetric flask. Dilute with dehydrated ethanol to volume and mix well. Measure the absorbance at 333 nm (Appendix IV A) and calculate the content of $C_{17}H_{18}N_2O_6$, taking 140 as the value of A (1%, 1 cm).

Category As described under Nifedipine.

Strength (1) 5 mg (2) 10 mg

Storage Preserve in tightly closed containers, protected from light.

Nifedipine Soft Capsules

Nifedipine Soft Capsules contain not less than 90.0% and not more than 110.0% of the labelled amount of nifedipine ($C_{17}H_{18}N_2O_6$).

Description Capsules containing yellow viscous liquid.

Identification (1) Extract a quantity of the contents equivalent to about 50 mg of nifedipine with 3 ml of acetone, allow to stand, the supernatant liquid complies with test (1) for Identification described under Nifedipine.

(2) Comply with test (2) for Identification described under Nifedipine, using the solution obtained in the Assay diluted with an equal volume of dehydrated ethanol.

Related substances Protect from light in the procedure. Shake a quantity of the contents with acetone to dissolve nifedipine and produce a suspension containing 10 mg of nifedipine per ml, allow to stand, use the supernatant liquid as test solution. Measure accurately a quantity of the test solution, dilute with acetone to produce a solution of 0.20 mg per ml as reference solution. Carry out the method for thin-layer chromatography (Appendix V B), using silica gel GF₂₅₄ as the coating substance and a mixture of benzene-chloroform-dehydrated ethanol (3 : 1 : 0.2) as the mobile phase. Apply separately to the plate 10 µl each of the above two solutions. After developing and removal of the plate, dry it in air and examine under ultra-violet light (254 nm). Any secondary spot in the chromatogram obtained with the test solution is not more intense than the principal spot obtained with the reference solution.

Content uniformity Protect from light throughout the procedure. Comply with the requirements (Appendix X E). Transfer the content of one capsule to a 50 ml volumetric flask, wash the shell with 35 ml of dehydrated ethanol in portions, shake thoroughly, dilute with dehydrated ethanol to volume and mix well. Filter with a dry filter paper. Measure accurately 10 ml of the successive filtrate into a 25 ml volumetric flask, dilute to volume and mix well. Measure the absorbance of the resulting solution at 333 nm (Appendix IV A), calculate the content of C₁₇H₁₈N₂O₆, taking 140 as the value of A (1%, 1 cm).

Other requirements Comply with the general requirements for capsules (Appendix I E).

Assay Protect from light throughout the procedure. Transfer an accurately weighed quantity of the mixed contents obtained in the test for weight variation of content equivalent to about 30 mg of nifedipine to a 100 ml volumetric flask, add dehydrated ethanol to volume, mix well and filter. Measure accurately 5 ml of the successive filtrate to a 50 ml volumetric flask, dilute with dehydrated ethanol to volume and mix well. Measure the absorbance at 333 nm (Appendix IV A) and calculate the content of C₁₇H₁₈N₂O₆, taking 140 as the value of A (1%, 1 cm).

Category, Storage As described under Nifedipine.

Strength 5 mg

Nifedipine Tablets

Nifedipine Tablets contain not less than 90.0% and not more than 110.0% of the labelled amount of nifedipine (C₁₇H₁₈N₂O₆).

Description Sugar-coated or film coated tablets with yellow core.

Identification (1) Shake a quantity of powdered tablets equivalent to about 50 mg of nifedipine with 3 ml of acetone and allow to stand, the clear supernatant liquid complies with test (1) for Identification described under Nifedipine.
(2) Comply with test (2) for Identification described under Nifedipine, using the solution obtained in the Assay, diluted with an equal volume of dehydrated ethanol.

Related substances Protect from light throughout the procedure. Comply with the test for Related substances described under Nifedipine. Shake a quantity of powdered tablets with acetone to dissolve nifedipine and produce a suspension containing 10 mg of nifedipine per ml allow to stand and use the supernatant liquid as solution (1). Dilute a quantity of solution (1) to produce a solution containing 0.2 mg of nifedipine per ml and use it as solution (2). Complete the test for Related Substances described under Nifedipine, beginning at the words "Dissolve 10 mg each of nifedipine related substance A CRS and B CRS,". Each peak area is not greater than 2.0%, and the sum of them is not greater than 3.0%, calculated on external standard method [the peaks other than the substance A or B are calculated on the peak area of nifedipine obtained with solution (4)]. Any peak area obtained with solution (1) which is less than 10% of the peak area of nifedipine obtained with solution (4) can be omitted.

Dissolution Protect from light throughout the procedure. Carry out the dissolution test (Appendix X C, method 2), using 900 ml of 0.25% sodium laurylsulfate solution as the dissolution medium, adjust the rotational speed of the paddle to 120 rpm. Withdraw 10 ml of the solution after exactly 60 minutes and filter. Take the successive filtrate as the test solution. Dissolve about 10 mg of nifedipine CRS, accurately weighed, with ethanol and dilute to 100 ml. Transfer 2 ml, accurately measured, to a 20 ml volumetric flask, dilute to volume with the dissolution medium as the reference solution. Carry out the method described under Related substances, inject 10 µl of the above two solutions into the column, and record the chromatogram. Calculate the dissolution of C₁₇H₁₈N₂O₆ from each tablet. Not less than 65% of the labelled amount is dissolved.

Content uniformity Comply with the test for content uniformity (Appendix X E). Protect from light throughout the procedure. Triturate 1 tablet with the coating removed in a mortar with 2 ml of chloroform. Transfer with dehydrated ethanol in portions to a 50 ml volumetric flask, dilute to volume and mix well. Filter and transfer 5 ml (for strength 10 mg) or 10 ml (for strength 5 mg) of the successive filtrate, accurately measured, to a 25 ml volumetric flask, dilute with dehydrated ethanol to volume and mix well. Measure the absorbance at 333 nm (Appendix IV A) and calculate the content of C₁₇H₁₈N₂O₆, taking 140 as the value of A (1%, 1 cm).

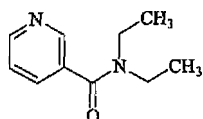
Other requirements Comply with the general requirements for tablets (Appendix I A), except that the tablets disintegrate within 30 minutes.

Assay Protect from light throughout the procedure. Weigh accurately and powder 20 tablets with the coating removed. Triturate an accurately weighed quantity of the powder equivalent to about 30 mg of nifedipine with 2 ml of chloroform. Transfer with dehydrated ethanol in portions to a 100 ml volumetric flask, shake to dissolve nifedipine, dilute to volume and mix well, filter. Transfer 5 ml of the successive filtrate, accurately measured, to a 50 ml volumetric flask, dilute with dehydrated ethanol to volume and mix well. Measure the absorbance at 333 nm (Appendix IV A) and calculate the content of C₁₇H₁₈N₂O₆, taking 140 as the value of A (1%, 1 cm).

Category, Storage As described under Nifedipine.

Strength (1) 5 mg (2) 10 mg

Nikethamide



$C_{10}H_{14}N_2O$ 178.23

[59-26-7]

Nikethamide is *N,N*-diethylpyridine-3-carboxamide. It contains not less than 98.5% (g/g) of $C_{10}H_{14}N_2O$.

Description A clear, colourless or pale yellow oily liquid, crystallizes at lower temperature; odour, slight and characteristic; taste, bitter; hygroscopic. Miscible with water, ethanol, chloroform or ether.

Relative density 1.058-1.066, at 25°C (Appendix VI A).

Congeeing point 22-24°C (Appendix VI D).

Refractive index 1.522-1.524, at 25°C (Appendix VI F).

Identification (1) Heat 10 drops with 3 ml of sodium hydroxide TS; diethylamine vapour is produced which turns moistened red litmus paper to blue.

(2) Mix 1 drop with 50 ml of water. To 2 ml of this solution add 2 ml of cyanogen bromide TS and 3 ml of 2.5% aniline solution, mix well, a yellow colour is produced.

(3) Mix 2 drops with 1 ml of water, add 2 drops of cupric sulfate TS and 3 drops of ammonium thiocyanate TS, a greenish yellow precipitate is produced.

(4) The infrared absorption spectrum (Appendix IV C) is concordant with the reference spectrum of nikethamide (Appendix XVI).

Acidity or alkalinity Dissolve 5.0 g in water to produce 20 ml, pH 6.5-7.8 (Appendix VI H).

Clarity and colour of solution A solution of 2.5 g in 10 ml of water is clear and colourless. Any opalescence produced is not more pronounced than that of reference suspension 1 (Appendix IX B); any colour produced is not more intense than that of reference solution Y₁ (Appendix IX A, method 1).

Chloride Carry out the limit test for chlorides (Appendix VIII A), using 5.0 g; any opalescence produced is not more pronounced than that of a reference using 7.0 ml of sodium chloride standard solution (0.0014%).

Related substances Carry out the method for thin-layer chromatography (Appendix V B), using silica gel GF₂₅₄ as the coating substance and chloroform-*n*-propanol (75:25) as the mobile phase. Apply separately to the plate 10 µl each of three solutions of the substance being examined in methanol containing (1) 40 mg per ml, (2) 0.4 mg per ml, (3) 0.04 mg per ml. After development and removal of the plate, dry it in air and examine under ultraviolet light (254 nm). Only one secondary spot in the chromatogram obtained with solution (1) may be more intense than the principal spot obtained with solution (3), and any spot is not more intense than the principal spot obtained with solution (2).

Oxidizable substances To 1.2 g add 5 ml of water and 0.05 ml of potassium permanganate (0.02 mol/L) VS; the pink colour persists for not less than two minutes.

Water To 0.5 g add 5 ml of carbon disulfide, mix well, the solution is clear.

Assay To about 0.15 g, accurately weighed, add 10 ml of

glacial acetic acid and 1 drop of crystal violet IS, titrate with perchloric acid (0.1 mol/L) VS until the colour changes to bluish-green. Perform a blank determination and make any necessary correction. Each ml of perchloric acid (0.1 mol/L) VS is equivalent to 17.82 mg of $C_{10}H_{14}N_2O$.

Category Central stimulant.

Storage Preserve in tightly closed containers, protected from light.

Preparation Nikethamide Injection

Nikethamide Injection

Nikethamide Injection is a sterile solution of Nikethamide in Water for Injection. It contains not less than 90.0% and not more than 110.0% of the labelled amount of nikethamide ($C_{10}H_{14}N_2O$).

Description A clear, colourless liquid.

Identification Saturate 5 ml with sodium carbonate, the oil layer (distinction from Nicotinamide Injection) complies with the tests (1), (2) and (3) for Identification described under Nikethamide.

pH value 5.5-7.8 (Appendix VI H).

Other requirements Complies with the general requirements for injections (Appendix I B).

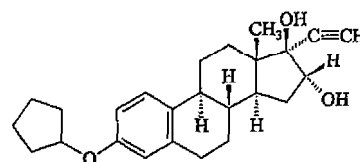
Assay Measure accurately 1 ml to a 100 ml volumetric flask with a "to contain" pipet. Wash the inner wall of pipet with several portions of 0.5% sulfuric acid solution and transfer the washings to the same flask, add 0.5% sulfuric acid solution to volume and mix well. Measure accurately a quantity of the solution and add 0.5% sulfuric acid solution to produce a solution of 20 µg per ml. Measure the absorbance at 263 nm (Appendix IV A). Calculate the content of $C_{10}H_{14}N_2O$, taking 292 as the value of *A* (1%, 1 cm).

Category As described under Nikethamide.

Strength (1) 1.5 ml:0.375 g (2) 2 ml:0.5 g

Storage Preserve in well closed containers, protected from light.

Nilestriol



$C_{25}H_{32}O_3$ 380.53

[39791-20-3]

Nilestriol is 17α-ethynylestra-1,3,5(10)-triene-3,16α,17β-triol-3-cyclopentyl ether. It contains not less than 97.0% and not more than 103.0% of $C_{25}H_{32}O_3$, calculated on the dried basis.

Description A white or almost white crystalline powder. Freely soluble in chloroform; soluble in acetone; sparingly soluble in ethanol; practically insoluble in water.

Melting range 160-165°C (Appendix VI C).

Specific optical rotation $+2^{\circ}$ to $+10^{\circ}$, in a solution of about 10 mg per ml in dehydrated ethanol (Appendix VI E).

Identification (1) To a quantity add 2-3 drops of sulfuric acid, a rose-red colour is produced, then changes to bluish-violet on pouring into 5 ml of water.

(2) The light absorption of the solution obtained under Assay exhibits maxima at 280 nm and 288 nm (Appendix IV A).

(3) The infrared absorption spectrum (Appendix IV C) is concordant with the reference spectrum of nilestriol (Appendix XVI).

Related substances Carry out the method for thin-layer chromatography (Appendix V B), using silica gel as the coating substance and a mixture of benzene-acetone (4:1) as the mobile phase. Apply separately to the plate 5 μ l each of the solution (1) containing 10 mg of the substance being examined per ml and the solution (2) containing 0.2 mg of nilestriol CRS per ml in a mixture of chloroform-methanol (9:1). After developing and removal of the plate, dry it in air, spray with a mixture of sulfuric acid-ethanol (4:1), heat at 105°C for 20 minutes, and examine under the ultraviolet light (365 nm). Any spot other than the principal spot in the chromatogram obtained with the solution (1) is not more intense than the principal spot in the chromatogram obtained with the solution (2).

Loss on drying When dried in vacuum at 80°C for 4 hours loses not more than 3.0% of its weight (Appendix VIII L).

Assay Carry out the method for high performance liquid chromatography (Appendix V D), using a column packed with octadecylsilane bonded silica gel and a mixture of methanol-water (80:20) as the mobile phase. Detection wavelength is 221 nm and the number of theoretical plates of the column is not less than 2500, calculate with reference to the peak of nilestriol.

Procedure Dissolve a quantity accurately weighed, with the mobile phase to produce a solution of 0.1 mg per ml. Inject 20 μ l of the solution into the column and record the chromatogram. Repeat the operation, using nilestriol CRS instead of the substance being examined. Calculate the content of $\text{C}_{25}\text{H}_{32}\text{O}_3$.

Category Antihypertensive.

Storage Preserve in tightly closed containers, Protected from light.

Preparation Nilestriol Tablets

Nilestriol Tablets

Nilestriol tablets contain not less than 90.0% and not more than 110.0% of the labelled amount of nilestriol ($\text{C}_{25}\text{H}_{32}\text{O}_3$).

Description White tablets.

Identification Weigh and powder a quantity of tablets, equivalent to about 20 mg of nilestriol, extract with 30 ml of chloroform, filter and evaporate to dryness. The residue complies with the tests (1) and (2) for Identification described under Nilestriol.

Content uniformity Complies with the requirement (Appendix X E). Triturate 1 tablet with dehydrated ethanol, ultrasonicate for 10 minutes to make nilestriol dissolved, add dehydrated ethanol to produce a solution containing nilestriol 0.1 mg per ml, mix well and filter. Proceed with the successive filtrate as described in the

Assay, beginning at the words "Measure the absorbance of the successive filtrate..."

Dissolution Carry out the dissolution test (Appendix X C, method 3), using 150 ml of 0.5% lauryl sodium sulfate solution as the dissolution medium, adjust the rotational speed of the paddle to 100 rpm. Withdraw 10 ml of the solution at 45 minutes and filter. Measure a quantity of the successive filtrate and dilute with the dissolution medium to produce a solution of about 6.5 μg per ml as the test solution. Dissolve a quantity of nilestriol CRS, weighed accurately, with the dissolution medium to produce a solution of about 6.5 μg per ml as the reference solution. Carry out the method as described in Assay under Nilestriol. Inject separately 50 μ l of the test solution and the reference solution into the column and record the chromatogram. Calculate the dissolution of $\text{C}_{25}\text{H}_{32}\text{O}_3$ from each tablet with respect to the peak area obtained in the chromatogram by the external standard method. Not less than 70% of the labelled amount is dissolved.

Other requirements Comply the general requirements for tablets (Appendix I A).

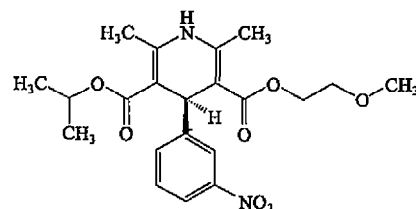
Assay Weigh accurately and powder 20 tablets. To a quantity of powdered tablets, equivalent to 10 mg of nilestriol, accurately weighed, in a 100 ml volumetric flask add a quantity of dehydrated ethanol, heat for 30 minutes on a water bath, shake frequently, allow it to cool, dilute with dehydrated ethanol to volume, and mix well. Filter. Measure the absorbance of the successive filtrate at 280 nm (Appendix IV A). Repeat the operation, using nilestriol CRS instead of the substance being examined. Calculate the content of $\text{C}_{25}\text{H}_{32}\text{O}_3$.

Category As described under Nilestriol.

Strength (1) 1 mg (2) 2 mg (3) 5 mg

Storage Preserve in tightly closed containers and a dry place.

Nimodipine



$\text{C}_{21}\text{H}_{26}\text{N}_2\text{O}_7$ 418.45

Nimodipine is 2,6-dimethyl-4-(3-nitrophenyl)-1,4-dihydropyridine-3,5-dicarboxylate 2-methoxyethyl 1-methylethyl. It contains not less than 98.5% and not more than 101.5% of $\text{C}_{21}\text{H}_{26}\text{N}_2\text{O}_7$, calculated on the dried basis.

Description A pale yellow crystalline powder or powder; odourless; tasteless; degraded on exposure to light. Freely soluble in acetone, chloroform, ethyl acetate; soluble in ethanol; slightly soluble in ether; practically insoluble in water.

Melting point $124-128^{\circ}\text{C}$ (Appendix VI C).

Identification (1) Dissolve about 20 mg in 2 ml of ethanol, add 2 ml of freshly prepared 5% ammonium ferrous sulfate hexahydrate solution, 1 drop of 1.5 mol/L sulfuric acid

solution and 1 ml 0.5 mol/L potassium hydroxide solution, shake strongly, a precipitate is produced which turns greyish-green to reddish-brown in 1 minute.

(2) The light absorption of a solution of 10 µg per ml in ethanol exhibits a maximum at 237 nm (Appendix IV A).

(3) The infrared absorption spectrum (Appendix IV C) is concordant with the reference spectrum of nimodipine (Appendix XXIII).

Related substances Protect from light throughout the procedure. Carry out the method for high performance liquid chromatography (Appendix V D), using a column packed with octadecylsilane bonded silica gel and a mixture of methanol-acetonitrile-water (35 : 38 : 27) as the mobile phase. Detection wavelength is 235 nm and the number of theoretical plates of the column is about 8000, calculated with reference to the peak of nimodipine. The resolution factor between the peaks complies with related requirements. Dissolve a quantity, accurately weighted, in mobile phase to produce a solution of 0.2 mg per ml as the test solution. Dilute the test solution with the mobile phase to produce a solution of 2 µg per ml as reference solution. Inject 10 µl of the reference solution into the column, adjust the sensitivity of the detector so that the principal peak height in the chromatogram is half of the full scale of the recorder. Inject separately 10 µl each of the two solutions into the column, and record the chromatogram for 4.5 times the retention time of the principal peak. The sum of the areas of all peaks other than the principal peak in the chromatogram obtained with the test solution is not greater than the area of the principal peak in the chromatogram obtained with the reference solution.

Loss on drying When dried to constant weight at 105°C, loses not more than 0.5% of its weight (Appendix VIII L).

Residue on ignition Not more than 0.1% (Appendix VIII N).

Heavy metals Carry out the limit test for heavy metals (Appendix VII H, method 2), using the residue obtained in the test for Residue on ignition; not more than 0.001%.

Assay Dissolve about 0.18 g, accurately weighed, with gentle heating in 25 ml of dehydrate ethanol, add 25 ml of perchloric solution (Dilute 8.5 ml of 70% perchloric acid with water to 100 ml) and 4 drops of ferroin IS, titrate with cerium sulphate (0.1 mol/L) VS until the colour of solution turns orange to slightly yellowish-green. Perform a blank determination and make any necessary correction. Each ml of cerium sulphate (0.1 mol/L) VS is equivalent to 20.92 mg of $C_{21}H_{26}N_2O_7$.

Category Calcium-channel blockers.

Storage Preserve in tightly closed containers, protected from light, stored in a dry place.

Preparation (1) Nimodipine Tablets
(2) Nimodipine Dispersible Tablets
(3) Nimodipine Capsules
(4) Nimodipine Injection

Nimodipine Capsules

Nimodipine Capsules contain not less than 90.0% and not more than 110.0% of the labelled amount of nimodipine ($C_{21}H_{26}N_2O_7$).

Description Capsules containing slightly to pale yellow powder.

Identification (1) Weigh a quantity of mixed contents

equivalent to about 40 mg of nimodipine, add about 5 ml of ethanol, shake to dissolve nimodipine and filter. Measure 3 ml of the filtrate, add 2 ml of freshly prepared 5% w/v of ammonium ferrous sulfate hexahydrate solution, 1 drop of 1.5 mol/L sulfuric acid solution and 1 ml 0.5 mol/L potassium hydroxide solution, shake strongly, a precipitate is produced which turns greyish-green to reddish-brown in 1 minute.

(2) The retention time of principal peak of nimodipine in the substance being examined in the chromatogram obtained in the Assay is identical with that of the principal peak of nimodipine CRS in the chromatogram of the reference solution.

Carry out the following procedures protected from light.

Related substances Dissolve an accurately weighed quantity of the mixed contents obtained in the test for weight variation of contents equivalent to about 10 mg nimodipine in the mobile phase in a 50 ml volumetric flask, ultrasonicate for 15 minutes, cool to room temperature, dilute with the mobile phase to volume, mix well and centrifuge at 3000 rpm for 10 minutes. The supernatant liquid is as the test solution. Dilute the test solution with the mobile phase to produce a solution of 2 µg per ml as reference solution. Carry out the chromatography conditions as described under Assay and detection wavelength is 235 nm. Inject 10 µl of the reference solution into the column, adjust the sensitivity of the detector so that the principal peak height in the chromatogram is half of the full scale of the recorder. Inject separately 10 µl each of the two solutions into the column, and record the chromatogram for three times the retention time of the principal peak. Each peak area other than the principal peak in the chromatogram obtained with the test solution is not greater than the area of the principal peak in the chromatogram obtained with the reference solution. The sum of the areas of all peaks other than the principal peak in the chromatogram obtained with the test solution is not greater than twice of the area of the principal peak in the chromatogram obtained with the reference solution. Disregard any peak with the retention time less than 0.35 times relative to the principal peak in the chromatogram obtained with test solution.

Dissolution Carry out the dissolution test (Appendix X C, method 2), using 900 ml of acetate buffer pH 4.5 (Dissolve 0.299 g of sodium acetate in 50 ml of water, add 0.174 g glacial acetic acid and dilute to 100 ml with water.) containing 0.3% w/v of sodium dodecyl sulphate as the dissolution medium and adjust the rotational speed of the paddle to 75 rpm. Withdraw 10 ml of the solution at 30 minutes and filter. Measure accurately 10 ml of the successive filtrate in a 20 ml (for strength 20 mg) or 25 ml (for strength 30 mg) volumetric flask, dilute with the dissolution medium to volume as the test solution. Transfer 10 mg of nimodipine CRS to a 100 ml volumetric flask, accurately weighted, dissolve in 10 ml ethanol and dilute with the dissolution medium to volume, mix well. Measure accurately 5 ml of the solution in a 50 ml volumetric flask, dilute with the dissolution medium to volume as the reference solution. Measure the absorbance of the resulting solutions at 238 nm (Appendix IV A). Calculate the dissolution of $C_{21}H_{26}N_2O_7$ from each capsules, not less than 80% of the labelled amount is dissolved.

Other requirements Comply with the general requirements for capsules (Appendix I A).

Assay Carry out the method for high performance liquid chromatography (Appendix V D), using a column packed with octadecylsilane bonded silica gel and a mixture of methanol-acetonitrile-water (35 : 38 : 27) as the mobile phase. Detection wavelength is 237 nm and the number of

theoretical plates of the column is about 8000, calculated with reference to the peak of nimodipine. The resolution factor between the peaks complies with related requirements.

Reference solution Dissolve a quantity of nimodipine CRS, accurately weighed, in mobile phase to produce a solution of 20 µg per ml.

Test solution Dissolve an accurately weighed quantity of the mixed contents obtained in the test for weight variation of contents equivalent to about 10 mg nimodipine in the mobile phase in a 50 ml volumetric flask, ultrasonicate for 15 minutes, cool to room temperature, dilute with the mobile phase to volume, mix well and centrifuge at 3000 rpm for 10 minutes. Transfer accurately 5 ml the supernatant liquid to a 50 ml volumetric flask, dilute with the mobile phase to volume and mix well.

Procedure Inject 10 µl of the reference solution and the test solution into the column respectively and record the peak areas corresponding obtained in the chromatogram. Calculate the content of $C_{21}H_{26}N_2O_7$ with respect to the peak area obtained in the chromatogram by the external standard method.

Category As described under Nimodipine.

Strength (1) 20 mg (2) 30 mg

Storage Preserve in tightly closed containers, protected from light.

Nimodipine Dispersible Tablets

Nimodipine Dispersible Tablets contain not less than 90.0% and not more than 110.0% of the labelled amount of nimodipine ($C_{21}H_{26}N_2O_7$).

Description Slightly to pale yellow tablets.

Identification (1) Weigh a quantity of powdered tablets equivalent to about 40 mg of nimodipine, add about 5 ml of ethanol, shake to dissolve nimodipine and filter. Measure 3 ml of the filtrate, add 2 ml of freshly prepared 5% of ammonium ferrous sulfate hexahydrate solution, 1 drop of 1.5 mol/L sulfuric acid solution and 1 ml of 0.5 mol/L potassium hydroxide solution, shake strongly, a precipitate is produced which turns grayish-green to reddish-brown in 1 minute.

(2) The retention time of principal peak of nimodipine in the substance being examined in the chromatogram obtained in the Assay is identical with that of the principal peak of nimodipine CRS in the chromatogram of the reference solution.

Carry out the following procedures protected from light.

Related substances Dissolve an accurately weighted quantity of powdered tablets equivalent to about 10 mg nimodipine in the mobile phase in a 50 ml volumetric flask by ultrasonication for 15 minutes, cool to room temperature, dilute with the mobile phase to volume, mix well and centrifuge at 3000 rpm for 10 minutes. The supernatant liquid is as the test solution. Dilute the test solution with the mobile phase to produce a solution of 2 µg per ml as reference solution. Carry out the chromatography conditions as described under Assay and detection wavelength is 235 nm. Inject 10 µl of the reference solution into the column, adjust the sensitivity of the detector so that the principal peak height in the chromatogram is half of the full scale of the recorder. Inject separately 10 µl each of the two solutions into the column, and record the chromatogram for three times the retention time of the principal peak. Each peak area other than the principal peak in the chromatogram

obtained with the test solution is not greater than the area of the principal peak in the chromatogram obtained with the reference solution. The sum of the areas of all peaks other than the principal peak in the chromatogram obtained with the test solution is not greater than twice of the area of the principal peak in the chromatogram obtained with the reference solution. Disregard any peak with the retention time less than 0.35 times relative to the principal peak in the chromatogram obtained with test solution.

Dissolution Carry out the dissolution test (Appendix X C, method 2), using 900 ml of acetate buffer pH 4.5 (Dissolve 0.299 g of sodium acetate in 50 ml of water, add 0.174 g glacial acetic acid and dilute to 100 ml with water.) containing 0.3% of sodium dodecyl sulphate as the dissolution medium and adjust the rotational speed of the paddle to 75 rpm. Withdraw 10 ml of the solution at 30 minutes and filter. Measure accurately 10 ml of the successive filtrate in a 20 ml (for strength 20 mg) or 25 ml (for strength 30 mg) volumetric flask, dilute with the dissolution medium to volume as the test solution. Transfer 10 mg of nimodipine CRS to a 100 ml volumetric flask, accurately weighed, dissolve in 10 ml of ethanol and dilute with the dissolution medium to volume, mix well. Transfer accurately 5 ml of the solution in a 50 ml volumetric flask, dilute with the dissolution medium to volume as the reference solution. Measure the absorbance of the resulting solutions at 238 nm (Appendix IV A). Calculate the dissolution of $C_{21}H_{26}N_2O_7$ from each tablets, not less than 85% of the labelled amount is dissolved.

Other requirements Comply with the general requirements for tablets (Appendix I A).

Assay Carry out the method for high performance liquid chromatography (Appendix V D), using a column packed with octadecylsilane bonded silica gel and a mixture of methanol-acetonitrile-water (35 : 38 : 27) as the mobile phase. Detection wavelength is 237 nm and the number of theoretical plates of the column is about 8000, calculated with reference to the peak of nimodipine. The resolution factor between the peaks complies with related requirements.

Reference solution Dissolve a quantity of nimodipine CRS, accurately weighed, in mobile phase to produce a solution of 20 µg per ml.

Test solution Weigh accurately and powder 20 tablets. Dissolve an accurately weighed quantity of the powder equivalent to about 10 mg nimodipine in the mobile phase in a 50 ml volumetric flask, ultrasonicate for 15 minutes, cool to room temperature, dilute with the mobile phase to volume, mix well and centrifuge at 3000 rpm for 10 minutes. Transfer accurately 5 ml the supernatant liquid to a 50 ml volumetric flask, dilute with the mobile phase to volume and mix well.

Procedure Inject 10 µl of the reference solution and the test solution into the column respectively and record the peak areas corresponding obtained in the chromatogram. Calculate the content of $C_{21}H_{26}N_2O_7$ with respect to the peak area obtained in the chromatogram by the external standard method.

Category As described under Nimodipine.

Strength 20 mg

Storage Preserve in tightly closed containers, protected from light.

Nimodipine Injection

Nimodipine Injection is a sterile solution of Nimodipine in Water for Injection. It contains not less than 90.0% and not more than 110.0% of the labelled amount of nimodipine ($C_{21}H_{26}N_2O_7$).

Description A clear, almost colourless liquid.

Identification (1) Measure a quantity equivalent to about 20 mg of nimodipine to a separator. Extract with 30 ml of ether and allow it to stand. Evaporate the ether layer to dryness on a water bath, cool, dissolve the residue in 2 ml ethanol, stir to dissolve nimodipine and transfer to a tube, add 3 ml of 1% mercuric chloride, a precipitate is produced. (2) The retention time of principal peak of nimodipine in the substance being examined in the chromatogram obtained in the Assay is identical with that of the principal peak of nimodipine CRS in the chromatogram of the reference solution.

pH value 5.5-7.5 (Appendix VI H).

Colour Not more intense than that of reference solution YG₂ (Appendix IX A, method 1).

Related substances Protect from light throughout the procedure. The injection being examined is as the test solution. Dilute the test solution with the mobile phase to produce a solution of 2 µg per ml as reference solution. Carry out the chromatography conditions as described under Assay and detection wavelength is 235 nm. Inject 10 µl of the reference solution into the column, adjust the sensitivity of the detector so that the principal peak height in the chromatogram is half of the full of the scale of the recorder. Inject separately 10 µl each of the two solutions into the column, and record the chromatogram for three times the retention time of the principal peak. Each peak area other than the principal peak in the chromatogram obtained with the test solution is not greater than the area of the principal peak in the chromatogram obtained with the reference solution. The sum of the areas of all peaks other than the principal peak in the chromatogram obtained with the test solution is not greater than twice of the area of the principal peak in the chromatogram obtained with the reference solution. Disregard any peak with the retention time less than 0.45 times relative to the principal peak in the chromatogram obtained with test solution.

Pyrogens Comply with the test for pyrogens (Appendix XI D), using 2.5 ml per kg of the rabbit's weight.

Sterility Comply with the test for sterility (Appendix XII H, membrane filtration method).

Other requirements Comply with the general requirements for injections (Appendix I B).

Assay Protect from light throughout the procedure. Carry out the method for high performance liquid chromatography (Appendix V D), using a column packed with octadecylsilane bonded silica gel and a mixture of methanol-acetonitrile-water (35 : 38 : 27) as the mobile phase. Detection wavelength is 237 nm and the number of theoretical plates of the column is about 8000, calculated with reference to the peak of nimodipine. The resolution factor between the peaks complies with related requirements.

Reference solution Dissolve a quantity of nimodipine CRS, accurately weighed, in mobile phase to produce a solution of 20 µg per ml.

Test solution Measure accurately 5 ml in a 50 ml volumetric flask, dilute with the mobile phase to volume and mix well.

Procedure Inject 10 µl of the reference solution and the test solution, accurately measured, into the column respectively and record the peak areas corresponding obtained in the chromatogram. Calculate the content of $C_{21}H_{26}N_2O_7$ with respect to the peak area obtained in the chromatogram by external standard method.

Category As described under Nimodipine.

Strength (1) 20 ml:4 mg (2) 40 ml:8 mg
(3) 50 ml:10 mg

Storage Preserve in well closed containers, protected from light.

Nimodipine Tablets

Nimodipine Tablets contain not less than 90.0% and not more than 110.0% of the labelled amount of nimodipine ($C_{21}H_{26}N_2O_7$).

Description Pale yellow tablets, film or sugar coated tablets with pale yellow core.

Identification (1) Weigh a quantity of powdered tablets equivalent to about 40 mg of nimodipine, add about 5 ml of ethanol, shake to dissolve nimodipine and filter. Measure 3 ml of the filtrate, add 2 ml of freshly prepared 5% w/v of ammonium ferrous sulfate hexahydrate solution, 1 drop of 1.5 mol/L sulfuric acid solution and 1 ml 0.5 mol/L potassium hydroxide solution, shake strongly, a precipitate is produced which turns greyish-green to reddish-brown in 1 minute.

(2) The retention time of principal peak of nimodipine in the substance being examined in the chromatogram obtained in the Assay is identical with that of the principal peak of nimodipine CRS in the chromatogram of the reference solution.

Carry out the following procedures protected from light.

Related substances Dissolve an accurately weighted quantity of the powder equivalent to about 10 mg nimodipine in the mobile phase in a 50 ml volumetric flask, ultrasonicate for 15 minutes, cool, dilute with the mobile phase to volume, mix well and centrifuge at 3000 rpm for 10 minutes. The supernatant liquid is as the test solution. Dilute the test solution with the mobile phase to produce a solution of 2 µg per ml as reference solution. Carry out the chromatography conditions as described under Assay and detection wavelength is 235 nm. Inject 10 µl of the reference solution into the column, adjust the sensitivity of the detector so that the principal peak height in the chromatogram is half of the full scale of the recorder. Inject separately 10 µl each of the two solutions into the column, and record the chromatogram for three times the retention time of the principal peak. Each peak area other than the principal peak in the chromatogram obtained with the test solution is not greater than the area of the principal peak in the chromatogram obtained with the reference solution. The sum of the areas of all peaks other than the principal peak in the chromatogram obtained with the test solution is not greater than twice of the area of the principal peak in the chromatogram obtained with the reference solution. Disregard any peak with the retention time less than 0.35 times relative to the principal peak in the chromatogram obtained with test solution.

Dissolution Carry out the dissolution test (Appendix X C, method 2), using 900 ml of acetate buffer pH 4.5 (Dissolve

0.299 g of sodium acetate in 50 ml of water, add 0.174 g glacial acetic acid and dilute to 100 ml with water.) containing 0.3% w/v of sodium dodecyl sulphate as the dissolution medium and adjust the rotational speed of the paddle to 75 rpm. Withdraw 10 ml of the solution at 30 minutes and filter. Measure accurately 10 ml of the successive filtrate in a 20 ml (for strength 20 mg) or 25 ml (for strength 30 mg) volumetric flask, dilute with the dissolution medium to volume as the test solution. Transfer 10 mg of nimodipine CRS to a 100 ml volumetric flask, accurately weighed, dissolve in 10 ml ethanol and dilute with the dissolution medium to volume, mix well. Measure accurately 5 ml of the solution in a 50 ml volumetric flask, dilute with the dissolution medium to volume as the reference solution. Measure the absorbance of the resulting solutions at 238 nm (Appendix IV A). Calculate the dissolution of $C_{21}H_{26}N_2O_7$ from each tablets, not less than 85% of the labelled amount is dissolved.

Other requirements Comply with the general requirements for tablets (Appendix I A).

Assay Carry out the method for high performance liquid chromatography (Appendix V D), using a column packed with octadecylsilane bonded silica gel and a mixture of methanol-acetonitrile-water (35 : 38 : 27) as the mobile phase. Detection wavelength is 237 nm and the number of theoretical plates of the column is about 8000, calculated with reference to the peak of nimodipine. The resolution factor between the peaks complies with related requirements.

Reference solution Dissolve a quantity of nimodipine CRS, accurately weighed, in mobile phase to produce a solution of 20 µg per ml.

Test solution Weigh accurately and powder 20 tablets (sugar coated tablets remove coating). Dissolve an accurately weighed quantity of the powder equivalent to about 10 mg nimodipine in the mobile phase in a 50 ml volumetric flask, ultrasonicate for 15 minutes, cool to room temperature, dilute with the mobile phase to volume, mix well and centrifuge at 3000 rpm for 10 minutes. Transfer accurately 5 ml the supernatant liquid to a 50 ml volumetric flask, dilute with the mobile phase to volume and mix well.

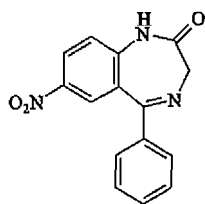
Procedure Inject 10 µl of the reference solution and the test solution into the column respectively and record the peak areas corresponding obtained in the chromatogram. Calculate the content of $C_{21}H_{26}N_2O_7$ with respect to the peak area obtained in the chromatogram by external standard method.

Category As described under Nimodipine.

Strength (1) 20 mg (2) 30 mg

Storage Preserve in tightly closed containers, protected from light.

Nitrazepam



$C_{15}H_{11}N_3O_3$ 281.27

[146-22-5]

Nitrazepam is 1,3-dihydro-7-nitro-5-phenyl-2H-

1,4-benzodiazepin-2-one. It contains not less than 99.0% of $C_{15}H_{11}N_3O_3$, calculated on the dried basis.

Description A light yellow crystalline powder; odourless; tasteless.

Sparingly soluble in chloroform; slightly soluble in ethanol or ether; practically insoluble in water.

Melting point 226-229°C, with decomposition (Appendix VI C).

Identification (1) To 10 mg add 1 ml of methanol, 2 drops of sodium hydroxide TS; a bright yellow colour is produced.

(2) The light absorption of a solution of 8 µg per ml in dehydrated ethanol exhibits three maxima at 220 nm, 260 nm and 310 nm; the ratio of the absorbance at 260 nm to that at 310 nm is 1.45-1.65 (Appendix IV A).

(3) The infrared absorption spectrum (Appendix IV C) is concordant with the reference spectrum of nitrazepam (Appendix XVI).

(4) Heat about 10 mg with 15 ml of dilute hydrochloric acid on a water bath for 15 minutes, cool, and filter. The filtrate yields the reactions characteristic of primary aromatic amines (Appendix III).

Related substances Carry out the method for thin-layer chromatography (Appendix V B), using silica gel G as the coating substance and a mixture of benzene-acetone (3:1) as the mobile phase. Apply separately to the plate 10 µl each of two solutions of the substance being examined in chloroform-methanol (1:1) containing (1) 25 mg per ml, (2) 0.25 mg per ml. After developing and removal of the plate, dry it in air and spray with potassium iodobismuthate TS. Any secondary spot in the chromatogram obtained with solution (1) is not more intense than the principal spot obtained with solution (2).

Loss on drying When dried to constant weight at 105°C, loses not more than 0.5% of its weight (Appendix VIII L).

Residue on ignition Not more than 0.1% (Appendix VIII N).

Assay Dissolve about 0.2 g, accurately weighed, in 15 ml of glacial acetic acid and 5 ml of acetic anhydride, add 1 drop of crystal violet IS, titrate with perchloric acid (0.1 mol/L) VS until the colour changes to yellowish-green. Perform a blank determination and make any necessary correction. Each ml of perchloric acid (0.1 mol/L) VS is equivalent to 28.13 mg of $C_{15}H_{11}N_3O_3$.

Category Anxiolytic and anticonvulsant.

Storage Preserve in tightly closed containers.

Preparation Nitrazepam Tablets

Nitrazepam Tablets

Nitrazepam Tablets contain not less than 99.0% and not more than 110.0% of the labelled amount of nitrazepam ($C_{15}H_{11}N_3O_3$).

Description White to pale yellow tablets.

Identification (1) Shake a quantity of the powdered tablets equivalent to 25 mg nitrazepam in 10 ml of chloroform to dissolve nitrazepam and filter. Evaporate the filtrate on a water bath to dryness. The residue complies with tests (1) and (4) for Identification described under Nitrazepam.

(2) The light absorption of the solution obtained in the

Assay exhibits three maxima at 220 nm, 260 nm and 310 nm (Appendix IV A).

Content uniformity Comply with the requirements (Appendix X E). Triturate 1 tablet with dehydrated ethanol and transfer to a 50 ml volumetric flask, dilute with dehydrated ethanol to volume, shake thoroughly and filter. Transfer accurately 5 ml of the successive filtrate to a 50 ml volumetric flask, proceed as described in Assay, beginning at the words "add dehydrated ethanol,..."

Other requirements Comply with the general requirements for tablets (Appendix I A).

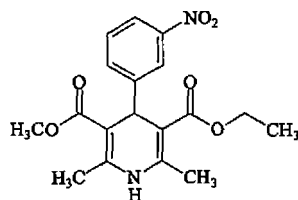
Assay Weigh accurately and powder 10 tablets. To a quantity of the powdered tablets equivalent to about 4 mg of nitrazepam, accurately weighed, in a 100 ml volumetric flask, add an amount of dehydrated ethanol, shake thoroughly, dilute with dehydrated ethanol to volume and mix well. Filter with a dry filter paper and discard the initial filtrate. Transfer accurately 10 ml of the successive filtrate to a 50 ml volumetric flask, dilute with dehydrated ethanol to volume and mix well. Measure the absorbance at 260 nm (Appendix IV A). Calculate the content of $C_{15}H_{11}N_3O_3$, taking 602 as the value of A (1%, 1 cm).

Category As described under Nitrazepam.

Strength 5 mg

Storage Preserve in tightly closed containers.

Nitrendipine



$C_{18}H_{20}N_2O_6$ 360.37 [39562-70-4]

Nitrendipine is 2,6-dimethyl-4-(3-nitrophenyl)-1,4-dihydro-3,5-pyridinedicarboxylic acid ethyl methyl ester. It contains not less than 99.0% of $C_{18}H_{20}N_2O_6$, calculated on the dried basis.

Description Yellow crystals or a crystalline powder; odourless; tasteless; deteriorated on exposure to light. Freely soluble in acetone or chloroform; sparingly soluble in methanol or ethanol; practically insoluble in water.

Melting point 157-161°C (Appendix VI C).

Identification (1) To about 50 mg add 1 ml of acetone and 3-5 drops of 20% sodium hydroxide TS, an orange red colour is produced.

(2) Protect from light in the procedure. The light absorption of a solution of 20 µg per ml in dehydrated ethanol exhibits two maxima at 236 nm and 353 nm and a minimum at 303 nm. The ratio of the absorbance at 353 nm to that at 303 nm is 2.1-2.3.

(3) The infrared absorption spectrum (Appendix IV C) is concordant with the reference spectrum of nitrendipine (Appendix XVI).

Chlorides Shake well 1.0 g with 50 ml of water, boil for 2-3 minutes, allow to cool and filter, using 25 ml of the successive filtrate, carry out the limit test for chlorides (Appendix VII A). Any opalescence produced is not more

pronounced than that of a reference solution using 5.0 ml of sodium chloride standard solution (0.01%).

Related substances Protect from light throughout the procedure. Dissolve a quantity of the substance being examined in methanol to produce solutions of 1 mg per ml (solution 1) and 40 µg per ml (solution 2). Carry out the method for high performance liquid chromatograph (Appendix V D), using a column packed with octadecylsilane bonded silica gel and a mixture of methanol-water (70:30) as the mobile phase. Detection wavelength is 237 nm and the number of the theoretical plates of the column is not less than 2000, calculated with reference to the peak of nitrendipine. Inject 10 µl of the solution 2 into the column, adjust the attenuation so that the principal peak height in the chromatogram is about 20%-30% of the full scale of the chart. Inject separately 10 µl of solution 1 and solution 2 into the column, and record the chromatogram for 2.5 times the retention time of the principal peak. The sum of the areas of all peaks other than the principal peak in solution 1 is not greater than the area of the principal peak in the chromatogram obtained with solution 2.

Loss on drying When dried to constant weight at 105°C, loses not more than 0.5% of its weight (Appendix VIII L).

Residue on ignition Not more than 0.1% (Appendix VIII N); using 1.0 g.

Heavy metals Carry out the limit test for heavy metals (Appendix VIII H, method 2), using the residue obtained in the test for Residue on ignition; not more than 0.001%.

Iron Incinerate 1.0 g at 500-600°C, allow to cool, dissolve in 4 ml of dilute hydrochloric acid on a water bath, any colour produced is not more intense than that of a reference solution using 1.0 ml of iron standard solution (0.001%) (Appendix VIII G).

Assay Dissolve about 0.13 g, accurately weighed, in 20 ml of glacial acetic acid and 10 ml of dilute sulfuric acid on warming, allow to cool, add 2-3 drops of o-phenanthroline IS, titrate with ceric sulfate (0.1 mol/L) VS until the red colour disappears. Perform a blank determination and make any necessary correction. Each ml of ceric sulfate (0.1 mol/L) VS is equivalent to 18.02 mg of $C_{18}H_{20}N_2O_6$.

Category Calcium channel blocker.

Storage Preserve in tightly closed containers, protected from light.

Preparation Nitrendipine Tablets

Nitrendipine Tablets

Nitrendipine Tablets contain not less than 90.0% and not more than 110.0% of the labelled amount of nitrendipine ($C_{18}H_{20}N_2O_6$).

Description Pale yellow tablets.

Identification (1) Shake a quantity of the powdered tablets equivalent to about 50 mg of nitrendipine with 2 ml of acetone, filter, add 2-3 drops of 20% sodium hydroxide solution to the filtrate and shake, an orange-yellow colour is produced.

(2) Protect from light in the procedure. Transfer a quantity of powdered tablets equivalent to about 10 mg of nitrendipine to a 100 ml volumetric flask, add a quantity of dehydrated ethanol, shake to dissolve nitrendipine, dilute with dehydrated ethanol to volume and filter, dilute the successive filtrate with dehydrated ethanol to produce a solution of 20

μg per ml. The resulting solution complies with test (2) for identification described under Nitrendipine.

Related substances Protect from light throughout the procedure. Dissolve a quantity of the powdered tablets, accurately weighed, in methanol to produce a solution containing 1 mg of nitrendipine per ml, filter, using the filtrate as solution 1; measure accurately 5 ml, dilute with mobile phase to 100 ml and mix well as solution 2. Carry out the method for high performance liquid chromatograph (Appendix V D), using a column packed with octadecylsilane bonded silica gel and a mixture of methanol-water (70:30) as the mobile phase. Detection wavelength is 237 nm and the number of the theoretical plates of the column is not less than 2000, calculated with reference to the peak of nitrendipine. Inject 10 μl of the solution 2 into the column, adjust the attenuation so that the principal peak height in the chromatogram is about 20%-30% of the full scale of the chart. Inject separately 10 μl of solution 1 and solution 2 into the column, and record the chromatogram for 2.5 times the retention time of the principal peak. The sum of the areas of all peaks other than the principal peak in solution 1 is not greater than the area of the principal peak in the chromatogram obtained with solution 2.

Content uniformity Protect from light in the procedure. Comply with the requirements (Appendix X E). Triturate 1 tablet and transfer to a 100 ml volumetric flask with dehydrated ethanol in divided portions, shake frequently to dissolve nitrendipine in a 50-60°C water bath and cool to room temperature. Dilute with dehydrated ethanol to volume, mix well and filter. Transfer 5 ml of the successive filtrate to another 100 ml volumetric flask, dilute with dehydrated ethanol to volume and mix well. Measure the absorbance at 236 nm (Appendix IV A). Calculate the content of $\text{C}_{18}\text{H}_{20}\text{N}_2\text{O}_6$.

Dissolution Protect from light throughout the procedure. Carry out the dissolution test (Appendix X C, method 2), using 900 ml of 0.1 mol/L hydrochloric acid solution as the dissolution medium, adjust the rotational speed of the paddle to 100 rpm. Withdraw a quantity of the solution at 60 minutes and filter. Measure the absorbance of the successive filtrate at 237 nm (Appendix IV A). Dissolve 14 mg of Nitrendipine CRS, accurately weighed, in 25 ml of ethanol, mix well. Transfer accurately 2 ml, to a 100 ml volumetric flask, dilute to volume with the dissolution medium, repeat the operation. Calculate the dissolution of $\text{C}_{18}\text{H}_{20}\text{N}_2\text{O}_6$ from each tablet. Not less than 60% of the labelled amount is dissolved.

Other requirements Comply with the general requirements for tablets (Appendix I A).

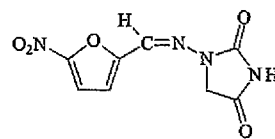
Assay Weigh accurately and powder 30 tablets. Dissolve a quantity of the powdered tablets equivalent to about 0.13 g of nitrendipine, accurately weighed, in 20 ml of glacial acetic acid and 10 ml of dilute sulfuric acid on warming. Complete the Assay described under Nitrendipine, beginning at the words "allow to cool...".

Category As described under Nitrendipine.

Strength 10 mg

Storage Preserve in tightly closed containers, protected from light.

Nitrofurantoin



$\text{C}_8\text{H}_6\text{N}_4\text{O}_5$ 238.16

[67-20-9]

Nitrofurantoin is 1-[[5-nitro-2-furanyl]methylene]-2,4-imidazolidinedione. It contains not less than 98.0% and not more than 102.0% of $\text{C}_8\text{H}_6\text{N}_4\text{O}_5$, calculated on the dried basis.

Description A yellow crystalline powder; odourless; taste, bitter. Darkens gradually on exposure to light. Soluble in dimethylformamide; slightly soluble in acetone; very slightly soluble in ethanol; practically insoluble in water or chloroform.

Identification (1) Dissolve about 5 mg in a mixture of 5 ml of water and 5 ml of sodium hydroxide TS, a deep orange-red colour is produced.

(2) Dissolve about 5 mg in a mixture of 5 ml of water and 0.2 ml of ammonia TS, add 5 ml of silver nitrate TS, a yellow precipitate is produced (distinction from furacillin and furazolidone).

(3) The infrared absorption spectrum (Appendix IV C) is concordant with the reference spectrum of nitrofurantoin (Appendix XVI).

Acidity Shake 0.50 g with 50 ml of water for 10 minutes, filter; pH of the filtrate is 5.5-7.0 (Appendix VI H).

Related substances Protect from light throughout the procedure. Dissolve 0.25 g in 5 ml of dimethyl-formamide in a 10 ml volumetric flask, add acetone to volume, as test solution; transfer accurately 1 ml of the above solution to a 100 ml volumetric flask, add acetone to volume, as reference solution. Carry out the method for thin-layer chromatography (Appendix V B), using silica gel G as the coating substance, and a mixture of nitromethane-methanol (9:1) as the mobile phase. Apply to the plate separately 10 μl each of two solutions. After developing and removal of the plate, allow it to dry in air, dry at 105°C for 5 minutes, spray with phenylhydrazine hydrochloride solution (dissolve 0.75 g of phenylhydrazine hydrochloride in 50 ml of water, decolourise with charcoal, add 25 ml of hydrochloric acid and sufficient water to produce 200 ml), heat at 105°C for 10 minutes. Any secondary spot in the chromatogram obtained with the test solution is not more intense than the principal spot obtained with the reference solution.

Loss on drying When dried at 105°C to constant weight, loses not more than 1.0% of its weight (Appendix VIII L).

Residue on ignition Not more than 0.1% (Appendix VIII N).

Assay Protect from light throughout the procedure. Weigh accurately about 40 mg and dissolve in 10 ml of dimethylformamide in a 600 ml beaker, add rapidly 400 ml of water, mix well (if a precipitate is produced, warm gently to dissolve it). Transfer it to a 500 ml amber coloured volumetric flask, add water to volume, mix well. Transfer accurately 10 ml to a 100 ml amber coloured volumetric flask, dilute with water to volume, mix well. Measure the absorbance of the solution at 367 nm (Appendix IV A) within one hour, calculate the content of $\text{C}_8\text{H}_6\text{N}_4\text{O}_5$, taking

766 as the value of A (1%, 1 cm).

Category Antimicrobial agent.

Storage Preserve in tightly closed containers, protected from light.

Preparation Nitrofurantoin Enteric-coated Tablets

Nitrofurantoin Enteric-coated Tablets

Nitrofurantoin Tablets contain not less than 93.0% and not more than 107.0% of the labelled amount of nitrofurantoin ($C_8H_6N_4O_5$).

Description Enteric sugar coated tablets, with yellow core.

Identification Dissolve a quantity of the powdered tablets (equivalent to 25 mg of nitrofurantoin) in a mixture of 25 ml of water and 1 ml of ammonia TS with shaking, filter. The filtrate has an orange-yellow colour and complies with the tests (1) and (2) for Identification described under Nitrofurantoin.

Drug Release Protect from light throughout the procedure. Carry out the method for dissolution test (Appendix X D and X C, method 2), using 1000 ml of 0.1 mol/L hydrochloric acid solution as the released medium, adjust the rotational speed of the paddle to 150 rpm. No tablet cracks or disintegrates at 2 hours. Then repeat the operations using 1000 ml of phosphate BS (pH 7.2) instead of the released medium. Withdraw a quantity of the solution at 2 hours and filter. Transfer accurately 3 ml of the successive filtrate into a 25 ml volumetric flask and dilute with phosphate BS (pH 7.2) to volume, mix well. Measure the absorbance of the solution at 375 nm (Appendix IV A), calculate the drug release of $C_8H_6N_4O_5$ from each tablet, taking 753 as the value of A (1%, 1 cm). Not less than 70% of the labelled amount is released.

Other requirements Comply with the general requirements for tablets (Appendix I A).

Assay Protect from light throughout the procedure. Weigh and powder finely 10 tablets with enteric sugar coating removed. Dissolve a quantity of the powdered tablets equivalent to about 40 mg of nitrofurantoin in 10 ml of dimethylformamide in a 600 ml beaker, add rapidly 400 ml of water, mix well. Transfer to a 500 ml amber coloured volumetric flask, add water to volume and mix well. Filter through dry filter paper, discard the initial filtrate (carry out the above test at a temperature higher than 15°C). Transfer accurately 10 ml of the successive filtrate, complete the Assay described under Nitrofurantoin, beginning at the words "to a 100 ml amber coloured volumetric flask...". Calculate the content of $C_8H_6N_4O_5$.

Category As described under Nitrofurantoin.

Strength 50 mg

Storage Preserve in tightly closed containers, protected from light.

Nitroglycerin Aerosol

Nitroglycerin Aerosol is a solution of nitroglycerin in ethanol. It contains not less than 85.0% and not more than 115.0% of the labelled amount of nitroglycerin ($C_3H_5N_3O_9$).

Description A colourless to pale yellowish green, clear liquid in pressurized container; spray out as foggy particles on release of the delivery valve.

Identification (1) On the aluminum cover of the container punch a hole and insert an injection needle into the container (do not contact the surface of liquid). Allow the propellant to expel completely, remove the aluminum cover and transfer the residual content to an evaporating dish, add 1 ml of potassium hydroxide TS and mix, evaporate the ethanol on a water bath. Dissolve a quantity of the residue in 2 ml of water containing 1-3 drops of dilute sulfuric acid and add a few drops of diphenylamine TS, add cautiously 2 ml of sulfuric acid along the inner wall of the test tube, an intense blue colour is produced at the interface of the two layers. (2) The retention time of principal peak in the chromatogram of the test solution obtained in the Assay is identical with that of the principal peak in the chromatogram of the reference solution.

Colour of solution Select 2 aerosol containers, on the aluminum cover of the container punch a hole and insert an injection needle into the container (do not contact the surface of liquid). Allow the propellant to expel completely, remove the aluminum cover. Dilute the residual content of each container with the same volume of ethanol, any colour produced is not more intense than that of the same volume of reference solution YG₈ (Appendix IX A, method 1). If one of the containers fails to comply with the requirements, repeat the test on 3 additional containers and all of them should comply with the requirements.

Total number of deliveries per container Select 4 aerosol containers, shake thoroughly, discharge separately into a container containing a quantity of absorbent solution, count the number of discharges until the container is empty. Total number of discharges per container is not less than 200.

Content of active ingredient in an actuation Select 1 aerosol container, shake thoroughly. Discharge 5 deliveries, wash the mouthpiece with the mobile phase and dry completely. Place the container inverted perpendicularly in the vessel containing 30 ml of the mobile phase and discharge 10 deliveries below the surface of the solvent (at the interval of 5 seconds and with occasional shaking). Transfer the absorbent solution to a 50 ml volumetric flask. Remove the container, wash the mouthpiece and the vessel with the mobile phase for several times, add the washings to the same volumetric flask, dilute with the mobile phase to volume, and mix well. Determine the amount of active ingredient separately in the 6th to 15th deliveries, 91st to 100th deliveries and 181st to 190th deliveries by the method described under the Assay, by dividing the result by 10. The content of active ingredient in an actuation is not less than 80% and not more than 120% of the labelled amount.

Other requirements Comply with the general requirements for aerosol (Appendix I L).

Assay Carry out the method for high performance liquid chromatography (Appendix V D), using a column packed with octadecylsilane bonded silica gel and a mixture of acetonitrile-water (50:50) as the mobile phase. Detection wavelength is 215 nm and the number of theoretical plates of the column is not less than 2000, calculated with reference to the peak of nitroglycerin.

Procedure On the aluminum cover of the container punch a hole and insert an injection needle with a dry rubber tubing into the container (do not contact the surface of liquid). The other end of the rubber tubing is inserted into a 100 ml volumetric flask containing 50 ml of mobile phase, allow the propellant to expel completely, remove the aluminum cover. Transfer the residual content into the 100 ml volumetric

flask. Wash the aluminum cover and the container with mobile phase, add washings to the same volumetric flask, dilute with mobile phase to volume, mix well and filter. Transfer 5 ml of the successive filtrate, accurately measured to a 50 ml volumetric flask, dilute with mobile phase to volume and mix well. Inject 20 μ l of the resulting solution into the column. Dissolve an accurately weighed quantity of nitroglycerin CRS in mobile phase to produce a solution of 0.1 mg per ml, repeat the operation. Calculate the content of $C_3H_5N_3O_9$ with respect to the peak area obtained in the chromatogram by the external standard method.

Category As described under Nitroglycerin Solution.

Strength 0.1 g of nitroglycerin per container; 200 deliveries per container; 0.5 mg of nitroglycerin per delivery

Storage Preserve in well closed containers, stored in a cool place and protected from light.

Nitroglycerin Injection

Nitroglycerin Injection is a sterile solution of nitroglycerin in dehydrated ethanol. It contains not less than 90.0% and not more than 110.0% (g/ml) of the labelled amount of nitroglycerin ($C_3H_5N_3O_9$).

Description A clear, colourless liquid.

Identification 10 ml of the injection complies with tests for Identification described under Nitroglycerin Solution.

pH value Mix 5 ml with 1 drop of saturated potassium chloride solution, pH 3.0-6.5 (Appendix VI H).

Related substances Carry out the test for Related substances described under Nitroglycerin Solution. Apply separately to the same silica gel G plate 100 μ l each of two solutions in dehydrated ethanol containing (1) 1.0 mg per ml and (2) 10 μ g per ml. The results comply with the requirements.

Other requirements Complies with the general requirements for injections (Appendix I B).

Assay Carry out the assay described under Nitroglycerin Solution.

Category Vasodilating agent.

Strength (1) 1 ml:1 mg (2) 1 ml:2 mg
(3) 1 ml:5 mg (4) 1 ml:10 mg

Storage Preserved in well closed containers, stored in cool place and protected from light.

Nitroglycerin Solution

Nitroglycerin Solution is a solution of nitroglycerin in dehydrated ethanol. It contains not less than 9.0% and not more than 11.0% (g/ml) of nitroglycerin ($C_3H_5N_3O_9$).

Description A colourless, clear liquid; odour, ethanolic.

Relative density 0.835-0.850 (Appendix VI A).

Identification (1) Mix 1 ml with 0.5 ml of sodium hydroxide TS in an evaporating dish, evaporate ethanol to about 0.2 ml on a water bath, cool. Heat about 0.1 ml of the resulting solution with 20 mg of potassium bisulphate, an irritant odour of acrylic aldehyde is produced.

(2) To the above remaining solution add 1-2 drops of sulfuric acid, mix well, add 1 drop of diphenylamine TS, an intense blue colour is produced.

Related substances Carry out the method for thin-layer chromatography (Appendix V B), using silica gel G as the coating substance and a mixture of toluene-ethyl acetate-glacial acetic acid (16:4:1) as the mobile phase. Apply separately to the plate 20 μ l each of two solutions of nitroglycerin in dehydrated ethanol containing (1) 10 mg per ml, (2) 50 μ g per ml. After developing and removal of the plate, dry it in air and spray with ethanolic solution contained of 1% diphenylamine, irradiate for 5 minutes with an ultraviolet light (365 nm) and examine immediately. Any secondary spot in the chromatogram obtained with solution (1) is not more intense than the principal spot obtained with solution (2).

Assay Carry out the method for high performance liquid chromatography (Appendix V D), using a column packed with octadecylsilane bonded silica gel and a mixture of acetonitrile-water (50:50) as the mobile phase. Detection wavelength is 215 nm and the number of theoretical plates of the column is not less than 2000, calculated with reference to the peak of nitroglycerin. The resolution factor between nitroglycerin peak and adjacent peaks complies with related requirements.

Procedure Dilute a quantity of nitroglycerin CRS, accurately measured, with the mobile phase to produce a solution of 0.1 mg per ml. Inject 10 μ l of the solution into the column. Repeat the operation, using the substance being examined instead of nitroglycerin CRS, calculate the content of $C_3H_5N_3O_9$ with respect to the peak area obtained in the chromatogram by the external standard method.

Category Vasodilating agent.

Storage Preserve in tightly closed containers, protected from light and stored in a cool place.

Preparation (1) Nitroglycerin Injection
(2) Nitroglycerin Tablets
(3) Nitroglycerin Aerosol

Nitroglycerin Tablets

Nitroglycerin Tablets contain not less than 90.0% and not more than 115.0% of the labelled amount of nitroglycerin ($C_3H_5N_3O_9$).

Description White tablets.

Identification To a quantity of powdered tablets, equivalent to about 10 mg of nitroglycerin, add 10 ml of dehydrated ethanol. Shake to dissolve and filter. The filtrate complies with the tests for identification described under nitroglycerin solution.

Content uniformity Carry out the method described under Assay of nitroglycerin solution. Transfer 1 tablet in a 5 ml volumetric flask, add a quantity of mobile phase by ultrasonating for 3 minutes, and then shake for 30 minutes to dissolve nitroglycerin. Dilute to volume with the mobile phase, mix well and filter. Use the successive filtrate as the test solution. Calculate the content of each tablet. The results comply with the requirements (Appendix X E) except the deviation limit is $\pm 20\%$.

Other requirements Comply with the general requirements for tablets (Appendix I A), except the disintegration is within 2 minutes.

Assay Weigh accurately and powder 20 tablets. Weigh accurately a quantity of the powder equivalent to about 2.5 mg of nitroglycerin in a 25 ml volumetric flask. add a quantity of the mobile phase by ultrasonating for 3 minutes. shake for 30 minutes to dissolve nitroglycerin, and dilute to volume with the mobile phase, mix well. Filter. Carry out the Assay described under Nitroglycerin Solution, using the successive filtrate. Calculate the content of $C_3H_5N_3O_9$.

Category As described under Nitroglycerin Solution.

Strength 0.5 mg

Storage Preserve in tightly closed containers, stored at cool place and protected from light.

Nitrous Oxide

N_2O 44.01

[10024-97-2]

Nitrous oxide contains not less than 95.0% (ml/ml) of N_2O .

Description A colourless gas; odour not distinct; taste, sweetish; heavier than air.

At 20°C and under a pressure of 101.3 kPa (760 mm Hg), freely soluble in water or ethanol; soluble in ether.

Identification (1) A glowing splinter of wood bursts into flame on contact with the gas.

(2) Mix with an equal volume of nitrogen monoxide [Add 15 ml of water to dissolve 5 g of sodium nitrite and 2.5 g of potassium iodide in a test tube, nitrogen monoxide is evolved on adding dropwise sulfuric acid solution (1→3)], no red fume is evolved (distinction from ox^{en}).

Acidity or alkalinity To 0.3 ml each of methyl red IS and bromothymol blue IS add 400 ml of water, boil for 5 minutes and allow to cool. Transfer three portions each of 100 ml to three Nessler cylinders (A, B and C). Add 0.2 ml of hydrochloric acid (0.01 mol/L) VS to cylinder B and 0.4 ml of hydrochloric acid (0.01 mol/L) VS to cylinder C. Pass 2000 ml of the gas being examined through cylinder B with a flow rate of 4000 ml per hour. Any colour produced in cylinder B is not more intense than the orange red colour in cylinder C or the yellowish-green colour in cylinder A.

Carbon monoxide Pass 5000-10000 ml through the following scrubbers in series; (1) Saturated chromium trioxide-sulfuric acid solution, (2) Soli^o po assium hy^oroxide, (3) phosphorous pentoxide and then pass through a tube containing iodine pentoxide previously dried at 200°C, and keep the temperature of the tube at 120°C. Introduce the iodine vapour liberated to a conical flask containing potassium iodide TS. After the passing of the gas being examined, flush the apparatus with 5000 ml of carbon monoxide-free air (pass air through cuprous chloride solution to eliminate carbon monoxide) to expel residual carbon monoxide. Titrate the liberated iodine with sodium thiosulfate (0.002 mol/L) VS. Perform a blank determination with 5000 ml of carbon monoxide-free air and make any necessary correction. Each ml of sodium thiosulfate (0.002 mol/L) VS is equivalent to 0.112 ml of CO at 20°C under a pressure of 101.3 kPa (760 mmHg). The content of carbon monoxide in nitrous oxide is not more than 0.005% (ml/ml).

Carbon dioxide Pass 1000 ml into a Nessler cylinder containing 50 ml of clear barium hydroxide TS. The turbidity developed is not more pronounced than that of the reference solution prepared by dissolving 0.10 g of sodium bicarbonate in 100 ml of freshly boiled and cooled water and diluting 1.0 ml of the solution to 50 ml with clear barium

hydroxide TS.

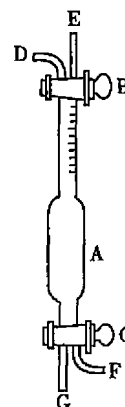
Halogens To each of two Nessler cylinders A and B add 1 ml of silver nitrate TS and 50 ml of water, mix well. Pass 2000 ml of the gas being examined into cylinder A. Any opalescence produced is not more pronounced than that produced in cylinder B.

Readily reducible substances To each of two Nessler cylinders A and B add 15 ml of freshly prepared potassium iodidestarch IS, acidify with 1 drop of glacial acetic acid. Pass 2000 ml of the gas being examined into cylinder A. Any colour produced is not more intense than that produced in cylinder B.

Readily oxidizable substances To each of two Nessler cylinders A and B add 50 ml of water and 0.20 ml of potassium permanganate (0.02 mol/L) VS. Pass 2000 ml of the gas being examined into cylinder A. The solution in cylinder B is not more intensely coloured than that in cylinder A.

Arsine and phosphine Remove conical flask A of the apparatus described under the Limit test for Arsenic (Appendix VIII J, method 1), place a disc of mercuric chloride TP between the contacting surfaces D and E. Slowly pass through the tube 2000 ml of the gas being examined. No stain is produced on the mercuric chloride TP.

Water Pass the gas being examined through an absorption tube containing phosphorous pentoxide to expel air. Weigh the tube. Pass through a quantity of the gas being examined, weigh again. Each 1000 ml of the gas contains not more than 2 mg of water.



Assay Apparatus As shown in the figure, A is a glass tube with a capacity of about 15 ml. It has a wide lower part and a long and slender upper part with graduation. The space between each graduation occupies 1% of the total volume of the tube. The volume at the connection of the tube and the two-way tap B is 100%, the first graduation is 99%, the lowest is 98% down to 90%. B and C are two-way taps; D and F are bended tubes; E and G are straight tubes.

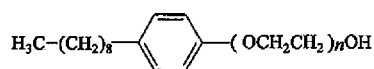
Procedure Invert the dried apparatus upside down, open tap C and close tap B. Using a thin rubber tube, siphon water from a reservoir and then connect it to tube E. Raise the apparatus, so that tap B is higher than the liquid surface in the reservoir. Open tap B, descend the apparatus slowly until water just fills into tap B, close tap B immediately. Turn the inverted apparatus over so that tap B is at the tip of the apparatus, twist tap B to make a connection between tube D and glass tube A. Pass the gas through tube F or G into the glass tube for a few minutes. Close successively tap G and B and keep the position of the apparatus below the

liquid level in the reservoir. Open slightly tap B, allow a few drops of water flow into the burette, close tap B and shake again. Open tap C to drain most part of the water and then close it. Take care not drain the water completely so as to avoid the inlet of air. Open tap B again and allow a small quantity of water flow into the burette, shake and drain the water again. Repeat the procedure several times until all the gas is dissolved in water and the volume of gas in burette is not further reduced. Close both tap B and C, connect the rubber tube of the reservoir to tube F or G, expel the air from tap C with water. Raise the apparatus and open tap C when the surface of the liquid in the tube reaches the same level as that of the liquid in the reservoir and the pressure within the burette is in equilibrium with atmospheric pressure. Close tap C and take reading from the graduation. Calculate the volume of nitrous oxide from the volume of gas unabsorbed. Gas cylinder must be kept at 23-27°C for not less than 6 hours before determination.

Category General anaesthetics administered by inhalation.

Storage Preserve in a pressure-resistant metal cylinder, protected from light and stored in a cool and dark place.

Nonoxinol



Nonoxinol is a mixture of nonoxinol and cyclohexylamine, it contains not less than 90.0% and not more than 110.0% of $\text{C}_9\text{H}_{19}\text{C}_6\text{H}_4(\text{OCH}_2\text{CH}_2)_n$.

Description A colourless to almost pale yellow viscous liquid; odour. Freely congealing not more than 10°C. Very soluble in ethanol; Freely soluble in water.

Cloud Point Dissolve 1.0 g in 100 ml of water in a 250 ml beaker. Heat the beaker on a water bath stirring continuously with a thermometer until the solution become cloudy. Remove the beaker from the bath immediately and continue stirring. The cloud point is the temperature at which the solution becomes sufficiently clear that the entire thermometer bulb is seen plainly; it is between 52°C and 56°C.

Acid value not more than 0.2 (Appendix VII H).

Identification (1) The retention time of principal peaks of nonoxinol in substance being examined in the chromatogram obtained in Assay is identical with that of the principal peaks of nonoxinol CRS in the chromatogram of the reference solution. Nonoxinol in the chromatogram obtained under Assay.

(2) The infrared absorption spectrum (Appendix IV C) is concordant with the reference spectrum of Nonoxinol (Appendix XVI).

Macrogol Dissolve 10 g in 100 ml of ethyl acetate in a 250 ml beaker, transfer to 500 ml separator, add 100 ml of 3% sodium chloride solution, shake well for 1 minute, insert separator on the 50°C water bath, transfer sodium chloride to other 500 L of separator and extract chloroform one times, filtrate drying filtrate on water bath, cool and add 250 ml of acetone dry at 60°C for 1 hour, cool, not more than 1.6% of macrogol.

Dioxane Measure accurately a quantity, add nonoxinol which stand at 160°C for 5 hours to produce 5 µg per g. Carry out the method for gas chromatography (Appendix V E), using a column packed with ethyl diethylphenyl,

maintain the column temperature at 160°C, chromatography temperature at 200°C. The content complies with the related requirements.

Free ethylene Oxide Measure accurately a quantity, add nonoxinol which stand at 150°C for 3 hours to produce 5 µg per g. Carry out the method for gas chromatography (Appendix V E), using a column packed with ethyl diethylphenyl, maintain the column temperature at 80°C, chromatography temperature at 160°C, Transfer accurately 5 µg to a small glass bottle, preserve in well closed containers, and stand to 100°C for 30-50 minutes. Inject 100 µl of the resulting solution into column, comply with the related requirements.

Water Not more than 0.5% (Appendix VII M, method 1 A).

Assay Carry out the method for high performance liquid chromatography (Appendix V D), using a column packed with octadecylsilane bonded silica gel and a mixture of methanol-water (88 : 12) as the mobile phase. Detection wavelength is 280 nm and the number of the theoretical plates of the column is not less than 1000.

Procedure Dissolve about 0.1 g, accurately weighed, in mobile phase in a 50 ml volumetric flask, and dilute to volume, mix well. Injection 10 µl of the resulting solution into the column. Repeat the operation, using the Nonoxinol CRS instead of the substance being examined, calculate the content of Nonoxinol with respect to the peak area obtained in the chromatogram by the external standard method.

Category Surfactant, spermicide.

Storage Preserve in tightly closed containers, protected from light.

Preparation (1) Nonoxinol Pellicles
(2) Nonoxinol Suppositories
(3) Nonoxinol Vaginal Tablets

Ethylene oxide solution *Preparation* Dissolve 25 ml ethylene oxide CRS in isopropanol in 500 ml volumetric flask. Shake well and preserve in ice containers.

Standardization Transfer accurately 25 ml of ethanol hydrochloride in a conical flask with 40 mg of $\text{MgCl}_2 \cdot 6\text{H}_2\text{O}$, 10 ml of ethylene oxide solution accurately and 1 ml of 0.05% bromocresol green IS, a yellow colour is produced. Titrate with 10 ml of ethanol hydrochloride (0.5 mol/L) VS, stand on ice bath for 30 minutes, titrate with ethanolic potassium hydroxide (0.5 mol/L) VS. Perform a blank determination and make any necessary correction. Each ml of ethanol hydrochloride (0.5 mol/L) VS is equivalent to 22.02 mg of ethylene oxide.

Nonoxinol Pellicles

Nonoxinol pellicles contains not less than 90.0% and not more than 115.0% of the labelled amount of nonoxinol.

Description clear, white to pale yellow translucent pellicles.
Freely soluble in water.

Identification (1) Dissolve 1 piece of pellicle in 5 ml of water, 5 drops of hydrochloric acid and 0.1 g of sodium chloride, shake well, add potassium ferrocyanide TS, a white precipitate is produced.
(2) The retention time of principal peaks of nonoxinol in substance being examined in the chromatogram obtained in

Assay is identical with that of the principal peaks of nonoxinol CRS in the chromatogram of reference solution.

Acidity Dissolve 1 piece of pellicle in 10 ml of water, pH 5.0-7.0 (Appendix VI H).

Weight variation Complies with the weight variation described under pellicles (Appendix I M).

Disintegration Hold separately between two sieve with pore 3.5 cm in diameter, to 20 pieces of pellicles on a 37°C water bath, not more than 3 minutes.

Assay Weigh and cut 20 pieces of pellicle. To a quantity of the cut pellicles equivalent to about 100 mg of nonoxinol in a 100 ml volumetric flask, Dilute with water to volume, mix well and filter, take the successive filtrate as the test solution. Dissolve a quantity of nonoxinol CRS, weighed accurately, with mobile phase to produce a solution of about 1 mg per ml as the reference solution. Carry out the Assay under Nonoxinol. Calculate the content of $C_{33}H_{60}O_{10}$.

Category As described under Nonoxinol.

Strength 50 mg (10 cm×5 cm, 7 cm×5 cm, 5 cm×5 cm)

Storage Preserve in tightly closed containers, stored in a dry place and protected from light.

Nonoxinol Suppositories

Nonoxinol Suppositories contain not less than 90.0% and not more than 115.0% of the labelled amount of nonoxinol ($C_{33}H_{60}O_{10}$).

Description White or creamy white suppositories.

Identification (1) Dissolve 1 suppository with 10 ml of water and filter, transfer 2 ml of the filtrate, add 3 drops of hydrochloric acid and 0.1 g of Sodium chloride. Add 3 drops of potassium ferrocyanide TS, a white precipitate is produced.

(2) The retention time of principal peaks of nonoxinol in substance being examined in the chromatogram obtained in Assay is identical with that of the principal peaks of nonoxinol CRS in the chromatogram of reference solution.

(3) Dissolve an accurately weighed quantity in water to produce a solution of 0.2 mg per ml. The light absorption of the solution obtained in the Assay exhibits a maximum at 275 nm (Appendix IV A).

Acidity Dissolve 3 suppositories in 30 ml of water, pH 3.5-6.5 (water soluble base). Dissolve 3 suppositories, in 30 ml of water, on water bath of 40°C, pH 5.0-7.5 (fatty base) (Appendix VI H).

Disintegration not more than 25 minutes (Appendix X B).

Other requirements Comply with the general requirements for suppository (Appendix I D).

Assay Cut 10 suppositories, weighed accurately a quantity of the powder equivalent to about 50 mg of Nonoxinol to a small beaker, add 20 ml of methanol, dissolve nonoxinol on water bath at 40-50°C, transfer to 50 ml volumetric flask, cool to room temperature, dilute with methanol to volume, mix well allow to stand, take the supernatant liquid as the test solution. Dissolve a quantity of nonoxinol CRS, weighed accurately, in mobile phase to produce a solution of about 1 mg per ml as the reference solution. Carry out the method as described under Assay in Nonoxinol. Calculate the content of $C_{33}H_{60}O_{10}$.

Category As described under Nonoxinol.

Strength (1) 50 mg (2) 100 mg

Storage Preserve in tightly closed containers, protected from light.

Nonoxinol Vaginal Tablets

Nonoxinol Vaginal Tablets contains not less than 90.0% and not more than 110.0% of the labelled amount of Nonoxinol ($C_{33}H_{60}O_{10}$).

Description White tablets.

Identification (1) Dissolve 2 tablets in 10 ml of water, filter, dilute 2 ml of the filtrate, add 3 drops of hydrochloric acid, about 0.1 g of sodium chloride and 3 drops of potassium ferrocyanide TS, a white colour is produced.

(2) The retention time of principal peaks of the substance being examined in the chromatogram obtained in Assay is identical with that of principal peaks of nonoxinol CRS in the chromatogram of the reference solution.

(3) The light absorption of the solution of 0.2 mg per ml in water exhibits a maximum at 275 nm (Appendix IV A).

Acidity or Alkalinity Dissolve 3 tablets in 30 ml of water, filter, pH 6.0-8.0 (Appendix VI H).

Disintegration and effervescence Add 3 ml of water to each of six 25 ml cylinder separately, on a water bath at 37°C, add 1 tablet to each one, the maximum volume of effervescence is greater than 15 ml and disintegration time is not more than 5 minutes.

Other requirements Comply with the general requirements for tablets (Appendix I A).

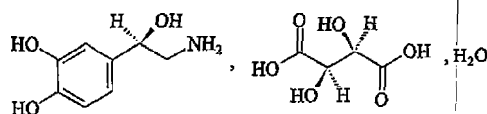
Assay Weigh accurately and powder 10 tablets. Dissolve an accurately weighed quantity equivalent to about 100 mg of nonoxinol in mobile phase in a 100 ml volumetric flask by shaking for 15 minutes, and dilute to volume, shake well, filter. Take the successive filtrate as the test solution. Dissolve a quantity of nonoxinol CRS, weighed accurately, in mobile phase to produce a solution of about 1 mg per ml as the reference solution. Carry out the method as described under Assay in Nonoxinol, calculate the content of $C_{33}H_{60}O_{10}$.

Category As described under Nonoxinol.

Strength 0.1 g

Storage Preserve in tightly closed containers, stored in a dry place and protected from light.

Noradrenaline Bitartrate



$C_8H_{11}NO_3 \cdot C_4H_6O_6 \cdot H_2O$ 337.28 [69815-49-2]

Noradrenaline Bitartrate is (R)-4-(2-amino-1-hydroxyethyl)-1,2-benzenediol, [R-(R*, R*)]-2,3-dihydroxybutanedioate (1:1) (salt), monohydrate. It contains not less than 99.0% of $C_8H_{11}NO_3 \cdot C_4H_6O_6$, calculated on the anhydrous basis.

Description A white or almost white crystalline powder; odourless; taste, bitter; deteriorated on exposure to light or air.

Freely soluble in water; slightly soluble in ethanol; insoluble in chloroform or ether.

Melting range 100-106°C, with decomposition and becomes turbid (Appendix VI C).

Specific optical rotation -10.0° to -12.0° , in a solution of 50 mg per ml in water (Appendix VI E).

Identification (1) Dissolve about 10 mg in 1 ml of water, add 1 drop of ferric chloride TS, shake, an emerald green colour is produced, which becomes blue and then red on addition of sodium bicarbonate TS slowly.

(2) Dissolve about 1 mg in 10 ml of a saturated solution of potassium hydrogen tartrate, add 1 ml of iodine TS. Allow to stand for 5 minutes, add 2 ml of sodium thiosulfate TS, the solution is colourless, or slightly red or pale purple in colour (distinction from adrenaline and isoprenaline).

(3) Dissolve about 50 mg in 1 ml of water, add 1 ml of a 10% solution of potassium chloride, a crystalline precipitate is produced within 10 minutes.

Clarity and colour of solution The solution obtained in Specific optical rotation is clear and colourless.

Ketone The absorbance of a solution of 2.0 mg per ml in water at 310 nm is not greater than 0.05 (Appendix IV A).

Water 5.0%-6.0% (Appendix VIII M, method 1A), using 50 mg.

Residue on ignition Not more than 0.1% (Appendix VIII N).

Assay Dissolve about 0.2 g accurately weighed in 10 ml of 10% acetic acid, add 1 drop of crystal violet IS and titrate with perchloric acid (0.1 mol/L) VS until the solution becomes bluish-green. Perform a blank determination and make any necessary correction. Each ml of perchloric acid (0.1 mol/L) VS is equivalent to 31.93 mg of $C_{20}H_{26}NO_2 \cdot C_4H_6O_6 \cdot H_2O$.

Category Adrenergic receptor stimulant.

Storage Preserve in hermetically sealed containers filled with inert gas, protected from light.

Preparation Noradrenaline Bitartrate Injection

Noradrenaline Bitartrate Injection

Noradrenaline Bitartrate Injection is a sterile, isotonic solution of Noradrenaline Bitartrate in Water for Injection, made isotonic by addition of sodium chloride. It contains not less than 90.0% and not more than 115.0% of the labelled amount of noradrenaline bitartrate ($C_8H_{11}NO_3 \cdot C_4H_6O_6 \cdot H_2O$). It may contain suitable stabilizers.

Description A clear, colourless or almost colourless liquid; deteriorated on exposure to light or air.

Identification (1) To 1 ml add 1 drop of ferric chloride TS, an emerald green colour is produced.

(2) Complies with test (2) for Identification described under Noradrenaline Bitartrate, using a quantity equivalent to about 1 mg of noradrenaline bitartrate.

pH value 2.5-4.5 (Appendix VI H).

Other requirements Complies with the general requirements for injections (Appendix I B).

Assay Carry out the method for high performance liquid chromatography (Appendix V D), using a column packed with octadecylsilane bonded silica gel and a mixture of 0.14% sodium heptanesulfonate solution-methanol (65:35), adjusting to pH 3.0 ± 0.1 with phosphoric acid, as the mobile phase. The flow rate is 1 ml per minute. The detection wavelength is 280 nm. The number of theoretical plate is not less than 3000, calculated with reference to the peak of noradrenaline bitartrate.

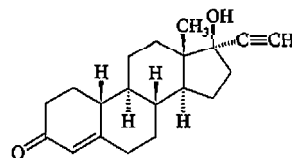
Procedure Transfer accurately a quantity of the substance being examined, equivalent to about 4 mg of noradrenaline bitartrate, in a 25 ml volumetric flask, dilute to volume with acetic acid solution (1→25), mix well. Inject 20 μ l of the resulting solution into the column and record the chromatogram. Repeat the operation, using a solution of 0.16 mg per ml prepared with noradrenaline bitartrate CRS instead of substance being examined, calculate the content of $C_8H_{11}NO_3 \cdot C_4H_6O_6 \cdot H_2O$ with respect to the peak area obtained in the chromatogram by the external standard method.

Category As described under Noradrenaline Bitartrate.

Strength (1) 1 ml : 2 mg (2) 1 ml : 5 mg
(3) 2 ml : 10 mg

Storage Preserve in well closed containers, protected from light and stored in a cool place.

Norethisterone



$C_{20}H_{26}O_2$ 298.43

[68-22-4]

Norethisterone is 17 β -hydroxy-19-nor-17 α -pregn-4-en-20-yn-3-one. It contains not less than 97.0% and not more than 102.0% of $C_{20}H_{26}O_2$, calculated on the dried basis.

Description A white or almost white crystalline powder; odourless, taste slightly bitter.

Soluble in chloroform; slightly soluble in ethanol; sparingly soluble in acetone; insoluble in water.

Melting range 202-208°C (Appendix VI C).

Specific optical rotation -22° to -28° , in a solution of 10 mg per ml in chloroform (Appendix VI E).

Identification (1) Dissolve about 10 mg in 1 ml of ethanol, add 5-6 drops of silver nitrate TS, a white precipitate is produced.

(2) The infrared absorption spectrum (Appendix IV A) is concordant with the reference spectrum of norethisterone (Appendix XVI).

Related substances Carry out the method as described under Assay. Dissolve a quantity of the substance being examined, with methanol to produce a solution of about 2 mg per ml as the test solution (1). Transfer accurately 3 ml of solution (1) into a 100 ml volumetric flask and dilute with methanol to volume, mix well as the reference solution (2). Inject 10 μ l of solution (2) into the column, adjust the attenuation so that the peak height of principal peak in the chromatogram is about 10% of full scale of the chart. Inject separately 10 μ l

each of the solution (1) and (2) into the column and record the chromatogram for twice of the retention time of the principal peak. The sum of the areas of all secondary peak is not greater than the area of the principal peak of solution (2) respectively.

Loss on drying When dried to constant weight at 105°C, loses not more than 0.5% of its weight (Appendix VIII L).

Assay Carry out the method for high performance liquid chromatography (Appendix V D) using a column packed with octadecylsilane bonded silica gel and a mixture of methanol-water (65:35) as the mobile phase. The detection wavelength is 244 nm. The number of the theoretical plates of the column is not less than 1500, calculated with reference to the peak of norethisterone. The resolution factors between the peaks of norethisterone and the internal standard, norethisterone and the impurity next to the principal peak comply with the related requirements.

Internal standard solution Dissolve 25 mg of progesterone, accurately weighed, with methanol in a 25 ml volumetric flask, and dilute to volume.

Procedure Dissolve 25 mg of norethisterone CRS, accurately weighed, in a 25 ml volumetric flask, with methanol and dilute to volume, mix well. Accurately transfer 2 ml of the above solution and 3 ml of the internal standard solution to a 10 ml volumetric flask, dilute to volume with methanol, and mix well. Inject 20 µl of the resulting solution into the column. Repeat the operation, using the substance being examined instead of norethisterone CRS. Calculate the content of $C_{20}H_{26}O_2$ with respect to the peak area obtained in the chromatogram by the internal standard method.

Category Progesteroide.

Storage Preserve in tightly closed containers, protected from light.

Preparation (1) Norethisterone Pills
(2) Norethisterone Tablets
(3) Compound Norethisterone Pellicles
(4) Compound Norethisterone Tablets

Norethisterone Pills

Norethisterone Pills contain not less than 90.0% and not more than 110.0% of the labelled amount of Norethisterone ($C_{20}H_{26}O_2$).

Description Creamy white to pale yellow dripping pills.

Identification The retention time of the principal peak of norethisterone in the substance being examined in the chromatogram obtained in the Assay is identical with that the principal peak of norethisterone CRS in the chromatogram of the reference solution.

Other requirements Comply with the general requirements for dripping pills (Appendix I H).

Assay Carry out the method for high performance liquid chromatography (Appendix V D), using a column packed with octadecylsilane bonded silica gel and a mixture of methanol-water (60:40) as the mobile phase. The detection wavelength is 240 nm. The number of the column is not less than 2500, calculated with reference to the peak of norethisterone. The resolution factor between the peaks of norethisterone and the internal standard complies with the related requirements.

Internal standard solution Dissolve 25 mg of hydrocortisone

acetate in 5 ml of methanol by heating in a hot water bath, cool to room temperature, and dilute to 100 ml with the mobile phase.

Procedure Transfer 10 mg of norethisterone CRS, accurately weighed, to a 50 ml volumetric flask, and a quantity of the mobile phase, dissolve by ultrasonating for several minutes. Dilute to volume with the mobile phase, and mix well. Accurately transfer 5 ml each of the above solution and the internal standard solution in a 25 ml volumetric flask and dilute to volume with the mobile phase, mix well. Inject 20 µl of the resulting solution into the column. Weigh accurately and powder 20 pills. Grind a quantity equivalent to about 10 mg of norethisterone. Transfer it to a 50 ml volumetric flask, add a quantity of the mobile phase, shake to dissolve in a hot water bath, cool to room temperature, dilute to volume with the mobile phase, mix well, and filter. Accurately transfer 5 ml each of the successive filtrate and the internal standard solution in a 25 ml volumetric flask. Dilute to volume with the mobile phase, and mix well. Inject 20 µl of the resulting solution into the column. Calculate the content of $C_{20}H_{26}O_2$ with respect to the peak area obtained in the chromatogram by the internal standard method.

Category As described under Norethisterone.

Strength 3 mg

Storage Preserve in tightly closed containers, protected from light.

Norethisterone Tablets

Norethisterone Tablets contain not less than 90.0% and not more than 110.0% of the labelled amount of Norethisterone ($C_{20}H_{26}O_2$).

Description Sugar coating or film-coated tablets with white or almost white core.

Identification (1) Dissolve a quantity of fine powder equivalent to about 10 mg of norethisterone in 1 ml of ethanol, centrifuge, the supernatant liquid complies with the test (1) for Identification described under norethisterone.

(2) Dissolve a quantity of fine powder in dehydrate ethanol to produce a solution of about 10 µg per ml and filter. The light absorption of the successive filtrate exhibits a maximum at 240 nm (Appendix IV A).

(3) The retention time of principal peak of the substance being examined is identical with that of principal peak of the reference solution in the chromatogram obtained in Assay.

Content uniformity Comply with the requirements (Appendix X E). Take 1 tablet into a 25 ml (for strength 0.625 mg) or 100 ml (for strength 2.5 mg) volumetric flask, add a quantity of mobile phase and ultrasonicate to make norethisterone dissolved, dilute with mobile phase to volume, mix well and centrifugate, take the supernate as the test solution Carry out the method as described under Assay, calculate the content of $C_{20}H_{26}O_2$ from each tablet. The limit of content uniformity is $\pm 20\%$.

Other requirements Comply with the general requirements for tablets (Appendix I A).

Assay Carry out the method for high performance liquid chromatography (Appendix V D), using a column packed with octadecylsilane bonded silica gel and a mixture of methanol-water (65:35) as the mobile phase. Detection Wavelength is 244 nm, and the number of theoretical plates of the column is not less than 1500, calculated with reference

to the peak of norethisterone. The resolution factor between the peaks of norethisterone and adjacent impurities complies with the related requirements.

Procedure Weigh accurately and powder 20 tablets removed the coat. To a quantity, weighed accurately, equivalent to about 1.25 mg of norethisterone, to a 50 ml volumetric flask, add a quantity of mobile phase and ultrasonicate to make norethisterone dissolved, cool to room temperature and dilute with mobile phase to volume, mix well and centrifugate, take the supernate as the test solution. Inject 20 μ l into the volume, record the chromatogram. Dissolve a quantity of norethisterone CRS, accurately weighed, in mobile phase to produce a solution of about 25 μ g per ml, repeat the operations instead of the test solution, calculate the content of $C_{20}H_{26}O_2$ with respect to the peak area obtained in the chromatogram by the external standard method.

Category As described under Norethisterone.

Strength (1) 0.625 mg (2) 2.5 mg

Storage Preserve in tightly closed containers, protected from light.

Compound Norethisterone Pellicles

Compound Norethisterone Pellicles contain 0.54-0.66 mg of norethisterone ($C_{20}H_{26}O_2$) and 31.5-38.5 μ g of ethinylestradiol ($C_{20}H_{24}O_2$) in each square.

Formula	Norethisterone	600 mg
	Ethinylestradiol	35 mg
	To make	1000 squares

Processing Disperse the active ingredients in a suitable solvent, apply evenly onto a piece of swellable paper and allow to dry.

Description Pellicles, swellable in water.

Identification The retention time of principal peak of the substance being examined is identical with that of principal peak of the reference solution in the chromatogram obtained in Assay.

Content uniformity Comply with the requirements (Appendix X E). Transfer 1 square to a 50 ml volumetric flask, add a quantity of dehydrated ethanol, break the pellicle with a glass rod. Heat in a hot water bath for 30 minutes with constant shaking to dissolve norethisterone, cool to room temperature, dilute to volume with dehydrated ethanol and mix well. Filter, and take the successive filtrate as the test solution. Carry out the method as described under Assay. Calculate the content of norethisterone ($C_{20}H_{26}O_2$).

Assay Carry out the method for high performance liquid chromatography (Appendix V D), using a column packed with octadecylsilane bonded silica gel and a mixture of acetonitrile-water (45:55) as the mobile phase. Detection Wavelength is 200 nm, and the number of theoretical plates of the column is not less than 3000, calculated with reference to the peak of norethisterone. The resolution factor between the peaks of norethisterone and ethinylestradiol complies with the related requirements.

Procedure Cut 8 squares into small pieces and transfer to a 100 ml volumetric flask. Add a quantity of dehydrated ethanol, in a hot water bath for 30 minutes with constant shaking to dissolve norethisterone and ethinylestradiol, cool

to room temperature, dilute to volume with dehydrated ethanol, mix well and filter, take the successive filtrate as the test solution. Inject 50 μ l into the column and record the chromatogram. Dissolve a quantity of norethisterone and ethinylestradiol CRS, accurately weighed, in 5 ml of acetonitrile to a 10 ml volumetric flask to produce a solution of about 60 μ g of norethisterone and 3.5 μ g of ethinylestradiol per ml, repeat the operations instead of the test solution, calculate the content of $C_{20}H_{26}O_2$ and $C_{20}H_{24}O_2$ with respect to the peak area obtained in the chromatogram by the external standard method.

Category Contraceptive.

Storage Preserve in tightly closed containers, protected from light.

Compound Norethisterone Tablets

Compound Norethisterone Tablets contain 0.54-0.66 mg of norethisterone ($C_{20}H_{26}O_2$) and 31.5-38.5 μ g of ethinylestradiol ($C_{20}H_{24}O_2$) in each tablet.

Formula	Norethisterone	600 mg
	Ethinylestradiol	35 mg
	To make	1000 tablets

Description Sugar coated tablets with white or almost white core.

Identification (1) Pulverize finely 2 tablets, add 5 ml of chloroform-methanol (9:1) and stir thoroughly, filter, evaporate the filtrate on a water bath to about 0.5 ml. Dissolve norethisterone CRS in chloroform-methanol (9:1) to produce a solution of 2.4 mg per ml. Dissolve ethinylestradiol CRS in chloroform-methanol (9:1) to produce a solution of 0.14 mg per ml. Carry out the method for thin-layer chromatography (Appendix V B), using silica gel G as the coating substance and a mixture of benzene-ethyl acetate (4:1) as the mobile phase. Apply separately to the plate 10 μ l each of the three solutions mentioned above. After developing and removal of the plate, dry it in air and spray with sulfuric acid-dehydrated ethanol (7:3), heat at 100°C for 5 minutes. The colour and position of the principal spots in the chromatogram obtained with the solution of substance being examined are identical with those in the chromatogram obtained with the other two solutions, respectively.

(2) The retention time of principal peak of the substance being examined is identical with that of principal peak of the reference solution in the chromatogram obtained in Assay. Test (1) and (2) may be used alternatively.

Content uniformity Comply with the requirements (Appendix X E). Take 1 tablet into a 10 ml volumetric flask, add 0.5 ml of water to make the tablet disintegrated, then add 5 ml of acetonitrile and ultrasonicate for 15 minutes to dissolve norethisterone and ethinylestradiol, dilute to volume with water, shake well and centrifugate, take the supernate as the test solution. Carry out the method as described under Assay, calculate the content of $C_{20}H_{26}O_2$. The limit of the content variation is $\pm 20\%$.

Dissolution Carry out the dissolution test (Appendix X C, method 3), using 200 ml of 0.5% lauryl sodium sulfate solution as the dissolution medium, adjust the rotational speed of the paddle to 100 rpm. Withdraw a quantity of the solution at 60 minutes and filter. Take the successive filtrate as the test solution. Dissolve about 12 mg of norethisterone

CRS, weighed accurately, with 10 ml of ethanol in a 200 ml volumetric flask and dilute to volume with the dissolution medium, mix well. Transfer accurately 5 ml of the solution into a 100 ml volumetric flask and dilute with the dissolution medium to volume, mix well as the reference solution. Carry out the method as described under Assay. Inject separately 20 μ l of the test solution and the reference solution into the column and record the chromatogram. Calculate the dissolution of $C_{20}H_{25}O_2$ from each tablet with respect to the peak area obtained in the chromatogram by the external standard method. Not less than 60% of the labelled amount is dissolved.

Other requirements Comply with the general requirements for tablets (Appendix I A).

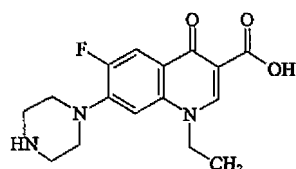
Assay Carry out the method for high performance liquid chromatography (Appendix V D), using a column packed with octadecylsilane bonded silica gel and a mixture of acetonitrile-water (45:55) as the mobile phase. Detection wavelength is 200 nm and the number of theoretical plates of the column is not less than 3000, calculated with reference to the peak of norethisterone. The resolution factor between the peaks of norethisterone and ethinylestradiol complies with the related requirements.

Procedure Weigh accurately and powder 20 tablets. To a quantity, weighed accurately, equivalent to about 3 mg of norethisterone, to a 50 ml volumetric flask, add 25 ml of acetonitrile and ultrasonicate to make norethisterone and ethinylestradiol dissolved, then dilute with water to volume, mix well and centrifugate, take the supernate as the test solution. Inject 50 μ l of the test solution into the column and record the chromatogram. Dissolve a quantity of norethisterone and ethinylestradiol CRS, accurately weighed, with 5 ml of acetonitrile in a 10 ml volumetric flask and dilute to produce a solution of about 60 μ g of norethisterone and 3.5 μ g of ethinylestradiol per ml as the reference solution. Repeat the operations using the reference solution instead of the test solution, calculate the content of $C_{20}H_{25}O_2$ and $C_{20}H_{24}O_2$ with respect to the peak area obtained in the chromatogram by the external standard method.

Category Contraceptive.

Storage Preserve in tightly closed containers, protected from light.

Norfloxacin



$C_{16}H_{18}FN_3O_3$ 319.34

[70458-96-7]

Norfloxacin is 1-ethyl-6-fluoro-1, 4-dihydro-4-oxo-7-(1-piperazinyl)-3-quinolinecarboxylic acid. It contains not less than 98.5% and not more than 102.0% of $C_{16}H_{18}FN_3O_3$, calculated on the dried basis.

Description An almost white to yellowish crystalline powder; odourless; taste, slightly bitter; hygroscopic in air; colour deepens gradually on exposure to light. Sparingly soluble in dimethylformamide; very slightly

soluble in water or ethanol; freely soluble in acetic acid, hydrochloric acid or sodium hydroxide solution.

Melting range 218-224°C (Appendix VI C).

Identification (1) Dissolve a quantity of the substance being examined and norfloxacin CRS with a mixture of chloroform-methanol (1:1) respectively to produce two solutions of 2.5 mg per ml each. Carry out the thin-layer chromatography (Appendix V B) using silica gel G as the coating substance and a mixture of chloroform-methanol-concentrated ammonia solution (15:10:3) as the mobile phase. Apply separately to the plate 10 μ l each of the solutions, after developing and removal of the plate, dry it in air. Examine under ultraviolet light (365 nm). The fluorescence and position of the principal spot in the chromatogram obtained with the substance being examined correspond to the principal spot obtained with reference solution.

(2) The retention time of principal peak of the substance being examined in the chromatogram obtained in the Assay is identical with that of norfloxacin CRS.

Test (1) and (2) may be used alternatively.

Clarity of solution To 5 portions each of 0.5 g add 10 ml of sodium hydroxide TS respectively, the solutions are clear and colourless; Any opalescence produced is not more pronounced than that of reference suspension II (Appendix IX B).

Related substances Carry out the method as described under assay. Dissolve a quantity of the substance being examined with 0.1 mol/L hydrochloric acid solution (each 12.5 mg add 1 ml), and dilute with the mobile phase as described under Assay to produce solutions of 1 μ g per ml (solution 1) and 0.1 mg per ml (solution 2). Inject 20 μ l of solution (1) into the column. Adjust the attenuation so that the principal peak height in the chromatogram is 20%-25% of the full scale of the chart. And then inject separately 20 μ l each of solution (1) and (2) into the column, and record the chromatogram for 2.5 times of the retention time of the principal peak. The sum of the areas of all peaks other than the principal peak in the chromatogram obtained with solution (2) is not greater than the area of the principal peak in the chromatogram obtained with solution (1).

Loss on drying When dried to constant weight at 105°C, loses not more than 2.0% of its weight (Appendix VIII L).

Residue on ignition Not more than 0.2% (Appendix VIII N), using 1.0 g and a platinum crucible.

Heavy metals Carry out the limit test for heavy metals (Appendix VIII H, method 2), using the residue obtained in g i : r n . 02 .

Assay Carry out the method for high performance liquid chromatography (Appendix V D), using a column packed with octadecylsilane bonded silica gel and a mixture of 0.025 mol/L phosphoric acid solution (adjust pH to 3.1 \pm 0.1 with triethylamine)-acetonitrile (87:13) as the mobile phase. The flow rate is 0.8 ml per minute. The detection wavelength is 278 nm. The number of the theoretical plates of the column is not less than 2000, calculated with reference to the peak of norfloxacin. The resolution factor between norfloxacin and adjacent peak of the impurities complies with the related requirements.

Procedure Dissolve about 25 mg of the substance being examined, accurately weighed, in a 100 ml volumetric flask with 2 ml of 0.1 mol/L hydrochloric acid solution. Dilute to volume with water, and mix well. Transfer 5 ml, accurately measured, to a 50 ml volumetric flask and dilute to volume with the mobile phase, mix well. Inject 20 μ l of the resulting solution into the column. Repeat the operation,

using about 25 mg of norfloxacin CRS instead of the substance being examined. Calculate the content of $C_{16}H_{18}FN_3O_3$ with respect to the peak area obtained in the chromatogram by the external standard method.

Category Antibiotic.

Storage Preserve in tightly closed containers, protected from light, stored in a dry place.

Preparation (1) Norfloxacin Capsules
(2) Norfloxacin Cream
(3) Norfloxacin Eye Drops
(4) Norfloxacin Ointment

Norfloxacin Capsules

Norfloxacin Capsules contain not less than 90.0% and not more than 110.0% of the labelled amount of norfloxacin ($C_{16}H_{18}FN_3O_3$).

Description Capsules containing white to pale yellow powder.

Identification Complies with the test for identification described under norfloxacin.

Dissolution Carry out the dissolution test (Appendix X C, method 2), using 1000 ml of hydrochloric acid solution (9→1000) as the dissolution medium, adjust the rotational speed of the paddle to 50 rpm. Withdraw 10 ml of the solution at 45 minutes and filter. Transfer accurately 5 ml of the successive filtrate, to a 100 ml volumetric flask, dilute with the dissolution medium to volume and mix well. Measure the absorbance of the resulting solution at 280 nm (Appendix IV A); dissolve an accurately weighed quantity of theophylline CRS in hydrochloric acid solution (9→1000) to produce a solution of 5 µg per ml, measure the absorbance in the same manner. Calculate the dissolution of $C_{16}H_{18}FN_3O_3$ from each capsule. Not less than 75% of the labelled amount is dissolved.

Other requirements Comply with the general requirements for capsules (Appendix I E).

Assay Transfer an accurately weighed quantity of the mixed contents of capsules obtained in the test for weight variation of contents, equivalent to about 125 mg of norfloxacin in a 500 ml volumetric flask, add 10 ml of 0.1 mol/L hydrochloric acid to dissolve, and dilute to volume with water, mix well and filter. Dilute 5 ml of the successive filtrate, accurately measure, to volume in a 50 ml of volumetric flask, mix well. Complete the Assay as described under Norfloxacin, using 20 µl of the resulting solution.

Category As described under Norfloxacin.

Strength 0.1 g

Storage Preserve in tightly closed containers, protected from light.

Norfloxacin Eye Drops

Norfloxacin Eye Drops contain not less than 90.0% and not more than 110.0% of labelled amount of norfloxacin ($C_{16}H_{18}FN_3O_3$).

Description A colourless and clear solution.

Identification (1) The retention time of principal peak of the substance being examined in the chromatogram obtained in the Assay is identical with that of norfloxacin CRS.

(2) The light absorption of the solution of 5 µg per ml in phosphate buffer (pH 7.4) exhibits the maximum at 271 nm (Appendix IV A).

pH value 5.0-5.6 (Appendix VI H).

Other requirements Comply with the general requirements for eye preparations (Appendix I G).

Assay Dilute a quantity, accurately measured, with mobile phase to produce a solution of about 25 µg per ml. Complete the Assay as described under Norfloxacin, using the resulting solution.

Category As described under Norfloxacin.

Strength 8 ml:24 mg

Storage Preserve in tightly closed containers and protected from light.

Norfloxacin Cream

Norfloxacin Cream contains not less than 90.0% and not more than 110.0% of labelled amount of norfloxacin ($C_{16}H_{18}FN_3O_3$).

Description A creamy yellow cream.

Identification (1) Evaporate 5 ml of the solution obtained in Assay to dryness on water bath. To the residue add 50 mg of malonic acid and 1 ml of acetic anhydride and heat on 80-90°C water bath for a few minutes, a reddish brown colour is produced.

(2) The light absorption of a solution containing 5 µg per ml in 0.4% sodium hydroxide solution exhibits the maximum at 273 nm (Appendix IV A).

Other requirements Comply with the general requirements for cream (Appendix I F).

Assay Mix well a quantity equivalent to about 4 mg of norfloxacin accurately weighed with 15 ml of chloroform in a separator. Extract with 25 ml, 20 ml, 20 ml and 10 ml of 0.1% sodium hydroxide solution saturated with sodium chloride separately. Transfer the extracts to 100 ml volumetric flask, dilute with sufficient 0.1% sodium hydroxide solution to volume, shake well and filter. Measure accurately 10 ml of the successive filtrate and add 0.4% sodium hydroxide solution to produce a solution of 5 µg per ml. Measure the absorbance of the resulting solution at 273 nm. Repeat the operation using the solution of 5 µg of norfloxacin CRS per ml in 0.4% sodium hydroxide solution instead of the solution of the substance being examined and calculate the content of $C_{16}H_{18}FN_3O_3$ accordingly.

Category As described under norfloxacin.

Strength (1) 10 g : 0.1 g (2) 250 g : 2.5 g

Storage Preserve in tightly closed container, stored in a dry place and protected from light.

Norfloxacin Ointment

Norfloxacin Ointment contains not less than 90.0% and not more than 110.0% of labelled amount of norfloxacin ($C_{16}H_{18}FN_3O_3$).

Description A yellow ointment.

Identification (1) Evaporate 5 ml of the solution obtained in Assay to dryness on water bath. To the residue add 50 mg of malonic acid and 1 ml of acetic anhydride and heat on 80–90°C water bath for a few minutes, a reddish brown colour is produced.

(2) The light absorption of a solution containing 5 µg per ml in 0.4% sodium hydroxide solution exhibits the maximum at 273 nm (Appendix IV A).

Other requirements Comply with the general requirements for ointment (Appendix I F).

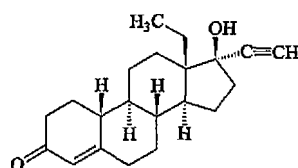
Assay Mix well a quantity equivalent to about 4 mg of norfloxacin accurately weighed with 15 ml of chloroform in a separator, extract with 25 ml, 20 ml, 20 ml and 10 ml of 0.1% sodium hydroxide solution saturated with sodium chloride separately. Transfer the extracts to 100 ml volumetric flask, dilute with sufficient 0.1% sodium hydroxide solution to volume, shake well and filter. Measure accurately 10 ml of the successive filtrate and add 0.4% sodium hydroxide solution to produce a solution of 5 µg per ml. Measure the absorbance of the resulting solution at 273 nm. Repeat the operation using the solution of 5 µg of norfloxacin CRS per ml in 0.4% sodium hydroxide solution instead of the solution of the substance being examined and calculate the content of $C_{16}H_{13}FN_3O_3$ accordingly.

Category As described under norfloxacin.

Strength (1) 10 g : 0.1 g (2) 250 g : 2.5 g

Storage Preserve in tightly closed container, stored in a dry place and protected from light.

Norgestrel



$C_{21}H_{28}O_2$ 312.45

[6533-00-2]

Norgestrel is 13-ethyl-17 α -hydroxy-18, 19-dinorpregn-4-en-20-yn-3-one. It contains not less than 97.0% and not more than 103.0% of $C_{21}H_{28}O_2$.

Description A white or almost white crystalline powder; odourless; tasteless. Soluble in chloroform; slightly soluble in methanol; insoluble in water.

Melting range 204–212°C (Appendix VI C), melts within a range of 5°C.

Identification (1) The retention time of principal peak of the substance being examined is identical with that of principal peak of the reference solution in the chromatogram obtained in Assay.

(2) The infrared absorption spectrum (Appendix IV C) is concordant with the reference spectrum of norgestrel (Appendix XVI).

Ethynyl group Dissolve about 0.2 g, accurately weighed, in a 50 ml beaker with 20 ml of tetrahydrofuran, add 10 ml of 5% silver nitrate solution. Carry out the method for potentiometric titration (Appendix VII A). The indicator electrode is a glass electrode and the reference electrode is a saturated calomel electrode, using a saturated potassium

nitrate solution as the salt bridge. Titrate with sodium hydroxide (0.1 mol/L) VS. Each ml of sodium hydroxide (0.1 mol/L) VS is equivalent to 2.503 mg of $-C\equiv CH$. The content of ethynyl group is not less than 7.8% and not more than 8.2%.

Related substances Carry out the method as described under Assay. Dissolve a quantity with the mobile phase to produce a solution of about 75 µg per ml as solution 1, and dilute 2 ml of solution 1 to volume in a 100 ml volumetric flask with the mobile phase as solution 2. Inject 20 µl of solution 2 into the column. Adjust the attenuation so that the principal peak height in the chromatogram is 20% full scale of the chart. And then, inject 20 µl each of solution 1 and 2 into the column, and record the chromatogram for twice the retention time of the principal peak. The sum of the area of all peaks other than the principal peak obtained with solution 1 is not greater than the area of the principal peak in the chromatogram obtained with solution 2.

Assay Carry out the method for high performance liquid chromatography (Appendix V D), using a column packed with octadecylsilane bonded silica gel and a mixture of acetonitrile-water (70:30) as the mobile phase. Detection wavelength is 240 nm and the number of the theoretical plates of the column is not less than 2000, calculated with reference to the peak of norgestrel. The resolution factor between the peaks of norgestrel and the internal standard complies with the related requirements.

Internal standard solution Dissolve a quantity of megestrol acetate in acetonitrile to produce a solution of 1 mg per ml, mix well.

Procedure Dissolve 7.5 mg of norgestrel CRS, accurately weighed, in a 50 ml volumetric flask with the mobile phase, and dilute to column, mix well. Accurately measure 2 ml each of the above solution and the internal standard solution, mix well. Inject 20 µl of the resulting solution into the column. Repeat the operation, using the substance being examined instead of norgestrel CRS. Calculate the content of $C_{21}H_{28}O_2$ with respect to the peak area obtained in the chromatogram by internal standard method.

Category Progesteroide.

Storage Preserve in tightly closed containers, protected from light.

Preparation (1) Compound Norgestrel Pills
(2) Compound Norgestrel Tablets
(3) Norgestrel and Quinestrol Tablets

Norgestrel and Quinestrol Tablets

Norgestrel and Quinestrol Tablets contain not less than 90.0% and not more than 115.0% of the labelled amount of norgestrel ($C_{21}H_{28}O_2$), and not less than 94.0% and not more than 115.0% of that of quinestrol ($C_{25}H_{32}O_2$).

Formula	Norgestrel	12 g
	Quinestrol	3 g

To make	1000 tablets
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Description Sugar or film coated tablets with white or almost white core.

Identification Powder and mix thoroughly 1 tablet with 5 ml of chloroform, filter, use the filtrate as the test solution. Mix the chloroform solution containing 1 mg each of

norgestrel CRS and quinestrol CRS as the reference solution. Carry out the method for thin-layer chromatography (Appendix V B), using silica gel G as the coating substance and chloroform-methanol (9:1) as the mobile phase. Apply separately to the same plate 30 μ l each of the above two solutions. After developing and removal of the plate, dry it in air, spray with sulfuric acid-dehydrated ethanol (1:1), then heat at 105°C. The principal spots in the chromatogram obtained with the two solutions correspond in colour and position with respect to both ingredients.

Content uniformity Complies with the requirements for content uniformity (Appendix X E). Triturate 1 tablet, complete the operation as described under Assay from the beginning at the word "in a 50 ml volumetric flask".

Other requirements Comply with the general requirements for tablets (Appendix I A).

Assay Carry out the method for high performance liquid chromatography (Appendix V D), using a column packed with octadecylsilane bonded silica gel and a mixture of acetonitrile-water (80:20) as the mobile phase. Detection wavelength is 220 nm. The number of the theoretical is not less than 3000, calculated with reference to the peak of norgestrel. The resolution factors between the peaks of each component and the internal standard comply with the related requirements.

Internal standard solution Dissolve a quantity of progesterone caproate with acetonitrile to produce a solution of about 0.12 mg per ml.

Procedure Accurately weigh 20 tablets and powder. Accurately weigh a quantity, equivalent to about 12 mg of norgestrel, in a 50 ml volumetric flask, add a quantity of the mobile phase dissolve by ultrasonic generator, cool, and dilute to volume with the mobile phase, mix well, filter. Accurately measure 1 ml each of the successive filtrate and the internal standard solution, and mixture well. Inject 20 μ l of the resulting solution into the column. Repeat the operation, using a solution contained 0.12 mg of norgestrol and 0.06 mg of quinestrol prepared with norgestrol CRS and quinestrol CRS. Calculate the content of $C_{21}H_{28}O_2$ and $C_{25}H_{32}O_2$ respectively.

Category Progesteroïd.

Storage Preserved in tightly closed containers, protected from light.

Compound Norgestrel Pills

Compound Norgestrel pills contain not less than 0.270 mg and not more than 0.345 mg of norgestrel ($C_{21}H_{28}O_2$) and not less than 27.0 μ g and not more than 34.5 μ g of ethinylestradiol ($C_{20}H_{24}O_2$) in each pill.

Formula	Norgestrel	300 mg
	Ethinylestradiol	30 mg
to make		1000 pills

Description Sugar coated pills.

Identification (1) Remove the sugar coating of 1 pill, allow to disintegrate by warming with about 2 ml of ethanol and cool. Add 2 ml of alkaline trinitrophenol solution (mix 10 ml each of a 0.6% solution of trinitrophenol in ethanol, 7% sodium hydroxide solution and dilute ethanol immediately before use), and allow to stand for about 30 minutes. A

brownish-yellow colour is produced.

(2) Remove the sugar coating of 10 pills, allow to disintegrate by warming with 4 ml of water in a small beaker. Cool and transfer into a separator. Add 20 ml of ether, shake and allow to separate. Discard the water layer, wash the ethereal layer with water and filter through a funnel packed with anhydrous sodium sulfate and a wade of cotton wool. Evaporate the ether extract to dryness at low temperature over a water bath. Dissolve the residue in 0.3 ml of chloroform (solution 1). Dissolve a quantity of ethinylestradiol in chloroform to produce a solution of 1 mg per ml (solution 2). Carry out the method for thin-layer chromatograph (Appendix V B), using silica gel G as the coating substance and a mixture of chloroform-methanol (9:1) as the mobile phase. Apply separately to the plate 30 μ l each of the two solutions. After developing and removal of the plate, dry it in air and spray with sulfuric acid-dehydrated ethanol (1:1), then heat at 105°C for 10 minutes. The colour and position of the principal spots in the chromatogram obtained with the two solutions are identical.

Other requirements Comply with the general requirements for pills (Appendix I H).

Assay Remove the sugar coating of 10 pills, allow to disintegrate by warming with 12 ml of ethanol in a 20 ml volumetric flask. Cool to room temperature, dilute with ethanol to volume and mix well. Filter and use the successive filtrate as the test solution. Dissolve a quantity of norgestrel and ethinylestradiol CRS in acetonitrile to produce a solution of about 0.15 mg of norgestrel and 15 μ g of ethinylestradiol per ml as the reference solution.

Norgestrel Transfer separately 1 ml each of the test solution and reference solution, accurately measured, into two conical flasks with stopper. To each flask add exactly 3 ml of ethanol and 4 ml of alkaline trinitrophenol solution, allow to stand in the dark for 80 minutes and measure the absorbances at 490 nm (Appendix IV A). Calculate the content of $C_{21}H_{28}O_2$.

Ethinylestradiol Transfer separately 2 ml each of the test solution and reference solution, accurately measured, into two conical flasks with stopper, cool in an ice bath for 30 seconds. To each flask add exactly 8 ml of sulfuric acid-ethanol (4:1) with shaking, cool again in the ice bath for 30 seconds and then allow to stand at room temperature for 20 minutes, measure the absorbances at 530 nm (Appendix IV A). Calculate the content of $C_{20}H_{24}O_2$.

Category Contraceptive.

Storage Preserve in tightly closed containers, protected from light.

Compound Norgestrel Tablets

Compound Norgestrel Tablets contain 0.270-0.345 mg of norgestrel ($C_{21}H_{28}O_2$) and 27.0-34.5 μ g of ethinylestradiol ($C_{20}H_{24}O_2$) in each tablets.

Formula	Norgestrel	300 mg
	Ethinylestradiol	30 mg
To make		1000 tablets

Description Sugar or film coated tablets with white or almost white core.

Identification Pulverize 1 tablet, add 5 ml of chloroform and stir thoroughly, filter, evaporate 1 ml of the filtrate on a water bath to a volume of about 50 μ l as the test solution.

Evaporate 8 ml of the reference preparation obtained in the Assay to dryness on a water bath, cool, dissolve the residue in 1 ml of chloroform as the reference solution. Carry out the method for thin-layer chromatography (Appendix V B), using silica gel G as the coating substance and a mixture of chloroform-methanol (9:1) as the mobile phase. Apply separately to the plate 50 μ l each of the two solutions mentioned above. After developing and removal of the plate, dry it in air and spray with sulfuric acid-dehydrated ethanol (1:1), then heat at 105°C. The colour and position of the principal spots in the chromatogram obtained with the test solution correspond to the principal spots obtained with the reference solution.

Other requirements Comply with the general requirements for tablets (Appendix I A).

Assay Carry out the method for high performance liquid chromatography (Appendix V D), using a column packed with octadecylsilane bonded silica gel and a mixture of acetonitrile-water (60:40) as the mobile phase. Detection wavelength is 220 nm and the number of the theoretical plates of the column is not less than 3000, calculated with reference to the peak of norgestrel. The resolution factor between the peaks of each component and the internal standard complies with the related requirements.

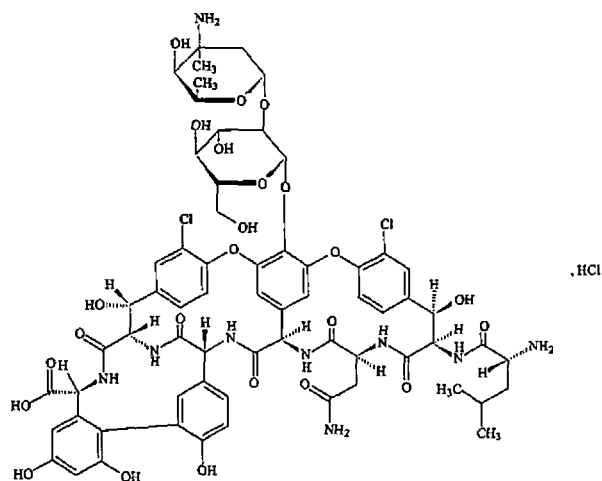
Internal standard solution Dissolve a quantity of megestrol acetate with acetonitrile to produce a solution of 1 mg per ml.

Procedure Weigh accurately and powder finely 20 tablets. Weigh accurately a quantity equivalent to about 1.5 mg of norgestrel to a 10 ml volumetric flask, adding 1 ml of internal standard solution and a quantity of the mobile phase and dissolving by ultrasonic generator, cool to room temperature, dilute to volume with the mobile phase, mix well, filter. Inject 20 μ l of the successive filtrate into the column. Prepare a solution of 1.5 mg of norgestrel CRS and 0.15 mg of ethinylestradiol CRS per ml in acetonitrile. Measure accurately 1 ml each of the solution and the internal standard solution to a 10 ml volumetric flask, dilute with the mobile phase, mix well. Inject 20 μ l of the resulting solution into the column. Calculate the content of $C_{21}H_{28}O_2$ and $C_{20}H_{24}O_2$.

Category Contraceptive.

Storage Preserve in tightly closed containers, protected from light.

Norvancomycin Hydrochloride



Norvancomycin hydrochloride is $(S_a)-(3S, 6R, 7R, 22R, 23S, 26S, 36R, 38aR)-44-[[2-O-(3-amino-2,3,6-trideoxy-3-C-methyl-\alpha-L-lyxo-hexopyranosyl)-\beta-D-glu-copyranosyl]oxy]-3-(carbamoylmethyl)-10,19-dichloro-2,3,4,5,6,7,23,24,25,26,36,37,38,38a-tetradecahydro-7,22,28,30,32-pentahydroxy-6-[(2R)-4-methyl-2-(amino) valer-amido]-2,5,24,38,39-pentaoxo-22H-8, 11:18,21-dietheno-23,36-(iminomethano)-13,16:31,35-dimetheno-1H,16H-[1,6,9] oxadiazacyclohexadecino [4,5-*m*] [10,2,16]-benzoxadiazacyclotetracosine-26-carboxylic acid, monohydrochloride. It contains not less than 88.0% of $C_{65}H_{73}Cl_2N_9O_{24}$, calculated on the anhydrous basis.$

Description A white to pale brown powder; odourless; taste bitter. Freely soluble in water; slightly soluble in methanol; insoluble in acetone, butanol or ether; precipitated by heavy metal salts in solution.

Identification (1) The retention time of principal peak of the substance being examined in the chromatogram obtained in the Assay is identical with that of Norvancomycin CRS in the chromatogram.

(2) The light absorption of a solution of 0.1 mg per ml in 0.1 mol/L hydrochloric acid solution exhibits a maximum at 282 nm (Appendix IV A).

(3) The aqueous solution yields the reactions characteristic of chlorides (Appendix III).

Acidity An aqueous solution of 50 mg per ml, pH 2.8-4.5 (Appendix VI H).

Clarity of solution To 5 portions add water respectively to produce solutions of 60 mg per ml, the solutions are clear; any opalescence produced is not more pronounced than that of reference suspension I (Appendix IX B).

Related substances Carry out the method as described under Assay. Dissolve a quantity in water to produce solution containing (1) 2 mg per ml and (2) 20 μ g per ml, respectively. Inject 20 μ l of solution (2) into the column. Adjust the attenuation so that the principal peak height in the chromatogram is about 20% of full scale of the chart. Inject separately 20 μ l each of solution (1) and (2) into the column and record the chromatograms. The area of any impurity peak in the chromatogram obtained with the solution (1) is not greater than that of the principal peak in the chromatogram obtained with solution (2) (not more than 4%).

Water Not more than 7.0% (Appendix VIII M, method 1 A).

Residue on ignition Not more than 1.0% (Appendix VIII N).

Pyrogens Complies with the test for pyrogens (Appendix IX D), using a solution of 20000 Units per ml in Sterile Water for Injection, inject 0.5 ml per kg of rabbit's weight.

Sterility Complies with the test for sterility (Appendix XI H, membrane filtration method), dissolving each portion and transfer to at least 500 ml of 0.9% sterile sodium chloride solution.

Assay Carry out the method for high performance liquid chromatography (Appendix V D) using a column packed with octadecylsilane bonded silica gel, a mixture of Triethylamine buffer (Mix 6 ml of triethylamine and 2000 ml of water, and adjust with phosphoric acid to pH 3.2), acetonitrile, and tetrahydrofuran (96:3:1) as the mobile phase A, and a mixture of Triethylamine buffer, acetonitrile, and tetrahydrofuran (20:20:1) as the mobile

phase B. The flow rate is 1.0 ml per minute and elute linear gradient. Detection wavelength is 280 nm. Changing the acetonitrile proportion in mobile phase A to obtain a retention time of 18 minutes to 22 minutes for the main norvancomycin peak, and the number of the theoretical plates of the column is not less than 1500, calculated with reference to the main peak of norvancomycin.

Time (min)	mobile phase A (percent V/V)	mobile phase B (percent V/V)
0	100	0
23	100	0
38	-	-
40	0	100
41	100	0
50	100	0

Procedure Dissolve a quantity of the substance being examined, accurately weighed, in water to produce a solution of 1 mg per ml. Inject 20 μ l of the above solution into the column. Repeat the operation, using norvancomycin CRS instead of the substance being examined. Calculate the content of $C_{65}H_{73}Cl_2N_9O_{24}$. 1000 Norvancomycin Units is equivalent to 1 mg $C_{65}H_{73}Cl_2N_9O_{24}$ with respect the peak area obtained in the chromatogram by external standard method.

Category Peptide Antibiotic.

Storage Preserve in hermetically sealed containers stored in a cool and dark place.

Preparation Norvancomycin Hydrochloride for Injection

Norvancomycin Hydrochloride for Injection

Norvancomycin Hydrochloride for injection is a sterile powder or lyophilized preparation of norvancomycin hydrochloride. It contains not less than 88.0% of norvancomycin ($C_{65}H_{73}Cl_2N_9O_{24}$), calculated on the anhydrous basis. It contains not less than 90.0% and not more than 110.0% of the labelled amount of norvancomycin, calculated with reference to the average weight of contents.

Description A white to pale brown powder or lyophilized mass.

Identification Comply with the tests for Identification described under Norvancomycin Hydrochloride.

Clarity of solution To each of 5 containers add water to produce solutions of 50 mg per ml, the solutions are clear; any opalescence produced is not more pronounced than that of reference suspension I (Appendix IX B).

Water Not more than 7.0% (Appendix VIII M, method 1).

Acidity, Related substances, Residue on ignition, Pyrogens, Sterility Comply with the corresponding requirements described under Norvancomycin Hydrochloride.

Other requirements Comply with the general requirements for injections (Appendix I B) except that the weight variation of contents is not greater than $\pm 7\%$.

Assay Carry out the method described under Assay of Norvancomycin Hydrochloride, using an accurately weighed quantity of the mixed contents obtained from the test for

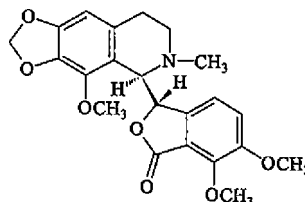
weight variation of contents.

Category As described under Norvancomycin hydrochloride.

Strength 0.4 g (400000 norvancomycin Units, calculated as $C_{65}H_{73}Cl_2NaO_{24}$)

Storage Preserve in tightly closed containers, stored in a cool and dark place.

Noscapine



$C_{22}H_{23}NO_7$ 413.43

[128-62-1]

Noscapine is 6,7-dimethoxy-3-(5,6,7,8-tetrahydro-4-methoxy-6-methyl-1,3-dioxolo[4,5-g]isoquinolin-5-yl), [*S*-(*R**, *S**)]-(3*H*)-isobenzofuranone. It contains not less than 99.0% of $C_{22}H_{23}NO_7$, calculated on the dried basis.

Description A white crystalline powder or prismatic crystals with lustrous; odourless.

Freely soluble in chloroform; sparingly soluble in benzene; slightly soluble in ethanol or ether; practically insoluble in water.

Melting point 174-177°C (Appendix VI C).

Specific optical rotation +42° to +48°, in a solution of 20 mg per ml in 0.1 mol/L hydrochloric acid solution (Appendix VI E).

Identification (1) Dissolve 1 mg in 1 drop of sulfuric acid, a yellow green colour is produced; the colour changes to red on warming and turns to violet finally.

(2) To about 1 mg add 1 drop of molybdenum sulfuric acid TS, a deep green colour is produced, and changes gradually to purple-red on warming.

(3) The infrared absorption spectrum (Appendix IV C) is concordant with the reference spectrum of noscapine (Appendix XVI).

Clarity and colour of solution in acetone A solution of 0.2 g in 10 ml of acetone is clear and colourless; any colour produced is not more intense than that of reference solution Y₂ (Appendix IX A, method 1).

Related substances Carry out the method for thin-layer chromatography (Appendix V B), using silica gel G as the coating substance and a mixture of acetone-toluene-ethanol-concentrated ammonia solution (20:20:3:1) as the mobile phase. Apply separately to the plate 10 μ l each of two solutions of the substance being examined in acetone containing (1) 25 mg per ml, (2) 0.125 mg per ml. After developing and removal of the plate, dry it in air and spray with dilute potassium iodobismuthate TS. Any spot, other than the principal spot in the chromatogram, obtained with solution (1) is not more intense than the principal spot obtained with solution (2).

Loss on drying When dried to constant weight at 105°C, loses not more than 1.0% of its weight (Appendix VIII L).

Residue on ignition Not more than 0.1% (Appendix VIII

N).

Assay Dissolve about 0.3 g, accurately weighed, in 10 ml of glacial acetic acid, add 1 drop of crystal violet IS, titrate with perchloric acid (0.1 mol/L) VS until the colour changes from pink to blue. Each ml of perchloric acid (0.1 mol/L) VS is equivalent to 41.34 mg of $C_{22}H_{23}NO_7$.

Category Antitussive.

Storage Preserve in tightly closed containers, protected from light.

Preparation Noscapine Tablets

Noscapine Tablets

Noscapine Tablets contain not less than 93.0% and not more than 107.0% of the labelled amount of noscapine ($C_{22}H_{23}NO_7$).

Description Sugar coated tablets with white core.

Identification To a quantity of the powdered tablets equivalent to about 20 mg of noscapine add 10 ml of chloroform. Stir to dissolve the noscapine and filter, evaporate the filtrate on a water bath to dryness. The residue complies with tests (1) and (2) for Identification described under Noscapine.

Content uniformity Comply with the requirements for content uniformity (Appendix X E). Triturate 1 tablet with a quantity of ethanol and transfer to a 50 ml volumetric flask, shake thoroughly to dissolve the noscapine. Dilute with ethanol to volume, mix well and filter. Transfer accurately 5 ml of the successive filtrate into a 25 ml volumetric flask, dilute with ethanol to volume and mix well, use as the test solution. Dissolve a quantity of noscapine CRS in ethanol, accurately measured, to produce the reference solution of 40 µg per ml. Measure the absorbance of the test and reference solution at 310 nm (Appendix IV A). Calculate the content of $C_{22}H_{23}NO_7$ in each tablet.

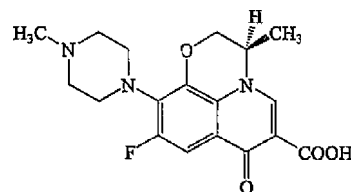
Other requirements Comply with the general requirements for tablets (Appendix I A).

Assay Weigh accurately and powder 30 tablets with sugar coating removed. To a quantity, accurately weighed, of the powdered tablets equivalent to about 0.1 g of noscapine add 20 ml of chloroform, shake to dissolve noscapine and filter. Wash the container and filter with 5 ml each of chloroform for 8 times. Combine the filtrate and the washings, add 10 ml of glacial acetic acid and 1 drop of crystal violet IS. Titrate with perchloric acid (0.05 mol/L) VS until the colour turns to pure blue. Perform a blank determination and make any necessary correction. Each ml of perchloric acid (0.05 mol/L) VS is equivalent to 20.67 mg of $C_{22}H_{23}NO_7$.

Category, Storage As described under Noscapine.

Strength 10 mg

Ofloxacin



$C_{18}H_{20}FN_3O_4$ 361.38

Ofloxacin is (±)-9-fluoro-2,3-dihydro-3-methyl-10-(4-methyl-1-piperazinyl)-7-oxo-7H-pyrido[1,2,3-de]-1,4-benzoxazine-6-carboxylic acid. It contains not less than 98.5% of $C_{18}H_{20}FN_3O_4$, calculated on the dried basis.

Description A white to slightly yellow crystalline powder; odourless; taste, bitter; colour deepens gradually on exposure to light.

Sparingly soluble in chloroform; slightly soluble in methanol; freely soluble in glacial acetic acid; sparingly soluble in dilute acid solution or 0.1 mol/L sodium hydroxide solution.

Specific optical rotation -1° to 1° , in a solution of 10 mg per ml in chloroform (Appendix VI E).

Identification (1) Dissolve an accurately weighed quantity in 0.1 mol/L hydrochloric acid solution to produce a solution of 0.12 mg per ml as the test solution. Prepare the reference solution using ofloxacin CRS instead of the substance being examined in the same manner. Carry out the method for high performance liquid chromatography as described under the Related substances. The retention time of the principal peak of the substance being examined in the chromatogram is identical with that of ofloxacin CRS in the chromatogram.

(2) The infrared absorption spectrum (Appendix IV C) is concordant with the reference spectrum of ofloxacin (Appendix XVI).

Clarity of solution Dissolve 0.50 g in 10 ml of sodium hydroxide TS, the solution is clear; an opalescence produced is not more pronounced than that of reference suspension II (Appendix IX B).

Light absorption Dissolve 0.1 g in 10 ml of sodium hydroxide TS, the absorbance at 450 nm (Appendix IV B) is not more than 0.25.

Related substances Carry out the method for high performance liquid chromatography (Appendix V D), using a column packed with octadecylsilane bonded silica gel and a mixture of ammonium acetate solution (dissolve 4.0 g of ammonium acetate and 7.0 g of sodium perchlorate in 1300 ml of water, mix well, and adjust pH to 2.2 with phosphate acid)-acetonitrile (85 : 15) as the mobile phase, detection wavelength is 294 nm. Dissolve a quantity of ofloxacin in 0.1 mol/L hydrochloric acid solution to produce a solution of 1 mg per ml, lighted under ultraviolet light (254 nm) for four hours. Inject 10 µl of the solution into the column, the number of the theoretical plate of the column is not less than 5000, calculated with reference to the peak of ofloxacin. The resolution factor between the peak of ofloxacin and the adjacent impurity in front of the peak of ofloxacin complies with the related requirements.

Procedure Dissolve an accurately weighed quantity in 0.1 mol/L hydrochloric acid solution to produce a solution of 1.2

mg per ml as the test solution. Accurately measure a quantity of above solution in 0.1 mol/L hydrochloric acid solution to produce a solution of 2.4 µg per ml as the reference solution. Inject 10 µl of the reference solution into the column. Adjust the attenuation so that the principal peak height in the chromatogram is 20%-25% of the full scale of the chart. Inject 10 µl of the test solution and the reference solution separately into the column, and record the chromatogram for 2.5 times the retention time of the principal peak. The area of any peak other than the principal peak is not greater than the peak area of ofloxacin in the reference solution (0.2%). The sum of the areas of all the peaks other than the principal peak (disregard any peak with an area less than 0.05 times of the peak area of ofloxacin in the reference solution) is not greater than 2.5 times of the peak area of ofloxacin in the reference solution (0.5%).

Loss on drying When dried to constant weight at 105°C, loses not more than 0.5% of its weight (Appendix VIII L).

Residue on ignition Not more than 0.2% (Appendix VIII N), using 1.0 g in a platinum crucible.

Heavy metals Carry out the limit test for heavy metals (Appendix VIII H, method 2), using the residue obtained in the test for Residue on ignition; not more than 0.001%.

Bacterial endotoxin Carry out the test for bacterial endotoxin (Appendix XI E); less than 0.75 EU per mg (for injection).

Assay Dissolve about 0.2 g, accurately weighed, in 50 ml of glacial acetic acid, carry out the method for potentiometric titration (Appendix VII A), titrate with perchloric acid (0.1 mol/L) VS. Perform a blank determination and make any necessary correction. Each ml of perchloric acid (0.1 mol/L) VS is equivalent to 36.14 mg of $C_{18}H_{20}FN_3O_4$.

Category Antibiotic.

Storage Preserve in tightly closed containers, protected from light.

Preparation (1) Ofloxacin and Sodium Chloride Injection
(2) Ofloxacin Capsules
(3) Ofloxacin Ear Drops
(4) Ofloxacin Eye Drops
(5) Ofloxacin Eye Ointment
(6) Ofloxacin Tablets

Ofloxacin and Sodium Chloride Injection

Ofloxacin and Sodium Chloride Injection is a sterile and isotonic solution of ofloxacin and sodium chloride in Water for Injection. It contains not less than 90.0% and not more than 110.0% of the labelled amount of ofloxacin ($C_{18}H_{20}FN_3O_4$) and sodium chloride (NaCl).

Description A clear, pale yellow green liquid.

Identification (1) The retention time of principal peak of the substance being examined in the chromatogram obtained in the Assay is identical with that of ofloxacin CRS.

(2) Yields the reactions characteristic of chlorides (Appendix III).

(3) Yields the reactions characteristic of sodium salts (Appendix III).

pH value 3.5-7.5 (Appendix VI H).

Light absorbance The absorbance at 450 nm (Appendix IV

A) is not more than 0.03.

Related substances Carry out the method for high performance liquid chromatography (Appendix V D). The chromatography conditions and system suitability test are the same as described under the Related substances of Ofloxacin.

Procedure Dissolve an accurately measured quantity in 0.1 mol/L hydrochloric acid solution to produce a solution of 1.2 mg per ml as the test solution. Dissolve an accurately measured quantity in 0.1 mol/L hydrochloric acid to produce a solution of 2.4 µg per ml as the reference solution. The area of any peak other than the principal peak is not greater than the peak area of ofloxacin in the reference solution (0.2%). The sum of the areas of all the peaks other than the principal peak (disregard any peak less than 0.05 times of the peak area of ofloxacin in the reference solution) is not greater than 2.5 times of the peak area of ofloxacin in the reference solution (0.5%).

Heavy metals Evaporate 20 ml on a water bath to dryness. Carry out the limit test for heavy metals (Appendix VIII H, method 2), using the residue; not more than 0.0001%.

Particulate matter Complies with the test for particulate matter in injections (Appendix IX C), using one container.

Bacterial endotoxin Carry out the test for bacterial endotoxin (Appendix XI E); less than 0.5 EU per ml.

Sterility Complies with test for Sterility (Appendix XI H, membrane filtration method), to each portion not more than 500 ml of 0.9% sterile sodium chloride solution.

Other requirements Complies with the general requirements for injections (Appendix I B).

Assay Ofloxacin Carry out the method for high performance liquid chromatography (Appendix V D), using a column packed with octadecylsilane bonded silica gel and a mixture of ammonium acetate solution (dissolve 4.0 g of ammonium acetate and 7.0 g of sodium perchloric in 1300 ml of water, mix well, and adjust pH to 2.2 with phosphate acid)-acetonitrile (85 : 15) as the mobile phase, detection wavelength is 294 nm. Measure accurately a quantity of ofloxacin in 0.1 mol/L hydrochloric acid solution to produce a solution of 1 mg per ml, lighted under ultraviolet light (254 nm) for four hours. Inject 10 µl of the solution into the column, the number of the theoretical plate of the column is not less than 5000, calculated with reference to the peak of ofloxacin. The resolution factor between the peak of ofloxacin and that of the adjacent impurity in front of the peak of ofloxacin complies with the related requirements.

Procedure Inject 10 µl of the test solution into the column and record the chromatogram. Dissolve an accurately weighed quantity of ofloxacin CRS in 0.1 mol/L hydrochloric acid solution to produce a solution of 0.12 mg per ml as the reference solution. Repeat the operation, using the reference solution instead of the test solution. Calculate the content of $C_{18}H_{20}FN_3O_4$ with respect to the peak area obtained in the chromatogram by the external standard method.

Sodium chloride Measure accurately 10 ml, add 30 ml of water, 5 ml of dextrin solution (1→50) and 5-3 drops of fluorescein IS, mix well, titrate with silver nitrate (0.1 mol/L) VS. Each ml of silver nitrate (0.1 mol/L) VS is equivalent to 5.844 mg of sodium chloride (NaCl).

Category As described under Ofloxacin.

Strength 100 ml : 0.2 g of ofloxacin and 0.9 g of sodium chloride

Storage Preserve in tightly closed containers, protected from light

Ofloxacin Capsules

Ofloxacin Capsules contain not less than 90.0% and not more than 110.0% of the labelled amount of ofloxacin ($C_{18}H_{20}FN_3O_4$).

Description Capsules containing white or slightly yellow power or granules.

Identification (1) Carry out the method for high performance liquid chromatography as described under the Assay. The retention time of the principal peak of the substance being examined in the chromatogram is identical with that of ofloxacin CRS in the chromatogram.

(2) Dissolve a quantity of the contents in 0.1 mol/L hydrochloric acid solution to produce a solution of 6 µg of ofloxacin per ml, filter. The light absorption of the filtrate exhibits a maximum at 294 nm (Appendix IV A).

Related substances Carry out the method for high performance liquid chromatography (Appendix V D). The chromatography conditions and system suitability test are the same as described under the Related substances of Ofloxacin.

Procedure Take the stored test solution as described under the Assay as the test solution. Dissolve an accurately measured quantity of ofloxacin CRS in 0.1 mol/L hydrochloric acid solution to produce a solution of 6 µg per ml as the reference solution. The area of any peak other than the principle peak is not greater than the peak area of ofloxacin in the reference solution (0.5%). The sum of the areas of all peaks other than the principle peak (disregard any peak less than 0.05 times of the peak area of ofloxacin in the reference solution) is not greater than twice of the peak area of ofloxacin in the reference solution (1.0%).

Dissolution Carry out the dissolution test (Appendix X C, method 1), using 900 ml of hydrochloric acid solution (9→1000) as the dissolution medium, adjust the rotational speed of the paddle to 50 rpm. Withdraw 10 ml of the solution at 30 minutes and filter. Dilute 2 ml of the successive filtrate, accurately measured, with hydrochloric acid solution (9→1000) to 50 ml and mix well. Measure the absorbance of the resulting solution of $C_{18}H_{20}FN_3O_4$ from each capsule. Dissolve an accurately weighed quantity of ofloxacin CRS, in hydrochloric acid solution (9→1000) to produce a solution of 4.5 µg per ml. Repeat the operation, using the reference solution instead of the test solution. Calculate the dissolution of $C_{18}H_{20}FN_3O_4$ from each capsule. Not less than 80% of the labelled amount is dissolved.

Other requirements Comply with the general requirements for capsules (Appendix I A).

Assay Carry out the method for high performance liquid chromatography (Appendix V D), using a column packed with octadecylsilane bonded silica gel and a mixture of ammonium acetate solution (dissolve 4.0 g of ammonium acetate and 7.0 g of sodium perchloric as the mobile phase in 1300 ml of water, mix well, and adjust pH to 2.2 with phosphate acid)-acetonitrile (85:15) as the mobile phase, detection wavelength is 294 nm. Dissolve a quantity of ofloxacin in 0.1 mol/L hydrochloric acid solution to produce a solution of 1 mg per ml, lighted under ultraviolet light (254 nm) for four hours. Inject 10 µl of the solution into the column, the number of the theoretical plate of the peak of ofloxacin is not less than 5000, calculated with reference to the peak of ofloxacin. The resolution factor between the peak of ofloxacin and that of the adjacent impurity in front of the

Procedure Dissolve an accurately weighed quantity of the mixed contents obtained in the test for weight variation of content, equivalent to about 120 mg of ofloxacin in a 100 ml volumetric flask with 0.1 mol/L hydrochloric acid solution, dilute to volume, mix well and filter, use the successive filtrate as stored test solution. Measure accurately 5 ml in a 50 ml volumetric flask, dilute to volume with 0.1 mol/L hydrochloric acid and mix well as the test solution. Inject 10 µl of the test solution into the column and record the chromatogram. Dissolve an accurately weighed quantity of ofloxacin CRS in 0.1 mol/L hydrochloric acid solution to produce a solution of 0.12 mg per ml as the reference solution. Measure the reference solution as the test solution. Calculate the content of $C_{18}H_{20}FN_3O_4$ with respect to the peak area obtained in the chromatogram by the external standard method.

Category As described under Ofloxacin.

Strength 0.1 g

Storage Preserve in tightly closed containers, protected from light.

Ofloxacin Ear Drops

Ofloxacin Ear Drops contain not less than 90.0% and not more than 110.0% of the labelled amount of ofloxacin ($C_{18}H_{20}FN_3O_4$).

Description A clear, slightly yellow liquid.

Identification (1) Carry out the method for high performance liquid chromatography as described under the Assay. The retention time of the principal peak of the substance being examined in the chromatogram is identical with that of ofloxacin CRS in the chromatogram.

(2) Dilute a quantity in 0.1 mol/L hydrochloric acid solution to produce a solution of 6 µg of ofloxacin per ml. The light absorption of the solution exhibits a maximum at 294 nm (Appendix IV A).

pH value 6.0-7.0 (Appendix VI H).

Absorbance The light absorption of the solution obtained from Identification (2) is not more than 0.04 at 450 nm (Appendix IV A).

Related substances Carry out the method for high performance liquid chromatography (Appendix V D). The chromatography conditions and system suitability test are the same as described under the Related substances of Ofloxacin.

Procedure Dilute accurately a quantity in 0.1 mol/L hydrochloric acid solution to produce a solution of 1.2 mg per ml as the test solution. Accurately measure a quantity, dilute with 0.1 mol/L hydrochloric acid solution to produce a solution of 2.4 µg per ml as the reference solution. The area of any peak other than the principal peak is not greater than the peak area of ofloxacin in the reference solution (1.0%). The sum of the areas of all the peaks other than the principal peak (disregard any peak less than 0.05 times of the peak area of ofloxacin in the reference solution) is not greater than twice times of the peak area of ofloxacin in the reference solution (2.0%).

Other requirements Comply with the general requirements for ear preparations (Appendix I Q).

Assay Carry out the method for high performance liquid chromatography (Appendix V D), using a column packed with octadecylsilane bonded silica gel and a mixture of

acetate and 7.0 g of sodium perchlorate in 1300 ml of water, mix well, and adjust pH to 2.2 with phosphate acid)-acetonitrile (85 : 15) as the mobile phase, detection wavelength is 294 nm. Measure a quantity in 0.1 mol/L hydrochloric acid solution to produce a solution of 1 mg per ml, lighted under ultraviolet light (254 nm) for four hours. Inject 10 μ l of the solution into the column, the number of the theoretical plate of the column is not less than 5000, calculated with reference to the peak of ofloxacin. The resolution factor between the peak of ofloxacin and that of the adjacent impurity in front of the peak of ofloxacin complies with the related requirements.

Procedure Measure accurately 2 ml, equivalent to about 6 mg of ofloxacin in 0.1 mol/L hydrochloric acid solution in a 50 ml volumetric flask, dilute to volume, mix well and filter, using the successive filtrate as the test solution. Inject 10 μ l of the test solution into the column and record the chromatogram. Dissolve an accurately weighed quantity of ofloxacin CRS in 0.1 mol/L hydrochloric acid solution to produce a solution of 0.12 mg per ml as the reference solution. Repeat the operation, using the reference solution instead of the test solution. Calculate the content of $C_{18}H_{20}FN_3O_4$ with respect to the peak area obtained in the chromatogram by the external standard method.

Category As described under Ofloxacin.

Strength 5 ml:15 mg

Storage Preserve in tightly closed containers, protected from light.

Ofloxacin Eye Drops

Ofloxacin Eye Drops contain not less than 90.0% and not more than 110.0% of the labelled amount of ofloxacin ($C_{18}H_{20}FN_3O_4$).

Description A clear, slightly yellow liquid.

Identification (1) Carry out the method for high performance liquid chromatography as described under the Assay. The retention time of the principal peak of the substance being examined in the chromatogram is identical with that of ofloxacin CRS in the chromatogram.

(2) Measure a quantity in 0.1 mol/L hydrochloric acid solution to produce a solution of 6 μ g of ofloxacin per ml. The light absorption of the solution exhibits a maximum at 294 nm (Appendix IV A).

pH value 6.0-7.0 (Appendix VI H).

Absorbance The light absorption of the solution obtained from Identification (2) is not more than 0.04 at 450 nm (Appendix IV A).

Related substances Carry out the method for high performance liquid chromatography (Appendix V D). The chromatography conditions and system suitability test are the same as described under the Related substances of Ofloxacin.

Procedure Measure accurately a quantity in 0.1 mol/L hydrochloric acid solution to produce a solution of 1.2 mg per ml as the test solution. Measure accurately a quantity in 0.1 mol/L hydrochloric acid solution to produce a solution of 6 μ g per ml as the reference solution. The area of any peak other than the principal peak is not greater than the peak area of ofloxacin in the reference solution (0.5%). The sum of areas of all peaks other than the principal peak (disregard any peak less than 0.05 times of the peak area of ofloxacin in the reference solution) are not greater than twice the peak

Other requirements Comply with the general requirements for eye preparations (Appendix I Q).

Assay Carry out the method for high performance liquid chromatography (Appendix V D), using a column packed with octadecylsilane bonded silica gel and a mixture of ammonium acetate solution (dissolve 4.0 g of ammonium acetate and 7.0 g of sodium perchloric in 1300 ml of water, mix well, and adjust pH to 2.2 with phosphate acid)-acetonitrile (85 : 15) as the mobile phase, detection wavelength is 294 nm. Dissolve a weighed quantity of ofloxacin in 0.1 mol/L hydrochloric acid to produce a solution of 1 mg per ml, lighted under ultraviolet light (254 nm) for four hours. Inject 10 μ l of the solution into the column, the number of the theoretical plate of the column is not less than 5000, calculated with reference to the peak of ofloxacin. The resolution factor between the peak of ofloxacin and that of the adjacent impurity in front of the peak of ofloxacin complies with the related requirements.

Procedure Measure accurately 2 ml, equivalent to about 6 mg of ofloxacin in 0.1 mol/L hydrochloric acid solution in a 50 ml volumetric flask, dilute to volume, mix well and filter as the test solution. Inject 10 μ l of the test solution into the column and record the chromatogram. Dissolve an accurately weighed quantity of ofloxacin CRS in 0.1 mol/L hydrochloric acid solution to produce a solution of 0.12 mg per ml as the reference solution. Repeat the operation, using the reference solution instead of the test solution. Calculate the content of $C_{18}H_{20}FN_3O_4$ with respect to the peak area obtained in the chromatogram by the external standard method.

Category As described under Ofloxacin.

Strength (1) 5 ml:15 mg (2) 8 ml:24 mg
(3) 10 ml:30 mg

Storage Preserve in tightly closed containers, protected from light.

Ofloxacin Eye Ointment

Ofloxacin Eye Ointment contains not less than 90.0% and not more than 110.0% of the labelled amount of ofloxacin ($C_{18}H_{20}FN_3O_4$).

Description White to yellow ointment or pale yellow gel base ointment.

Identification (1) Carry out the method for high performance liquid chromatography as described under the Assay. The retention time of the principal peak of the substance being examined in the chromatogram is identical with that of ofloxacin CRS in the chromatogram.

(2) Dissolve a quantity in 0.1 mol/L hydrochloric acid solution to produce a solution of 6 μ g of ofloxacin per ml, filter. The light absorption of the filtrate exhibits a maximum at 294 nm (Appendix IV A).

Other requirements Complies with the general requirements for eye preparation (Appendix I A).

Assay Carry out the method for high performance liquid chromatography (Appendix V D), using a column packed with octadecylsilane bonded silica gel and a mixture of ammonium acetate solution (dissolve 4.0 g of ammonium acetate and 7.0 g of sodium perchloric in 1300 ml of water, mix well, and adjust pH to 2.2 with phosphate acid)-acetonitrile (85 : 15) as the mobile phase, detection wavelength is 294 nm. Dissolve a weighed quantity of ofloxacin in 0.1 mol/L hydrochloric acid solution to produce

(254 nm) for four hours. Inject 10 μ l of the solution into the column, the number of the theoretical plate of the column is not less than 5000, calculated with reference to the peak of ofloxacin. The resolution factor between the peak of ofloxacin and that of the adjacent impurity in front of the peak of ofloxacin complies with the related requirements.

Procedure Dissolve an accurately weighed quantity of about 2 g of the Ofloxacin Eye Ointment in 40 ml petroleum ether, shake and extract for three times using 15 ml of 0.1 mol/L hydrochloric acid each time in a 50 ml volumetric flask, dilute to volume using 0.1 mol/L hydrochloric acid solution, mix well and filter, as the stored test solution. Measured accurately 5 ml in a 50 ml volumetric flask, dilute with 0.1 mol/L hydrochloric acid solution and mix well as the test solution. Inject 10 μ l of the test solution into the column and record the chromatogram. Dissolve an accurately weighed quantity of ofloxacin CRS in 0.1 mol/L hydrochloric acid solution to produce a solution of 0.12 mg per ml as the reference solution. Repeat the operation, using the reference solution instead of the test solution. Calculate the content of $C_{18}H_{20}FN_3O_4$ with respect to the peak area obtained in the chromatogram by the external standard method.

Category As described under Ofloxacin.

Strength (1) 0.25 g \pm 0.75 mg (2) 2 g \pm 6 mg
(3) 3.5 mg \pm 10.5 mg

Storage Preserve in tightly closed containers, protected from light.

Ofloxacin Tablets

Ofloxacin Tablets contain not less than 90.0% and not more than 110.0% of the labelled amount of ofloxacin ($C_{18}H_{20}FN_3O_4$).

Description Almost white or slightly yellow tablets or film coated tablets with almost white to slightly yellow core.

Identification (1) The retention time of principal peaks of the substance being examined in the chromatogram obtained in the Assay is identical with that of ofloxacin CRS.

(2) Dissolve a quantity of the powdered tablets in 0.1 mol/L hydrochloric acid solution to produce a solution of 6 μ g of ofloxacin per ml, filter. The light absorption of the filtrate exhibits a maximum at 294 nm (Appendix IV A).

Related substances Carry out the method for high performance liquid chromatography (Appendix VI D). The chromatography conditions and system suitability test are the same as described under the Related substances of Ofloxacin.

Procedure Take the stored test solution as described under the Assay as the test solution. Measured accurately 5 ml in a 50 ml volumetric flask, dilute with 0.1 mol/L hydrochloric acid solution to produce a solution of 6 μ g per ml as the reference solution. The area of any peak other than the principal peak is not greater than the peak area of ofloxacin in the reference solution (0.5%). The sum of the areas of all peaks other than the principal peak (disregard any peak less than 0.05 times of the peak area of ofloxacin in the reference solution) is not greater than twice of the peak area of ofloxacin in the reference solution (1.0%).

Dissolution Carry out the dissolution test (Appendix X C, method 1), using 900 ml of hydrochloric acid solution (9 \rightarrow 1000) as the dissolution medium, adjust the rotational speed of the basket to 50 rpm. Withdraw 10 ml of the solution at 30 minutes and filter. Dilute 2 ml of the successive filtrate, accurately measured, with hydrochloric acid solution (9 \rightarrow 1000) to 50 ml and mix well. Measure the absorbance of the

(Appendix IV A). Dissolve an accurately weighed quantity of ofloxacin CRS, in hydrochloric acid solution (9 \rightarrow 1000) to produce a solution of 4.5 μ g per ml. Repeat the operation. Calculate the dissolution of $C_{18}H_{20}FN_3O_4$ from each tablet. Not less than 80% of the labelled amount is dissolved.

Other requirements Comply with the general requirements for tablets (Appendix I A).

Assay Carry out the method for high performance liquid chromatography (Appendix V D), using a column packed with octadecylsilane bonded silica gel and a mixture of ammonium acetate solution (dissolve 4.0 g of ammonium acetate and 7.0 g of sodium perchloric in 1300 ml of water, mix well, and adjust pH to 2.2 with phosphate acid)-acetonitrile (85 : 15) as the mobile phase, detection wavelength is 294 nm. Dissolve a weighed quantity of ofloxacin in 0.1 mol/L hydrochloric acid to produce a solution of 1 mg per ml, lighted under ultraviolet light (254 nm) for four hours. Inject 10 μ l of the solution into the column, the number of the theoretical plate of the column is not less than 5000, calculated with reference to the peak of ofloxacin. The resolution factor between the peak of ofloxacin and that of the adjacent impurity in front of the peak of ofloxacin complies with the related requirements.

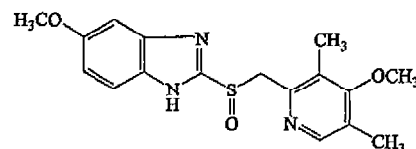
Procedure Weigh accurately and powder 10 tablets. Dissolve an accurately weighed quantity of the powder equivalent to about 120 mg of ofloxacin in a 100 ml volumetric flask, dilute to volume, mix well and filter, as the stored test solution. Measured accurately 5 ml in a 50 ml volumetric flask, dilute with 0.1 mol/L hydrochloric acid solution and mix well as the test solution. Inject 10 μ l of the test solution into the column and record the chromatogram. Dissolve an accurately weighed quantity of ofloxacin CRS in 0.1 mol/L hydrochloric acid solution to produce a solution of 0.12 mg per ml as the reference solution. Repeat the operation, using the reference solution instead of the test solution. Calculate the content of $C_{18}H_{20}FN_3O_4$ with respect to the peak area obtained in the chromatogram by the external standard method.

Category As described under Ofloxacin.

Strength 0.1 g

Storage Preserve in tightly closed containers, protected from light.

Omeprazole



$C_{17}H_{19}N_3O_3S$ 345.42

[73590-58-6]

Omeprazole is 5-methoxy-2-[[[4-methoxy-3,5-dimethyl-2-pyridinyl]methyl]sulfinyl]-1H-benzimidazole. It contains not less than 98.5% of $C_{17}H_{19}N_3O_3S$, calculated on the dried basis.

Description A white or almost white crystalline powder; odourless; The colour deepened on exposure to light. Freely soluble in dichloromethane; sparingly soluble in methanol or in ethanol; slightly soluble in acetone; insoluble in water; soluble in 0.1 mol/L sodium hydroxide solution.

sodium hydroxide solution, add 1 ml of silicotungstic acid TS, mix well, add a few drops of dilute hydrochloric acid; a white flocculent precipitate is produced immediately.

(2) The light absorption of a solution of about 15 µg per ml in 0.1 mol/L sodium hydroxide solution exhibits maxima at 276 nm and 305 nm, and minima at 256 nm and 281 nm (Appendix IV A).

(3) The infrared absorption spectrum (Appendix IV C) is concordant with the reference spectrum of omeprazole (Appendix XVI).

Clarity and colour of dichloromethane solution Dissolve 0.5 g in 25 ml of dichloromethane, the solution is clear and colourless; any colour is produced, measure the absorbance at 440 nm (Appendix IV A). The absorbance is not greater than 0.10.

Related substance Protect from light throughout the procedure. Carry out the method for high performance liquid chromatography (Appendix V D), using a column packed with octylsilane silica gel and a mixture of 0.01 mol/L disodium hydrogen phosphate solution (adjust to pH 7.6 with phosphoric acid)-acetonitrile (75 : 25) as the mobile phase. Detection wavelength is 280 nm. Dissolve an accurately weighed quantity of the substance being examined in mobile phase to produce a solution of 0.2 mg per ml as the test solution and a solution of 2 µg per ml as the reference solution; Dissolve 1 mg of omeprazole CRS and 1 mg of omeprazole sulphone (5-methoxy-2 [[(4-methoxy-3, 5-dimethyl-2-pyridinyl) methyl] -sulphonyl] -1H-benzimidazole) CRS in 10 ml of mobile phase, shake thoroughly. Inject 20 µg of the resulting solution into the column, the number of theoretical plates of the column is not less than 2000, calculated with reference to the peak of omeprazole; the resolution factor between omeprazole and omeprazole sulphone is greater than 2.0. Inject 20 µl of the reference solution into the column. Adjust the attenuation so that the principal peak height in the chromatogram is about 15% full scale of the chart. Inject separately 20 µl each of the test solution and the reference solution into the column, and record the chromatogram for three times the retention time of the principal peak. Each secondary peak and the sum of the secondary peaks other than the principal peak are not greater than 3/10 or the area of the principal peak in the chromatogram obtained with reference solution respectively.

Residual solvents Dissolve 0.5 g, accurately weighed, in 3 ml of dimethylacetamide in a head-space vial (as the test solution). Weigh accurately a quantity of dichloromethane, acetonitrile, methanol and acetone, dissolve in dimethylacetamide to produce a solution containing 100 µg, 60 µg, 160 µg per ml correspondingly, as the reference solution. Measure accurately 3 ml of the reference solution to a head-space vial. Carry out the test for Residual solvents (Appendix VIII P, method 2), using a column packed with polyethylene glycol 20 M as the stationary phase. Maintain the column temperature at 45°C for 8 minutes, then raising the temperature at a rate of 45°C per minute to 200°C. Comply with the related requirements of Residual solvents.

Loss on drying when dried in vacuum at 60°C for 4 hours, loses not more than 0.5% of its weight (Appendix VIII L).

Residue on ignition Not more than 0.1% (Appendix VIII N), using 1.0 g.

Heavy metals Carry out the limit test for heavy metals (Appendix VIII H, method 2), using the residue obtained in the test for Residue on ignition; not more than 0.002%.

Assay Weigh accurately about 0.2 g, dissolve in 50 ml of a solution of ethanol-water (4:1). Carry out the method for potentiometric titration (Appendix VII A), titrate with sodium hydroxide (0.1 mol/L) VS. Each ml of sodium

hydroxide (0.1 mol/L) VS is equivalent to 34.54 mg of $C_{17}H_{19}N_3O_3S$.

Category Proton pump inhibitor.

Storage Preserve in tightly closed containers, stored in a cold place, protected from light.

Preparation (1) Omeprazole Enteric-coated Tablets
(2) Omeprazole Enteric-coated Capsules

Omeprazole Enteric-coated Capsules

Omeprazole Enteric-coated capsules contain not less than 90.0% and not more than 110.0% of the labelled amount of omeprazole ($C_{17}H_{19}N_3O_3S$).

Description Capsules containing white or almost white small enteric-coated pills or granules.

Identification (1) To a quantity of powdered contents, equivalent to about 10 mg of omeprazole, add 20 ml of 0.1 mol/L sodium hydroxide solution, shake to dissolve omeprazole, filter. Add 1 ml of silicotungstic acid TS to 3 ml of the filtrate, mix well. Add a few drops of dilute hydrochloric acid; a white flocculent precipitate is produced immediately.

(2) The retention time of principal peak in the substance being examined in the chromatogram obtained in the Assay is identical with that of the principal peak in the chromatogram of the reference solution correspondingly.

(3) To a quantity of the powdered contents, add 0.1 mol/L sodium hydroxide solution to produce a solution of 15 µg per ml and filter. The light absorption of the filtrate exhibits maxima at 276 nm and 305 nm, and minima at 256 nm and 281 nm (Appendix IV A).

Content uniformity Comply with the requirements for content uniformity (Appendix X E). Transfer 1 capsule (for strength 10 mg) to a 50 ml volumetric flask, add a quantity of phosphate BS (Mix 110 ml of 0.25 mol/L sodium phosphate solution with 220 ml of 0.5 mol/L disodium hydrogen phosphate solution, dilute with water to 1000 ml and mix well, adjust to pH 11.0), disintegrated by ultrasonication, add 10 ml of ethanol, ultrasonicate for 15 minutes, cool to room temperature, dilute with phosphate BS (pH 11.0) to volume and mix well, filter. Transfer 5 ml of the successive filtrate, accurately measured, to a 50 ml volumetric flask, dilute with water to volume and mix well. Carry out the method as described under the Assay, calculate the content of $C_{17}H_{19}N_3O_3S$.

Drug Release Carry out the method for dissolution test (Appendix X D, method 2 and X C, method 2), using 500 ml of sodium chloride in hydrochloric acid solution (To 1 g of sodium chloride add 3.5 ml of hydrochloric acid, dilute to 500 ml with water) as the dissolution medium and adjust the rotational speed of the basket to 100 rpm. Stop rotating at 120 minutes, neither the enteric-coated granules nor the solvent discolour obviously. Add 400 ml of 0.235 mol/L of disodium hydrogen phosphate solution previously heated to 37°C in the vessel immediately, keep the same rotational speed as above. Withdraw the sample at 45 minutes and filter. To 5 ml of the successive filtrate, accurately measured, add 1.0 ml of 0.25 mol/L sodium hydroxide solution, mix well, taking, the resulting solution as test solution. Dissolve about 20 mg of omeprazole CRS, accurately weighed, with 10 ml of ethanol in a 100 ml volumetric flask, dilute with the mixed dissolution medium [sodium chloride in hydrochloric acid solution -0.235 mol/L of disodium hydrogen phosphate solution (5:4)] to volume.

mix well. Transfer accurately 5 ml of the solution to a 50 ml (for 20 mg) or to a 100 ml (for 100 mg) volumetric flask, dilute with the mixed dissolution medium to volume, mix well. To 5 ml of the solution, accurately measured, add 1.0 ml of 0.25 mol/L sodium hydroxide solution and mix well, taking the resulting solution as reference solution. Carry out the method as described under the Assay, calculate the dissolution of $C_{17}H_{19}N_3O_3S$ from each capsule. Not less than 80% of the labelled amount is dissolved.

Other requirements Comply with the general requirements for capsules (Appendix I E).

Assay Carry out the method for high performance liquid chromatography (Appendix V D), using a column packed with octylsilane silica gel and a mixture of 0.01 mol/L disodium hydrogen phosphate solution (adjust to pH 7.6 with phosphoric acid)-acetonitrile (75 : 25) as the mobile phase. Detection wavelength is 302 nm and the number of theoretical plates of the column is not less than 2000, calculated with reference to the peak of omeprazole.

Procedure Weigh accurately and powder the contents of 20 capsules, weigh accurately a quantity equivalent to about 20 mg of omeprazole into a 100 ml volumetric flask, add 20 ml of ethanol and about 60 ml of phosphate BS (pH 11.0), treated with aid of ultrasonicator to dissolve omeprazole, dilute with phosphate BS (pH 11.0) to volume, mix well and filter. Measure accurately 5 ml of the successive filtrate to a 50 ml volumetric flask, dilute with water to volume, mix well. Inject 20 μ l of the resulting solution into the column, record the peak areas obtained in the chromatogram. Weigh accurately about 20 mg of omeprazole CRS into a 100 ml volumetric flask, repeat the operation, beginning at the words "add 20 ml of ethanol and about 60 ml of phosphate BS (pH 11.0)...", calculate the content of $C_{17}H_{19}N_3O_3S$ with respect to the peak area obtained in the chromatogram by the external standard method.

Category As described under Omeprazole.

Strength (1) 10 mg (2) 20 mg

Storage Preserve in tightly closed containers, stored in a dry place, protected from light.

Omeprazole Enteric-coated Tablets

Omeprazole Enteric-coated Tablets contain not less than 90.0% and not more than 110.0% of the labelled amount of omeprazole ($C_{17}H_{19}N_3O_3S$).

Description Enteric-coated tablets with white or almost white core.

Identification (1) To a quantity of the powdered tablets, equivalent to about 10 mg of omeprazole, add 20 ml of 0.1 mol/L sodium hydroxide solution, shake to dissolve omeprazole, filter. To 3 ml of the filtrate, add 1 ml of silicotungstic acid TS, mix well, add a few drops of dilute hydrochloric acid; a white flocculent precipitate is produced immediately.

(2) The retention time of principal peak in the substance being examined in the chromatogram obtained in the Assay is identical with that of the principal peak in the chromatogram of the reference solution correspondingly.

(3) To a quantity of the powdered tablets, add 0.1 mol/L sodium hydroxide solution to produce a solution of 15 μ g per ml and filter. The light absorption of the filtrate exhibits maxima at 276 nm and 305 nm, and minima at 256 nm and

Content uniformity Comply with the requirements for content uniformity (Appendix X E). Transfer 1 tablet (for 10 mg) to a 50 ml volumetric flask, add a quantity of phosphate BS (Mix 110 ml of 0.25 mol/L sodium phosphate solution with 220 ml of 0.5 mol/L disodium hydrogen phosphate solution, dilute with water to 1000 ml and mix well, adjust pH to 11.0), disintegrate by ultrasonicator, add 10 ml of ethanol, in ultrasonicate bath for 15 minutes, cool to room temperature, dilute with phosphate BS (pH 11.0) to volume and mix well, filter. Transfer 5 ml of the successive filtrate, accurately measured, to a 50 ml volumetric flask, dilute with water to volume and mix well. Carry out the method as described under the Assay, calculate the content of $C_{17}H_{19}N_3O_3S$.

Drug Release Carry out the method for dissolution test (Appendix X D, method 2 and X C, method 1), using 500 ml of sodium chloride in hydrochloric acid solution (To 1 g of sodium chloride add 3.5 ml of hydrochloric acid, dilute to 500 ml with water) as the dissolution medium and adjust the rotational speed of the basket to 100 rpm. Stop rotating at 120 minutes, elevate the basket from the liquid immediately, no table discolours, cracks or disintegrates. Add 400 ml of 0.235 mol/L of disodium hydrogen phosphate solution previously heated to 37°C in the vessel immediately, replace the basket into the new dissolution medium, keep the same rotational speed as above. Withdraw the sample at 45 minutes and filter. To 5 ml of the successive filtrate, accurately measured, add 1.0 ml of 0.25 mol/L sodium hydroxide solution, mix well, taking the resulting solution as test solution. Dissolve about 20 mg of omeprazole CRS, accurately weighed, with 10 ml of ethanol in a 100 ml volumetric flask, dilute with the mixed dissolution medium [sodium chloride in hydrochloric acid solution-0.235 mol/L of disodium hydrogen phosphate solution (5:4)] to volume, mix well. Transfer accurately 5 ml of the solution to a 50 ml (for strength 20 mg) or to a 100 ml (for strength 10 mg) volumetric flask, dilute with the mixed dissolution medium to volume, mix well. To 5 ml of the solution, accurately measured, add 1.0 ml of 0.25 mol/L sodium hydroxide solution and mix well, taking the resulting solution as reference solution. Carry out the method as described under the Assay, calculate the dissolution of $C_{17}H_{19}N_3O_3S$ from each tablet. Not less than 75% of the labelled amount is dissolved.

Other requirements Comply with the general requirements for tablets (Appendix I A).

Assay Carry out the method for high performance liquid chromatography (Appendix V D), using a column packed with octylsilane silica gel and a mixture of 0.01 mol/L disodium hydrogen phosphate solution (adjust to pH 7.6 with phosphoric acid)-acetonitrile (75 : 25) as the mobile phase. Detection wavelength is 302 nm and the number of theoretical plates of the column is not less than 2000, calculated with reference to the peak of omeprazole.

Procedure Weigh accurately and powder 20 tablets, weigh accurately a quantity, equivalent to about 20 mg of omeprazole, into a 100 ml volumetric flask, add 20 ml of ethanol and about 60 ml of phosphate BS (pH 11.0), treated with aid of ultrasonicator to dissolve omeprazole, dilute with phosphate BS (pH 11.0) to volume, mix well and filter. Measure accurately 5 ml of the successive filtrate in a 50 ml volumetric flask, dilute with water to volume, mix well. Inject 20 μ l of the resulting solution into the column, record the peak areas obtained in the chromatogram. Weigh accurately about 20 mg of omeprazole CRS into a 100 ml volumetric flask, repeat the operation, beginning at the words "add 20 ml of ethanol and about 60 ml of phosphate BS (pH 11.0)...", calculate the content of

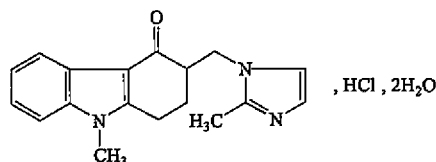
$C_{17}H_{19}N_3O_3S$ with respect to the peak area obtained in the chromatogram by the external standard method.

Category As described under Omeprazole.

Strength (1) 10 mg (2) 20 mg

Storage Preserve in tightly closed container, stored in a cool and dry place, protected from light.

Ondansetron Hydrochloride



$C_{18}H_{19}N_3O \cdot \text{HCl} \cdot 2\text{H}_2\text{O}$ 365.86 [103639-04-9]

Ondansetron Hydrochloride is (\pm) -2,3-Dihydro-9-methyl-3-[(2-methylimidazol-1-yl)methyl]carbazol-4(1*H*)-one monohydrochloride dihydrate. It contains not less than 98.0% and not more than 102.0% of $C_{18}H_{19}N_3O \cdot \text{HCl}$, calculated on the anhydrous basis.

Description White or almost white crystalline powder; odourless; taste, bitter. Freely soluble in methanol; sparingly soluble in water; slightly soluble in acetone; sparingly soluble in 0.1 mol/L hydrochloric acid solution.

Melting range 175-180°C, with decomposition (Appendix VI C), determined after drying over phosphorous pentoxide for 30 minutes.

Identification (1) Dissolve about 10 mg in 5 ml of water, add 1 ml of dilute potassium iodobismuthate TS, a scarlet colour is produced.

(2) The light absorption of a solution of 10 μg per ml in 0.1 mol/L hydrochloric acid solution exhibits maxima at 248 nm, 267 nm and 310 nm, and minima at 282 nm and 257 nm (Appendix IV A).

(3) The infrared absorption spectrum (Appendix IV C) is concordant with the reference spectrum of ondansetron hydrochloride (Appendix XVI).

(4) Yields the reactions characteristic of chlorides (Appendix III).

Acidity Dissolve 0.10 g in 10 ml of water, pH 4.0-5.5 (Appendix VI H).

Clarity and colour of solution Dissolve 0.1 g in 10 ml of water, the solution is clear and colourless; any opalescence produced is not more pronounced than that of reference suspension I (Appendix IX B); any colour produced is not more intense than that of reference solution Y1 (Appendix IX A).

Related substances Carry out the method as described under Assay, except the detection wavelength is 216 nm. Dissolve a quantity of the substance being examined, accurately weighed, in mobile phase to produce a solution of 0.5 mg per ml as test solution. Transfer accurately 1 ml of the resulting solution, into a 100 ml volumetric flask, dilute with mobile phase to produce a solution of 5 μg per ml as reference solution. Inject 10 μl of the reference solution into the column, adjust the attenuation so that the principal peak height in the chromatogram is about 10% to 15% full scale of the chart. Inject separately 20 μl each of the test solution and the reference solution into the column, and record the

chromatogram for twice the retention time of the principal peak. The sum of the areas of all peaks other than the principal peak is not greater than 1/2 area of the principal peak in the chromatogram obtained with the reference solution.

Toluene and acetone Dissolve a quantity of the substance being examined, accurately weighed, in water to produce a solution of 20 mg per ml as test solution; Dissolve an accurately weighed quantity of toluene and acetone in water, to produce a solution of 17.8 μg per ml of toluene and 100 μg per ml of acetone as reference solution. Comply with the test for residual solvents (Appendix VIII P, method 3), using a capillary column packed with phenyl (5%)—methyl polysiloxane (95%) as the stationary phase, and maintain the column temperature at 50°C. The detector is FID. The resolution factor between the peaks of toluene and acetone complies with the related requirements. Inject separately 1 to 3 μl each of the test solution and the reference solution into the column, and record the chromatograms, calculate the content of toluene and acetone with respect to the peak area obtained in the chromatogram by the external standard method.

Water 9.0%-10.5% (Appendix VIII M, method 1 A).

Residue on ignition Not more than 0.1% (Appendix VIII N), using 1.0 g.

Heavy metals Carry out the limit test for heavy metals (Appendix VIII H, method 2), using the residue obtained in the test for Residue on ignition; not more than 0.002%.

Assay Carry out the method for high performance liquid chromatography (Appendix V D), using a column packed with cyano silane group bonded silica gel and a mixture of 0.02 mol/L sodium dihydrogen phosphate solution (adjust to pH 5.4 with sodium hydroxide TS)-acetonitrile (50:50) as the mobile phase. Detection wavelength is 310 nm and the number of theoretical plates of the column is not less than 2000, calculated with reference to the peak of ondansetron hydrochloride.

Procedure Dissolve an accurately weighed quantity of the substance being examined, in mobile phase to produce a solution of 0.1 mg per ml. Inject 10 μl of the resulting solution into the column. Repeat the operation, using ondansetron hydrochloride CRS instead of the substance being examined, calculate the content of $C_{18}H_{19}N_3O \cdot \text{HCl}$ with respect to the peak area obtained in the chromatogram by the external standard method.

Category Antiemetics for sickness caused by chemotherapy and radiotherapy.

Storage Preserve in tightly closed container, protected from light.

Preparation (1) Ondansetron Hydrochloride Tablets
(2) Ondansetron Hydrochloride Injection

Ondansetron Hydrochloride Injection

Ondansetron Hydrochloride Injection is a sterile solution of Ondansetron Hydrochloride in Water for Injection. It contains not less than 97.0% and not more than 107.0% of the labelled amount of ondansetron ($C_{18}H_{19}N_3O$).

Description A clear, colourless liquid.

Identification (1) The retention time of principal peak of ondansetron hydrochloride in the substance being examined in

the chromatogram obtained in the Assay is identical with that of the principal peak of ondansetron hydrochloride CRS in the chromatogram of the reference solution correspondingly.

(2) The light absorption of a solution of 10 µg per ml in 0.1 mol/L hydrochloric acid solution exhibits maxima at 248 nm, 267 nm and 310 nm, and minima at 282 nm and 257 nm (Appendix IV A).

(3) Yields the reactions characteristic of chlorides (Appendix III).

pH value 3.0-4.0 (Appendix VI H).

Related substances Carry out the method as described under Assay except the detection wavelength is 216 nm. To a quantity of the injection add mobile phase to produce a solution of 0.5 mg per ml as test solution. Measure accurately a quantity of the resulting solution, dilute with the mobile phase to produce a solution of 5 µg per ml as reference solution. Inject 10 µl of the reference solution into the column, adjust the attenuation so that the principal peak height in the chromatogram is about 10% to 15% full scale of the chart. Inject separately 20 µl each of the test solution and the reference solution into the column, and record the chromatogram for twice the retention time of the principal peak. The sum of the areas of all peaks other than the principal peak is not greater than 1/2 area of the principal peak in the chromatogram obtained with the reference solution.

Bacterial endotoxin Carry out the test for bacterial endotoxin (Appendix XI E); less than 9.9 EU per mg of ondansetron.

Other requirements Comply with the general requirements for injections (Appendix I B).

Assay Measure accurately a quantity of the injection, dilute with mobile phase to produce a solution of 80 µg per ml, complete the assay as described under Ondansetron Hydrochloride, and multiply the result by 0.8895.

Category As described under Ondansetron Hydrochloride.

Strength calculated as $C_{18}H_{19}N_3O$
(1) 2 ml:4 mg (2) 4 ml:8 mg

Storage Preserve in well closed containers, stored in a cool place and protected from light.

Ondansetron Hydrochloride Tablets

Ondansetron Hydrochloride Tablets contain not less than 90.0% and not more than 110.0% of the labelled amount of ondansetron ($C_{18}H_{19}N_3O$).

Description White or almost white tablets or film coated tablets with white or almost white core.

Identification (1) The retention time of principal peak of ondansetron hydrochloride in the substance being examined in the chromatogram obtained in the Assay is identical with that of the principal peak of ondansetron hydrochloride CRS in the chromatogram of the reference solution correspondingly.

(2) The light absorption of the test solution obtained in Content uniformity exhibits maxima at 248 nm, 267 nm and 310 nm, and minima at 282 nm and 257 nm (Appendix IV A).

(3) Shake a quantity of powdered tablets with a quantity of water to dissolve ondansetron hydrochloride, filter. The filtrate yields the reactions characteristic of chlorides (Appendix III).

Assay except the detection wavelength is 216 nm. Transfer a quantity of powdered tablets, equivalent to about 4 mg of ondansetron, to a 10 ml volumetric flask, dissolve ondansetron hydrochloride and dilute with mobile phase to volume, filter, take the successive filtrate as test solution. Measure accurately a quantity of the resulting solution, dilute with mobile phase to produce a solution of 4 µg per ml as reference solution. Inject 10 µl of the reference solution into the column, adjust the attenuation so that the principal peak height in the chromatogram is about 10% to 15% full scale of the chart. Inject separately 10 µl each of the test solution and the reference solution into the column, and record the chromatogram for twice the retention time of the principal peak. The sum of the areas of all peaks other than the principal peak is not greater than the area of the principal peak in the chromatogram obtained with the reference solution.

Content uniformity Comply with the requirements for content uniformity (Appendix X E). Transfer 1 tablet to a 100 ml volumetric flask, add a quantity of 0.1 mol/L hydrochloric acid solution, shake to dissolve ondansetron hydrochloride, dilute with 0.1 mol/L hydrochloric acid solution to volume and mix well, filter. Transfer 10 ml of the successive filtrate to 50 ml volumetric flask (for strength 4 mg) or 100 ml volumetric flask (for strength 8 mg), dilute with 0.1 mol/L hydrochloric acid solution to volume and mix well, take it as test solution. Dissolve an accurately weighed quantity of ondansetron hydrochloride CRS in 0.1 mol/L hydrochloric acid solution, to produce a solution of 8 µg per ml as reference solution. Measure the absorbance of the resulting solutions at 310 nm (Appendix IV A), calculate the content of $C_{18}H_{19}N_3O$.

Dissolution Carry out the dissolution test (Appendix X C, method 2), using 500 ml (for strength 4 mg) or 1000 ml (for strength 8 mg) of 0.1 mol/L hydrochloric acid solution as the dissolution medium, adjust the rotational speed of the paddle to 50 rpm. Withdraw a quantity of the solution at 30 minutes and filter, take the successive filtrate as test solution. Dissolve ondansetron hydrochloride CRS in 0.1 mol/L hydrochloric acid solution, to produce a solution of 8 µg per ml as reference solution. Measure the absorbance of the resulting solutions at 310 nm (Appendix IV A), calculate the dissolution of $C_{18}H_{19}N_3O$ from each tablet. Not less than 80% of the labelled amount is dissolved.

Other requirements Comply with the general requirements for tablets (Appendix I A).

Assay Weigh accurately and powder 20 tablets. Weigh accurately a quantity of the powder equivalent to about 8 mg of ondansetron, dissolve in mobile phase to produce a solution of 80 µg per ml, and filter. Measure accurately a quantity of the successive filtrate, complete the Assay as described under Ondansetron hydrochloride, and multiply the result by 0.8895.

Category As described under Ondansetron Hydrochloride.

Strength calculated as $C_{18}H_{19}N_3O$
(1) 4 mg (2) 8 mg

Storage Preserve in tightly closed containers, stored in a cool and dry place, protected from light.

Opium

Opium is the dried latex obtained by incision from the unripe capsules of *Papaver somniferum* L. It contains not less than 10.0% of anhydrous morphine

($C_{17}H_{19}NO_3$).

Description A brown or dark brown pasty mass. Fresh mass is slightly soft and becomes hard or brittle on storage. Odour, characteristic; taste, very bitter.

Identification (1) Heat and macerate about 0.1 g in 5 ml of water, filter. To the filtrate add a few drops of ferric chloride TS, a purple red colour is produced; the colour is not changed on the addition of a few drops of dilute hydrochloric acid or mercuric chloride TS.

(2) Shake about 0.1 g with 5 ml of chloroform and a few drops of ammonia TS for 10 minutes. Transfer the chloroform layer to a watch glass and evaporate to dryness on a water bath, the residue is greyish white crystals and a deep red colour is produced on the addition of 2 drops of formaldehyde-sulfuric acid TS.

(3) Triturate 0.2 g with 5 ml of water and 5 ml of ammonia TS, add 20 ml of chloroform-ethanol (1:1) solution, shake gently in a separator and allow it to stand. Evaporate the extract to dryness on a water bath, dissolve the residue in 1 ml of chloroform-ethanol (1:1) solution as test solution. Prepare reference solutions of morphine CRS, codeine phosphate CRS, papaverine hydrochloride CRS, noscapine CRS and thebaine CRS 1 mg each per ml of a mixture of chloroform-ethanol (1:1), respectively. Carry out the thin-layer chromatography (Appendix V B), using silica gel G as the coating substance and a mixture of benzene-acetone-methanol-concentrated ammonia TS (8:4:0.6:0.25) as the mobile phase. Apply separately to the same plate 10 μ l each of above six solutions. After developing and removal of the plate, dry it in air, spray with potassium iodobismuthate TS. There are not less than seven spots in the chromatogram obtained with test solution, colour and position of the five spots among them obtained with the test solution correspond to the principal spots obtained with the five reference solutions respectively.

Assay Carry out the method for high performance liquid chromatography (Appendix V D), using a column packed with octasilane bonded silica gel and a mixture of 0.05 mol/L potassium dihydrogen phosphate solution — 0.0025 mol/L sodium heptanesulfonate solution-acetonitrile (5:5:2) as the mobile phase. Detection wavelength is 220 nm. The number of theoretical plates of the column is not less than 1000, calculated with reference to the peak of morphine.

Carry out the treatment and elution described under the procedure, using a column packed with octadecylsilane bonded silica gel. Measure accurately 0.5 ml of morphine CRS solution of 0.5 mg per ml, into treated column, elute with 5% acetic acid solution containing 20% of methanol. Collect the eluate with 5 ml volumetric flask to the volume, mix well. Inject 10 μ l of the eluate and the reference solution under Assay, accurately measured, respectively, record the chromatogram. The ratio of the morphine peak area of the eluate to that of the reference solution is 0.97-1.03.

Procedure A column packed with octadecylsilane bonded silica gel is filled with a mixture of methanol-water (3:1). Wash it using 15 ml of the mixture and 5 ml of water one after the other for one time each. Rinse with ammonia solution (to a quantity of water add ammonia TS to pH of 9) (pH \approx 9) until the pH value of the outflow is about 9. Triturate about 5 g of the substance being examined and let it through No. 5 sieve. Transfer about 1 g, accurately weighed, into a 200 ml volumetric flask, add a quantity of 5% acetic acid solution, dissolve by ultrasonic generator, for 30 minutes, cool to room temperature, dilute to volume with 5% acetic acid solution, mix well and filter. Accurately measure 0.5 ml of successive filtrate to the above column, add a few drops of ammonia TS, (measure the same volume of successive filtrate to adjust previously, and

examine the quantity of ammonia TS) mix well, rinse with 20 ml of water after no solvent drips. Elute with 5% acetic acid solution containing 20% of methanol. Collect the eluate with 5 ml volumetric flask to the volume and mix well. Inject 10 μ l of the eluate into the column.

Dissolve a quantity of morphine CRS, accurately measured, in 5% acetic acid solution containing 20% of methanol and dilute to produce reference solution of 0.05 mg per ml, repeat the operation. Calculate the content of $C_{17}H_{19}NO_3$ with respect to the peak area obtained in the chromatogram by the external standard method.

Category Analgesic, Antidiarrheal.

Storage Preserve in tightly closed containers.

Opium Tablets

Opium Tablets are prepared by powdered opium. It contains not less than 4.5 mg and not more than 5.5 mg of morphine in each tablet, calculated with reference to anhydrous morphine ($C_{17}H_{19}NO_3$).

Formula	Powdered Opium	50 g
	Excipient	a quantity
	To make	1000 tablets

Description Pale brown tablets.

Identification (1) To a quantity of powdered tablets equivalent to 0.1 g of powdered opium add 5 ml of water, rinse while heating and filter. To the filtrate add a few drops of ferric chloride TS, a purple colour is produced; the colour has no change when adding a few drops of dilute hydrochloric acid or mercuric chloride TS.

(2) Triturate a quantity of powdered tablets equivalent to 0.2 g of Powdered Opium with 5 ml of water and 5 ml of ammonia TS, transfer to a separator, add 20 ml of chloroform-ethanol (1:1) solution, shake gently and allow it to stand. Evaporate the extract to dryness on a water bath, dissolve the residue in 1 ml of chloroform-ethanol (1:1) solution as the test solution. Weigh separately a quantity of morphine CRS, codeine phosphate CRS, papaverine hydrochloride CRS, noscapine CRS and thebaine CRS in a mixture of chloroform-ethanol (1:1) to produce a solution containing 1 mg per ml respectively. Carry out the thin-layer chromatography (Appendix V B), using silica gel G as the coating substance and a mixture of benzene-acetone-methanol-concentrated ammonia solution (8:4:0.6:0.25) as the mobile phase. Apply separately to the plate 10 μ l of each of the above six solutions. After developing and removal of the plate, dry it in air and spray with dilute potassium iodobismuthate TS. There are not less than seven spots in the chromatogram obtained with the test solution, colour and position of the five spots among them obtained with the test solution correspond to the principal spots obtained with the five reference solutions.

Other requirements Comply with the general requirements for tablets (Appendix I A).

Assay Carry out the method for high performance liquid chromatography (Appendix V D), using a column packed with octasilane bonded silica gel and a mixture of 0.05 mol/L potassium dihydrogen phosphate solution — 0.0025 mol/L sodium heptanesulfonate solution-acetonitrile (2:2:1) as the mobile phase. Detection wavelength is 220 nm and the number of the theoretical plates of the column is not less than 1000, calculated with reference to the peak of morphine.

System suitability test of solid phase extraction column

Using a solid phase extraction column packed with octadecylsilane bonded silica gel. Carry out the test as described under the Procedure. Measure accurately 1 ml of a solution in 5% acetic acid solution containing 0.03 mg of morphine CRS per ml to the column pretreated. Collect the eluate into a 5 ml of volumetric flask to volume and mix well. Inject 10 μ l of the eluate and the reference solution as described under the Procedure into the column, record the peak areas correspondingly obtained in the chromatogram. The ratio of the peak area of morphine obtained in the chromatogram of the eluate to the reference solution is not less than 0.97 and not more than 1.03.

Procedure Wash a solid phase extraction column with 15 ml of a mixture of methanol-water (3:1) and 5 ml of water in sequence, then wash the column with the ammonia solution of pH about 9 (add drops of ammonia TS to a quantity of water until the pH value is about 9) until the pH value of the eluate is about 9. Weigh accurately and powder 20 tablets. Transfer an accurately weighed quantity of the powdered tablets equivalent to about 1.5 mg of morphine into a conical flask with stopper, add accurately 10 ml of 5% acetic acid solution, sonicate for 20 minutes to dissolve morphine, cool and filter. Measure accurately 1 ml of the successive filtrate to the above washed column, drop a quantity of ammonia TS to adjust pH value of the solution in the column to about 9 (define the quantity of ammonia TS by using another same volume of the successive filtrate previously), mix well, rinse with 20 ml of water to make the drips neutral after no solvent drips. Elute with 5% acetic acid solution, collect the eluate into a 5 ml of volumetric flask to volume and mix well. Inject 10 μ l of the eluate into the column, record the chromatogram. Repeat the operation, using a solution in 5% acetic acid solution of 0.03 mg of morphine CRS per ml instead of the eluate. Calculate the content of $C_{17}H_{19}NO_3$ with respect to the peak areas obtained in the chromatogram by the external standard method.

Category As described under Opium.

Storage Preserve in tightly closed containers, protected from light.

Opium Tincture

Opium Tincture contains not less than 0.95% and not more than 1.05% of morphine, calculated as anhydrous morphine ($C_{17}H_{19}NO_3$).

Description A brown liquid; foams on shaking with water.

Identification Evaporate a quantity to dryness on a water bath, the residue complies with the tests for Identification described under Opium.

Ethanol content 41%-46% (Appendix VII E).

Other requirements Comply with the general requirements for tincture (Appendix I C).

Assay Carry out the method for high performance liquid chromatography (Appendix V D), using a column packed with octasilane bonded silica gel and a mixture of 0.05 mol/L potassium dihydrogen phosphate solution — 0.0025 mol/L sodium heptanesulfonate solution-acetonitrile (5:5:2) as the mobile phase. Detection wavelength is 220 nm. The number of theoretical plates of the column is not less than 1000, calculated with reference to the peak of morphine.

Carry out the treatment and elution described under the

bonded silica gel. Measure accurately 0.5 ml of morphine CRS solution of 0.5 mg per ml, into treated column, elute with 5% acetic acid solution containing 20% of methanol. Collect the eluate with 5 ml volumetric flask to the volume, mix well. Inject 10 μ l of the eluate and the reference solution under Assay, accurately measured, respectively, record the chromatogram. The ratio of the morphine peak area of the eluate to that of the reference solution is 0.97-1.03.

Procedure A column packed with octadecylsilane bonded silica gel is filled with a mixture of methanol-water (3:1). Wash it using 15 ml of the mixture and 5 ml of water one after the other for one time each. Rinse with ammonia solution (to a quantity of water add ammonia TS to pH of 9) ($pH \approx 9$) until the pH value of the outflow is about 9. Triturate about 5 g of the substance being examined and let it through No. 5 sieve. Transfer about 1 g, accurately weighed, into a 200 ml volumetric flask, add a quantity of 5% acetic acid solution, dissolve by ultrasonic generator, for 30 minutes, cool to room temperature, dilute to volume with 5% acetic acid solution, mix well and filter. Accurately measure 0.5 ml of successive filtrate to the above column, add a few drops of ammonia TS (measure the same volume of successive filtrate to adjust previously and examine the quantity of ammonia TS) mix well, rinse with 20 ml of water after no solvent drips. Elute with 5% acetic acid solution containing 20% of methanol. Collect the eluate with 5 ml volumetric flask to the volume and mix well. Inject 10 μ l of the eluate into the column.

Dissolve a quantity of morphine CRS, accurately measured, in 5% acetic acid solution containing 20% of methanol and dilute to produce reference solution of 0.05 mg per ml, repeat the operation. Calculate the content of $C_{17}H_{19}NO_3$ with respect to the peak area obtained in the chromatogram by the external standard method.

Category As described under Powdered Opium.

Storage Preserve in tightly closed containers and stored at a temperature below 30°C.

Powdered Opium

Powdered Opium is opium dried at a temperature below 70°C, reduced to fine powder and prepared by the addition of lactose or other diluents after determining the content of morphine. It contains not less than 9.5% and not more than 10.5% of morphine, calculated with reference to anhydrous morphine ($C_{17}H_{19}NO_3$).

Description A light brown to yellowish-brown powder; odour, characteristic; taste, very bitter.

Identification Comply with the tests for Identification described under Opium.

Assay Carry out the assay described under Opium using a quantity of the powder.

Category As described under Opium.

Storage Preserve in tightly closed containers.

Preparation (1) Opium Tablets (2) Opium Tincture
(3) Compound Platycodon Tablets
(4) Compound Liquorice Tablets

Oral Rehydration Salts I

Oral Rehydration Salts I contains 1.575-1.925 g of sodium chloride (NaCl), 0.675-0.825 g of potassium chloride (KCl), 1.125-1.375 g of sodium bicarbonate and 9.90-12.10 g of glucose ($C_6H_{12}O_6 \cdot H_2O$), in each package.

Formula	Sodium chloride	1750 g
	Sodium Bicarbonate	1250 g
	Potassium Chloride	750 g
	Glucose	11000 g

to make 1000 packages

Preparation Triturate glucose and sodium chloride to fine powder, mix well, pack in bulk; triturate potassium chloride and sodium bicarbonate to fine powder, mix well, divide into small package; pack the bulk and small packages together in a container

Description A white crystalline powder.

Identification *Large bag* (1) Comply with the test (1) for Identification described under glucose.
(2) An aqueous solution yields the reactions characteristic of sodium salts and chlorides (Appendix III).

Small bag An aqueous solution yields the reactions characteristic of potassium salts, sodium salts, chlorides and bicarbonates (Appendix III).

Weight variation of contents Take 10 packages, weigh separately the contents of each large bag and small bag in each container. The difference between each bag and the labelled amount; large bag should be not more than $\pm 5\%$ and small bag should be not more than $\pm 7\%$. Not more than 2 bags exceeding the weight variation limit and none exceeding the double amount of weight variation limit.

Assay *Sodium chloride* Dissolve about 0.7 g of the contents of large bag, accurately weighed, in 50 ml of water, add 5 ml of 2% dextrin solution, about 0.1 g of calcium carbonate and 5 drops of fluorescein IS, titrate with silver nitrate (0.1 mol/L) VS. Each ml of silver nitrate (0.1 mol/L) VS is equivalent to 5.844 mg of NaCl.

Potassium chloride Dissolve about 0.4 g of the contents of small bag, accurately weighed, in 50 ml of water, add 1 drop of phenolphthalein IS, add a quantity of dilute sulfuric acid to discharge the red colour, add 5 ml of 2% dextrin solution, about 0.1 g of calcium carbonate and 5 drops of fluorescein IS, titrate with silver nitrate (0.1 mol/L) VS. Each ml of silver nitrate (0.1 mol/L) is equivalent to 7.455 mg of KCl.

Sodium bicarbonate Dissolve about 0.24 g of the contents of small bag, accurately weighed, in 50 ml of water, add 1 drop of methyl orange IS, titrate with sulfuric acid (0.05 mol/L) VS. Each ml of sulfuric acid (0.05 mol/L) VS is equivalent to 8.401 mg $NaHCO_3$.

Glucose Weigh accurately about 12 g of the contents of large bag in a 100 ml volumetric flask, add 80 ml of water to dissolve, add 0.2 ml of ammonia TS, dilute with water to volume, mix well, allow to stand for 30 minutes, carry out the determination of optical rotation (Appendix VI E). The observed rotation in degree multiplied by 2.0852 represents the weight in g of $C_6H_{12}O_6 \cdot H_2O$.

Category Electrolytes replenisher.

Strength 1.575 g sodium chloride, 0.675 g potassium chloride and 1.125 g sodium bicarbonate in each package.

sodium chloride in large bags; 0.75 g of potassium chloride and 1.25 g of sodium bicarbonate in small bags)

Storage Preserve in tightly closed containers, stored in a dry place.

Oral Rehydration Salts II

Oral Rehydration Salts II contains 0.370-0.452 g of sodium (Na), 0.138-0.173 g of potassium (K), 0.510-0.624 g of total chlorine (Cl); 0.522-0.638 g of sodium citrate ($C_6H_5Na_3O_7 \cdot 2H_2O$) and 3.60-4.40 g of anhydrous glucose ($C_6H_{12}O_6$) in each package (for 5.58 g strength); Oral Rehydration Salts II contains 0.926-1.131 g of sodium (Na), 0.354-0.433 g of potassium (K), 1.276-1.560 g of total chlorine (Cl); 1.305-1.595 g of sodium citrate ($C_6H_5Na_3O_7 \cdot 2H_2O$) and 9.00-11.00 g of anhydrous glucose ($C_6H_{12}O_6$) in each package (for 13.95 g strength); Oral Rehydration Salts II contains 1.852-2.262 g of sodium (Na), 0.708-0.866 g of potassium (K), 2.552-3.120 g of total chlorine (Cl); 2.610-3.190 g of sodium citrate ($C_6H_5Na_3O_7 \cdot 2H_2O$) and 18.00-22.00 g of anhydrous glucose ($C_6H_{12}O_6$) in each package (for 27.9 g strength);

Description A white crystalline powder.

Identification (1) Comply with the test (1) for Identification described under glucose.

(2) Dissolve 1 g in 1 ml of water, add 1 ml of dilute acetic acid, mix well, add 0.5 ml sodium cobaltinitrite TS; a yellow precipitate is produced.

(3) An aqueous solution yields the reactions characteristic of chlorides, sodium salts and citrates (Appendix III).

Alkalinity Dissolve 1.4 g in 50 ml of water, pH 7.0-8.8 (Appendix VI H).

Loss on drying When dried to constant weight at 60°C, loses not more than 2.0% of its weight (Appendix VIII L).

Weight variation of contents Take 10 packages, weigh accurately the contents in each of them. The difference of each weight with the labelled amount is not more than $\pm 5\%$ (for 5.58 g strength) or $\pm 3\%$ (for 13.95 g and 27.9 g strength). Not more than 2 packages exceeding the weight variation limit, and none exceeding the double weight variation limit.

Assay *Total sodium* Reference solution; Dissolve about 1.0 g weighed accurately, previously dried to constant weight at 110°C, of sodium chloride (AR), in water in a 200 ml volumetric flask, dilute to volume and mix well. Measure accurately 5 ml to a 100 ml volumetric flask, dilute with water to volume, mix well. Measure accurately 1, 2 and 3 ml to three 100 ml volumetric flasks separately, then add 2, 4 and 6 ml of 10% strontium chloride solution accordingly, dilute with water to volume and mix well.

Test solution; Dissolve about 13 g with water in a 250 ml volumetric flask, dilute with water to volume, mix well, as solution (1). Measure accurately 5 ml to a 100 ml volumetric flask, dilute with water to volume, mix well; then measure accurately 1 ml to a 100 ml volumetric flask, add 4 ml of 10% strontium chloride solution, dilute with water to volume and mix well.

Procedure Carry out the method for atomic absorption

spectrophotometry (Appendix IV D assay, method 1), measure the absorbances at 589.0 nm of the test solution and the reference solution. Calculate the content of total sodium (Na).

Potassium R : D v t l g, previously dried at 130°C to constant weight, of potassium chloride (AR), accurately weighed, in water in a 200 ml volumetric flask and dilute to volume, mix well. Measure accurately 5 ml to a 100 ml volumetric flask, dilute with water to volume, mix well. Measure accurately 1, 2 and 3 l fl s p ly, h , 6 and 9 ml of 10% strontium chloride solution accordingly, dilute with water to volume, mix well.

Test solution: Measure accurately 5 ml of the solution (1) obtained in the test for total sodium to a 50 ml volumetric flask, dilute with water to volume, mix well. Then measure accurately 2 ml to a 100 ml volumetric flask, add 6 ml of 10% strontium chloride solution, dilute with water to volume and mix well.

Procedure: Carry out the method for atomic adsorption spectrophotometry (Appendix IV D assay method 1), measure the absorbances of the two solutions at 766.5 nm. Calculate the content of potassium (K).

Total chlorine Dissolve about 2.8 g, accurately weighed in a 100 ml volumetric flask, with water and dilute to volume. Measure accurately 10 ml, add 3-5 drops of potassium chromate IS, titrate with silver nitrate (0.1 mol/L) VS slowly to the end point. Each ml of silver nitrate (0.1 mol/L) VS is equivalent to 3.545 mg of total chlorine (Cl).

Sodium citrate Weigh accurately about 2.8 g into a 100 ml volumetric flask, add 80 ml glacial acetic acid, shake well, heat at 50°C, cool to room temperature, dilute with glacial acetic acid to volume and mix well. Allow to stand, measure accurately 20 ml of the supernatant liquid, add 1 drop of crystal violet IS, titrate with perchloric acid (0.1 mol/L) VS, until the solution turns blue. Perform a blank determination and make any necessary correction. Each ml of perchloric acid (0.1 mol/L) VS is equivalent to 9.803 mg of $C_6H_5Na_3O_7 \cdot 2H_2O$.

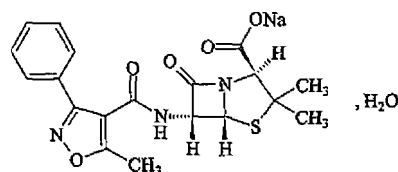
Anhydrous glucose Dissolve about 13 g, accurately weighed, in a 100 ml volumetric flask with 80 ml of water, add 0.2 ml of ammonia TS, dilute with water to volume and mix well. Allow to stand for 30 minutes, carry out the determination of optical rotation (Appendix IV E). The observed rotation in degree multiplied by 1.8954 represents the weight in g of $C_6H_{12}O_6$.

Category Electrolyte replenisher.

- Strength**
- (1) 5.58 g per package (0.7 g of sodium chloride, 0.3 g of potassium chloride, 0.58 g of sodium citrate, 4 g of anhydrous glucose. Dissolve with 500 ml of water before use.)
 - (2) 13.95 g per package (1.75 g of sodium chloride, 0.75 g of potassium chloride, 1.45 g of sodium citrate, 10 g of anhydrous glucose. Dissolve with 1000 ml of water before use.)
 - (3) 27.9 g per package (3.5 g of sodium chloride, 1.5 g of potassium chloride, 2.9 g of sodium citrate, 20 g of anhydrous glucose. Dissolve with 2000 ml of water before use.)

Storage Preserve in tightly closed containers, stored in a dry place.

Oxacillin Sodium



$C_{19}H_{18}N_3NaO_5S \cdot H_2O$ 441.44

[7240-38-2]

Oxacillin Sodium is Sodium (2S, 5R, 6R)-3,3-dimethyl-6-(5-methyl-3-phenyl-4-isoxazolecarboxamido)-7-oxo-4-thia-1-azabicyclo[3.2.0]-heptane-2-carboxylate monohydrate. It contains not less than 90.0% of $C_{19}H_{18}N_3NaO_5S$, Calculated on the anhydrous basis.

Description A white powder or crystalline powder; odourless or odour slightly.

Freely soluble in water; very slightly soluble in acetone, or butanol; practically insoluble in ethyl acetate, or petroleum ether.

Specific optical rotation +195° to +214°, in a solution of 10 mg per ml in water (Appendix VI E).

Identification (1) The retention time of principal peak in the substance being examined in the chromatogram obtained in the Assay is identical with that of the principal peak of oxacillin sodium CRS in the chromatogram of the reference solution correspondingly.

(2) The infrared absorption spectrum is concordant with the spectrum of oxacillin sodium CRS.

(3) Yields the flame reaction of sodium salts (Appendix III).

Acidity Dissolve a quantity in water to produce a solution of 20 mg per ml, pH 5.0-7.0 (Appendix VI H).

Clarity and colour of solution To 5 portions each of 0.6 g add 5 ml of water respectively, the solutions are clear and colourless; any opalescence produced is not more pronounced than that of reference suspension I (Appendix IX B).

Related substances Dissolve an accurately weighed quantity in water to produce a test solution of 1 mg per ml. Dilute an accurately measured quantity with water to produce a reference solution of 0.01 mg per ml. Carry out the method described under Assay, inject 10 μ l of the reference solution into the column, adjust the attenuation so that the principal peak height in the chromatogram is 20% of the full scale of the chart. Inject 10 μ l of the test solution and the reference solution respectively, and record the chromatogram for 3.5 times the retention time of the principal peak. In the chromatogram obtained with the test solution, the area of any peak, apart from the principal peak, is not greater than the area of the principal peak in the chromatogram obtained with the reference solution (1.0%); the sum of the areas of all the peaks, apart from the principal peak, is not greater than the area of the principal peak in the chromatogram obtained with the reference solution (5.0%).

Water Not more than 5.0% (Appendix VIII M, method 1 A).

Bacterial endotoxin Carry out the test for bacterial endotoxin (Appendix XI E); less than 0.1 EU per ml. (for parenteral use).

Carry out the test for sterility (Appendix XI

H. membrane filtration method), dissolving a quantity in the suitable solvent and transferring the solution to not less than 500 ml of 0.9% sterile sodium chloride solution for parenteral use.

Assay Carry out the method for high performance liquid chromatography (Appendix V D), using a column packed with phenylsilane bonded silica gel and a mixture of 0.02 mol/L potassium dihydrogen phosphate solution (adjust the pH with phosphoric acid to 3.6) -acetonitrile-methanol(700:225:75) as the mobile phase. Detection wavelength is 225 nm. Inject 10 μ l of the reference solution of oxacillin sodium CRS into the column and record the chromatogram. The number of the theoretical plates of the column is not less than 2000 calculated with reference to the peak of oxacillin. The tailing factor is not more than 1.8.

procedure Dissolve an accurately weighed quantity of oxacillin sodium in water to produce a solution of 0.1 mg per ml. Inject 10 μ l of the solution into the column and record the chromatogram. Repeat the operation, using oxacillin sodium CRS. Calculate the content of $C_{19}H_{19}N_3O_5S$ with respect to the peak area obtained in the chromatogram by the external standard method.

Category β -Lactam antibiotic, penicillins.

Storage Preserve in hermetically sealed containers, stored in a dry place.

Preparation Oxacillin sodium for Injection

Oxacillin Sodium for Injection

Oxacillin Sodium for Injection is a sterile powder of Oxacillin Sodium. It contains not less than 90.0% of oxacillin ($C_{19}H_{19}N_3O_5S$), calculated on the anhydrous basis. It contains not less than 95.0% and not more than 105.0% of the labelled amount of oxacillin ($C_{19}H_{19}N_3O_5S$), calculated on the basis of the average weight of contents.

Description A white, crystalline or amorphous powder.

Identification Comply with the tests for Identification described under Oxacillin Sodium.

Clarity and colour of solution To each of 5 containers add water to produce solutions of 0.1 g per ml, the solutions are clear and colourless; any opalescence produced is not more pronounced than that of reference suspension 1 (Appendix IX B).

Related substances Carry out the Assay described under Oxacillin Sodium, using an accurately weighed quantity of the mixed contents obtained from the test for weight variation of contents. In the chromatogram obtained with the test solution; the area of any peak, apart from the principal peak, is not greater than 2 times the area of the principal peak in the chromatogram obtained with the reference solution (2.0%); the sum of the areas of all the peaks, apart from the principal peak, is not greater than 5 times the area of the principal peak in the chromatogram obtained with the reference solution (5.0%).

Water Not more than 5.5% (Appendix VIII M, method 1 A).

Acidity, Bacterial endotoxin and sterility Complies with the corresponding tests described under Oxacillin Sodium.

Other requirements Comply with the general requirements for injections (Appendix I B), except the weight variation

of content is not more than $\pm 7.0\%$.

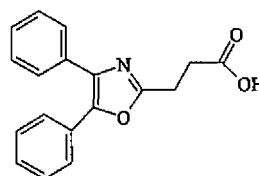
Assay Carry out the Assay described under Oxacillin Sodium, using an accurately weighed quantity of the mixed contents obtained from the test for weight variation of contents.

Category As described under Oxacillin Sodium.

Strength calculated as $C_{19}H_{19}N_3O_5S$
(1) 0.5 g (2) 1 g

Storage Preserve in well closed containers, stored in a dry place.

Oxaprozin



$C_{18}H_{15}NO_3$ 293.32

[21256-18-8]

Oxaprozin is (4,5-diphenyloxazol-2-yl) propionic acid. It contains not less than 98.5% of $C_{18}H_{15}NO_3$, calculated on the dried basis.

Description A white or almost white crystalline powder; odourless or with a slight characteristic odour; taste, slightly bitter.

Freely soluble in dimethylformamide or dioxane; soluble in chloroform or glacial acetic acid; sparingly soluble in dehydrated ethanol; slightly soluble in ether or benzene; practically insoluble in water.

Melting range 161-165°C (Appendix VI C).

Identification (1) The light absorption of a solution of 20 μ g per ml in ethanol exhibits two maxima at 286 nm and 222 nm (Appendix IV A).

(2) The infrared absorption spectrum (Appendix IV C) is concordant with the reference spectrum of oxaprozin CRS (Appendix XVI).

Acidity Dissolve 1 g in 20 ml of water and shake thoroughly, heat to boiling, cool to room temperature and filter. To the filtrate add 1 drop of phenolphthalein IS, titrate with sodium hydroxide (0.01 mol/L) VS; not more than 0.5 ml of sodium hydroxide (0.01 mol/L) VS is required.

Related substances Carry out the method for high performance liquid chromatography (Appendix V D), using a column packed with octadecylsilane bonded silica gel and a mixture of acetonitrile-water (adjust with phosphoric acid to pH of 2.5) (50:50) as the mobile phase. Detection wavelength is 254 nm, and the number of theoretical plates of the column is not less than 2000, calculated with reference to the peak oxaprozin. Dissolve a quantity in acetonitrile to produce a solution of 2.0 mg per ml as the test solution. Measure accurately a quantity of the test solution and dilute with acetonitrile to produce the reference solution of 20 μ g per ml. Inject 20 μ l of the reference solution into the column adjust the attenuation so that the principal peak height in the chromatogram is 10%-30% of the full scale of the chart. Inject separately 20 μ l each of the test and reference solution, both accurately measured, into the column and record the chromatogram for 5 times the retention time of the principal peak. The sum of peak areas due to impurities is not greater

than the principal peak area of the reference solution.

Loss on drying When dried to constant weight at 105°C, loses not more than 1.0% of its weight (Appendix VIII L).

Residue on ignition Not more than 0.1% (Appendix VIII N), using 1.0 g.

Heavy metals Carry out limit test for heavy metals (Appendix VIII H, method 2), using the residue obtained in the test for Residue on ignition; not more than 0.002%.

Assay To 0.3 g, accurately weighed, add 25 ml dehydrated ethanol (neutral to phenolphthalein), shake to dissolve. Add 2 drops of phenolphthalein IS and titrate with sodium hydroxide (0.1 mol/L) VS. Each ml of sodium hydroxide (0.1 mol/L) VS is equivalent to 29.33 mg of $C_{18}H_{15}NO_3$.

Category Antipyretic and analgesic non-steroids anti-inflammatory agent.

Storage Preserve in tightly closed containers, protected from light.

Preparation (1) Oxaprozin Enteric-coated Capsules
(2) Oxaprozin Enteric-coated Tablets

Oxaprozin Enteric-coated Capsules

Oxaprozin Enteric-coated Capsules contain not less than 90.0% and not more than 110.0% of the labelled amount of oxaprozin ($C_{18}H_{15}NO_3$).

Description Capsules containing white or almost white powder or granules.

Identification (1) Powder finely the content of the capsules and dissolve a quantity of the powder equivalent to about 0.1 g of oxaprozin in 20 ml of ethanol on a water bath, filter and evaporate the filtrate on a water bath to dryness, dissolve about 20 mg of the residue in warm dilute sulfuric acid, add dropwise potassium iodobismuthate TS, an orangere precipitate is produced.

(2) Protect from light throughout the procedure. Dissolve a quantity of the content equivalent to about 0.1 g of oxaprozin in 8 ml of methanol by shaking and filter, transfer the filtrate to a 10 ml volumetric flask and dilute to volume with methanol, mix well and use this solution as test solution. Prepare reference solution of 10 mg of oxaprozin CRS per ml in methanol. Carry out the method for thin-layer chromatography (Appendix V B), using silica gel GF254 as the coating substance and a mixture of chloroform-glacial acetic acid (40:0.5) as the mobile phase. Apply separately to the plate 5 μ l of each of above two solutions. After developing and removal of the plate, dry it in air, and examine under ultra-violet light (254 nm). The position and colour of the principal spot in the chromatogram obtained with the test solution correspond to the principal spot obtained with the reference solution.

(3) The light absorption of the solution obtained in the Assay exhibits two maxima at 222 nm and 286 nm (Appendix IV A).

Related substances Protect from light throughout the procedure. Dissolve a quantity of the content of the capsules in a quantity of acetonitrile to produce a solution of 2 mg per ml, filter and use the successive filtrate as solution 1; Measure accurately 1 ml into a 100 ml volumetric flask, dilute to volume with mobile phase, mix well as solution 2. Carry out the method for high performance liquid chromatography (Appendix V D), using a column packed

(adjust pH to 2.5 with phosphoric acid) -acetonitrile (50:50) as the mobile phase. The detection wavelength is 254 nm. The number of the theoretical plates of the column is not less than 2000, calculated with reference to the peak of oxaprozin. Inject 20 μ l of solution (2) into the column. Adjust the attenuation so that the principal peak height in chromatogram is between 10% and 30% of the full scale of the chart. And then inject separately 20 μ l of each of solution (1) and (2) into the column, and record the chromatogram for 5 times the retention time of the principal peak. The sum of the areas of all peaks other than the principal peak in the chromatogram obtained with solution (1) are not greater than 1.5 times the area of the principal peak in the chromatogram obtained with solution (2).

Drug Release Protect from light throughout the procedure. Carry out the Drug Release Test [(Appendix X D, method 2 (2)), using the apparatus of the dissolution test method II and 1000 ml of hydrochloric acid solution (9→1000) as the release medium initially, adjust the rotational speed of the paddle to 100 rpm. Any enteric-coated capsule shows no cracking or disintegrating at 2 hours. Then use 1000 ml of phosphate BS (pH 6.8) as the release medium, use the same rotational speed, continue to operate the apparatus, withdraw a quantity of the solution at 45 minutes and filter. Dilute 5 ml of successive filtrate, accurately measured, with above buffer to 100 ml and mix well.

Dissolve a quantity of oxaprozin CRS, accurately weighed, in phosphate BS (pH 6.8) to produce a solution containing 10 μ g per ml. Measure the absorbances of the resulting solutions at 285 nm (Appendix IV A). Calculate the dissolution of $C_{18}H_{15}NO_3$ from each capsule. Not less than 70% of the labelled amount is dissolved.

Other requirements Comply with the general requirements for capsules (Appendix I E).

Assay Protect from light throughout the procedure. Transfer a quantity of the content of the capsules equivalent to about 50 mg of oxaprozin, accurately weighed, to a 100 ml volumetric flask, add a quantity of ethanol, shake thoroughly to dissolve oxaprozin and dilute to volume with ethanol, mix well and filter, dilute 2 ml of successive filtrate, accurately measured, with ethanol to 100 ml and mix well. Dissolve a quantity of oxaprozin CRS, accurately weighed, in ethanol to produce a solution containing about 10 μ g per ml. Measure the absorbances of the resulting solutions at 286 nm (Appendix IV A), calculate the content of $C_{18}H_{15}NO_3$.

Category As described under Oxaprozin.

Strength 0.2 g

Storage Preserve in tightly closed containers and protected from light.

Oxaprozin Enteric-coated Tablets

Oxaprozin Enteric-coated Tablets contain not less than 90.0% and not more than 110.0% of the labelled amount of oxaprozin ($C_{18}H_{15}NO_3$).

Description Enteric coated tablets with white or almost white core.

Identification (1) Powder finely the tablets with coating removed and dissolve a quantity of the powder equivalent to about 0.1 g of oxaprozin in 20 ml of ethanol on a water bath, filter and evaporate the filtrate on a water bath to dryness, dissolve about 20 mg of the residue in warm dilute sulfuric acid, add dropwise potassium iodobismuthate TS and an

orange-red precipitate is produced.

(2) Protect from light throughout the procedure. Dissolve a quantity of the powder equivalent to about 0.1 g of oxaprozin in 8 ml of methanol by shaking and filter, transfer the filtrate to a 10 ml volumetric flask and dilute to volume with methanol, mix well and use this solution as a test solution. Prepare a reference solution of 10 mg of oxaprozin CRS per ml in methanol. Carry out the method for thin-layer chromatography (Appendix V B), using silica gel GF254 as the coating substance and a mixture of chloroform-glacial acetic acid (40:0.5) as the mobile phase. Apply separately to the plate 5 μ l of each of above two solutions. After developing and removal of the plate, dry it in air, and examine under ultra-violet light (254 nm). The position and colour of the principal spot in the chromatogram obtained with the test solution correspond to the principal spot obtained with the reference solution.

(3) The light absorption of the solution obtained in the Assay exhibits two maxima at 222 nm and 286 nm (Appendix IV A).

Related substances Protect from light throughout the procedure. Dissolve a quantity of the powdered tablets obtained in Assay in a quantity of acetonitrile to produce a solution of 2 mg per ml, filter and use the filtrate as solution 1; Measure accurately 1 ml into a 100 ml volumetric flask, dilute to volume with mobile phase, mix well as solution 2. Carry out the method for high performance liquid chromatography (Appendix V D), using a column packed with octadecylsilane bonded silica gel and a mixture of water (adjust pH to 2.5 with phosphoric acid) -acetonitrile (50:50) as the mobile phase. The detection wavelength is 254 nm. The number of the theoretical plates of the column is not less than 2000, calculated with reference to the peak of oxaprozin.

Inject 20 μ l of solution (2) into the column. Adjust the attenuation so that the principal peak height in chromatogram is between 10% and 30% of the full scale of the chart. And then inject separately 20 μ l of each of solution (1) and (2) into the column, and record the chromatogram for 5 times the retention time of the principal peak. The sum of the areas of all peaks other than the principal peak in the chromatogram obtained with solution (1) are not greater than 1.5 times the area of the principal peak in the chromatogram obtained with solution (2).

Drug Release Protect from light throughout the procedure. Carry out the Drug Release Test [Appendix X D, method 2 (2)], using the apparatus of the dissolution test method I and 1000 ml of hydrochloric acid solution (9 \rightarrow 1000) as the release medium initially, adjust the rotational speed of the basket to 100 rpm. Any enteric-coated tablet shows no cracking or disintegrating at 2 hours. Then use 1000 ml of phosphate BS (pH 6.8) as the release medium, use the same rotational speed, continue to operate the apparatus, withdraw a quantity of the solution at 45 minutes and filter. Dilute 5 ml of successive filtrate, accurately measured, with above buffer to 100 ml and mix well.

Dissolve a quantity of oxaprozin CRS, accurately weighed, in phosphate BS (pH 6.8) to produce a solution containing 10 μ g per ml. Measure the absorbances of the resulting solutions at 285 nm (Appendix IV A). Calculate the dissolution of $C_{18}H_{15}NO_3$ from each tablet. Not less than 70% of the labelled amount is dissolved.

Other requirements Comply with the general requirements for tablets (Appendix I A).

Assay Protect from light throughout the procedure. Weigh accurately and powder finely 10 tablets with enteric coating removed. Transfer a quantity of the powder equivalent to about 50 mg of oxaprozin, accurately weighed, to a 100 ml

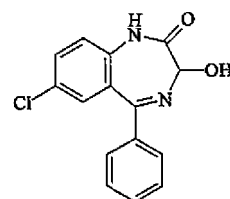
volumetric flask, add a quantity of ethanol, shake thoroughly to dissolve oxaprozin and dilute to volume with ethanol, mix well and filter, dilute 2 ml of successive filtrate, accurately measured, with ethanol to 100 ml and mix well. Dissolve a quantity of oxaprozin CRS, accurately weighed, in ethanol to produce a solution containing about 10 μ g per ml. Measure the absorbances of the resulting solutions at 286 nm (Appendix IV A), calculate the content of $C_{18}H_{15}NO_3$.

Category As described under Oxaprozin.

Strength 0.2 g

Storage Preserve in tightly closed containers, protected from light.

Oxazepam



$C_{15}H_{11}ClN_2O_2$ 286.72

[604-75-1]

Oxazepam is (\pm)-7-chloro-1,3-dihydro-3-hydroxy-5-phenyl-2H-1,4-benzodiazepin-2-one. It contains not less than 98.0% and not more than 102.0% of $C_{15}H_{11}ClN_2O_2$, calculated on the dried basis.

Description A white or almost white crystalline powder; almost odourless.

Slightly soluble in ethanol, chloroform or acetone; very slightly soluble in ether; practically insoluble in water.

Melting range 198-202°C, with decomposition (Appendix VI C).

Identification (1) To about 10 mg add 15 ml of hydrochloric acid solution (1 \rightarrow 2), heat gently to boiling and cool in an ice bath. Add 4 ml of sodium nitrite TS, dilute with water to produce 20 ml and allow to stand for 10 minutes in an ice bath. Add alkaline β -naphthol TS dropwise, an orange red precipitate is produced, which darkens on standing.

(2) The light absorption of a solution of 10 μ g per ml in ethanol exhibits two maxima at 229 nm and 315 nm (Appendix IV A).

(3) The infrared absorption spectrum (Appendix IV C) is concordant with the reference spectrum of oxazepam (Appendix XVI).

Related substances Carry out the method for thin-layer chromatography (Appendix V B), using silica gel HF₂₅₄ as the coating substance and a mixture of chloroform-methanol (100:10) as the mobile phase. Apply separately to the plate 20 μ l of each of the following solutions in acetone containing (1) 5 mg per ml, (2) 10 μ g per ml, (3) 5 μ g per ml of the substance being examined. After developing and removal of the plate, dry it in air, examine under ultra-violet light (254 nm). Any spot, other than the principal spot, obtained with solution (1) is not more intense than the principal spot obtained with solution (2); not more than one secondary spots are more intense than the principal spot in the chromatogram obtained with solution (3).

Acidity To 1.0 g add 50 ml of water to produce a

suspension; pH 5.0-7.0 (Appendix VI H).

Loss on drying When dried to constant weight at 105°C, loses not more than 1.0% of its weight (Appendix VIII L).

Residue on ignition Not more than 0.1% (Appendix VIII N).

Assay Weigh accurately about 15 mg to a 200 ml volumetric flask, add 150 ml of ethanol, warm on a water bath with frequent shaking to dissolve oxazepam, cool, dilute with ethanol to volume, mix well. Measure accurately 5 ml of the solution to a 100 ml volumetric flask, dilute with ethanol to volume, mix well. Measure the absorbance of the resulting solution at 229 nm (Appendix IV A). Repeat the operation using oxazepam CRS instead of the substance being examined, calculate the content of $C_{15}H_{11}ClN_2O_2$.

Category Anxiolytic.

Storage Preserve in tightly closed containers, protected from light.

Preparation Oxazepam Tablets

Oxazepam Tablets

Oxazepam Tablets contain not less than 90.0% and not more than 110.0% of the labelled amount of oxazepam ($C_{15}H_{11}ClN_2O_2$).

Description White tablets.

Identification (1) Place a quantity of the powdered tablets equivalent to about 15 mg of oxazepam in a separator, add 2 ml of water, shake with 15 ml of chloroform, evaporate the chloroform extract to dryness on a water bath. The residue complies with test (1) for Identification described under Oxazepam.

(2) The light absorption of the solution obtained in Assay exhibits two maxima at 229 nm and 315 nm (Appendix IV A).

Dissolution Carry out the dissolution test (Appendix X C, method 2), using 1000 ml of hydrochloric acid solution (9→1000) as the dissolution medium, adjust the rotational speed of the paddle to 50 rpm. Withdraw a quantity of the solution at 60 minutes and filter, use the successive filtrate as the test solution. Weigh accurately about 15 mg of oxazepam CRS to a 100 ml volumetric flask, add 10 ml of ethanol to dissolve oxazepam, dilute with dissolution medium to volume, mix well. Measure accurately 5 ml of the solution to a 50 ml volumetric flask, dilute with dissolution medium to volume, mix well, use it as the reference solution. Measure the absorbance of the resulting solutions at 283 nm (Appendix IV A). Calculate the dissolution of $C_{15}H_{11}ClN_2O_2$ from each tablet; not less than 70% of the labelled amount is dissolved.

Other requirements Comply with the general requirements for tablets (Appendix I A).

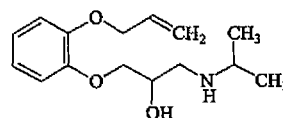
Assay Weigh accurately and powder 20 tablets. Transfer an accurately weighed quantity of the powder, equivalent to about 15 mg of oxazepam, to a 200 ml volumetric flask. Add 150 ml of ethanol and warm on a water bath with frequent shaking to dissolve oxazepam, cool, dilute with ethanol to volume and mix well. Measure accurately 5 ml of the successive filtrate to a 100 ml volumetric flask, dilute with ethanol to volume and mix well. Measure the absorbance at 229 nm (Appendix IV A), calculate the content of $C_{15}H_{11}ClN_2O_2$, taking 1252 as the value of A

Category As described under Oxazepam.

Strength 15 mg

Storage Preserve in tightly closed containers, protected from light.

Oxprenolol



$C_{15}H_{23}NO_3$ 265.21

[6452-71-7]

Oxprenolol is 1-[2-[(2-propenyl)oxy]phenoxy]-3-isopropylamino-2-propanol. It contains not less than 98.5% of $C_{15}H_{23}NO_3$, calculated on the dried basis.

Description A white crystalline powder; taste, bitter.

Freely soluble in ethanol or acetone; sparingly soluble in ether or chloroform; slightly soluble in water.

Identification (1) Dissolve 0.1 g in 2 ml of ethanol, add 1 ml of 0.1 mol/L potassium permanganate solution dropwise, shake for several minutes; the colour of potassium permanganate disappears, and a brown precipitate is produced.

(2) The light absorption of a solution of 40.0 µg per ml in ethanol exhibits a maximum at 275 nm (Appendix IV A).

Melting point 77°C to 80°C (Appendix VI C)

Loss on drying When dried in vacuum over phosphorous pentoxide for 24 hours, loses not more than 1.0% of its weight (Appendix VIII C).

Residue on ignition Not more than 0.1% (Appendix VIII N), using 1.0 g.

Heavy metals Carry out the limit test for heavy metals (Appendix VIII H, method 2), using the residue obtained in the test for Residue on ignition; not more than 0.002%.

Assay Dissolve 0.15 g, accurately weighed, in 10 ml of glacial acetic acid, add 1 drop of crystal violet IS, titrate with perchloric acid (0.1 mol/L) VS until the solution turns to blue green. Perform a blank determination and make any necessary connection. Each ml of perchloric acid (0.1 mol/L) VS is equivalent to 26.52 mg of $C_{15}H_{23}NO_3$.

Category β-Adrenergic blocker.

Storage Preserve in tightly closed containers, protected from light.

Preparation Oxprenolol Tablets

Oxprenolol Tablets

Oxprenolol Tablets contain not less than 95.0% and not more than 105.0% of the labelled amount of oxprenolol ($C_{15}H_{23}NO_3$).

Description White tablets.

Identification (1) To 0.3 g of the powdered tablets add 5 ml ethanol with shaking and filter. To the filtrate, add 1 ml

the colour of potassium permanganate disappears, and a brown precipitate is produced.

(2) The light absorption of the solution of 40 μg of oxprenolol per ml in ethanol exhibits a maximum at 275 nm (Appendix IV A).

Other requirements Comply with the general requirements for tablets (Appendix I A).

Assay Weigh accurately and triturate 30 tablets, weigh accurately a quantity equivalent to about 0.2 g of oxprenolol to an iodine flask, add accurately 50 ml of chloroform, extract by shaking and filter. Measure accurately 25 ml of the successive filtrate to a conical flask, add 2 drops of dimethyl yellow IS, titrate with perchloric acid (0.1 mol/L) VS until the colour turns to pink. Perform a blank determination and make any necessary correction. Each ml of perchloric acid (0.1 mol/L) is equivalent to 26.52 mg of $\text{C}_{15}\text{H}_{23}\text{NO}_3$.

Category As described under oxprenolol.

Strength 20 mg

Storage Preserve in tightly closed containers, protected from light.

Oxygen

O_2 32.00

[7782-44-7]

Oxygen contains not less than 99.0% (ml/ml) of O_2 .

Description A colourless gas; odourless; tasteless; with strong combustion-supporting property. Soluble in 7 volumes of ethanol or 32 volumes of water at 20°C under normal atmosphere pressure.

Identification Causes a glowing splinter of wood to burst into flame.

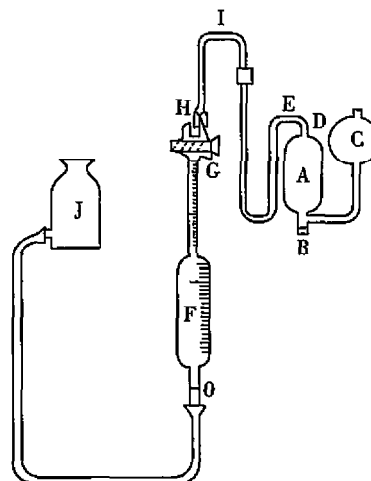
Acidity or alkalinity To 0.3 ml each of methyl red IS and bromothymol blue IS add 400 ml of water, boil for 5 minutes, allow to cool. Transfer 100 ml each of three portions to three Nessler cylinders (A, B and C). Add 0.20 ml of hydrochloric acid (0.01 mol/L) VS to cylinder B and 0.40 ml of hydrochloric acid (0.01 mol/L) VS to cylinder C. Pass 2000 ml of the gas being examined through cylinder B with a flow rate of 4000 ml per hour. Any colour produced in cylinder B is not more intense than the red colour in cylinder C or the green colour in cylinder A.

Carbon monoxide To each of two Nessler cylinders (A and B) add 25 ml of slightly warmed ammoniated silver nitrate TS and pass 1000 ml of the gas being examined through cylinder A with a flow rate of 4000 ml per hour. The solutions in both cylinders are clear and colourless.

Carbon dioxide To each of two Nessler Cylinders A and B add 100 ml of 5% barium hydroxide solution, transfer 1.0 ml of 0.04% sodium hydrogen carbonate solution to cylinder B. Pass 1000 ml of the gas being examined through cylinder A with a flow rate of 4000 ml per hour. Any opalescence produced is not more pronounced than that of cylinder B (0.01%).

Other oxides in gas state To a Nessler Cylinder add 100 ml of freshly prepared potassium iodide-starch solution (dissolve 0.5 g of potassium iodide in 100 ml of starch IS) and 1 drop of acetic acid. Pass 2000 ml of the gas being examined through the cylinder with a flow rate of 4000 ml per hour. The solution is colourless.

Assay Apparatus As shown in the figure. A and C are absorbers with total capacity of about 300 ml; B is a stopper; D, E and I are glass tubes; F is the main body of a gas burette 100 ml in capacity, graduated in divisions of 0.1 ml; G is a three-way tap; H is the gas inlet and outlet and J is a leveling bottle. Connect the absorber to the gas burette with rubber tubing before use. The burette is then connected to the leveling bottle.



Procedure Fill the absorber A with segments of copper wire (wind up a copper wire about 0.8 mm in diameter into a coil about 4 mm in diameter and cut the coil into small segments about 10 mm in length) and tightly seal it with stopper B. Fill A and part of C with ammonia-ammonium chloride solution (add 200 ml of water to 150 g of ammonium chloride and carefully add 200 ml of concentrated ammonia solution with constant stirring and mix well). Introduce a saturated sodium chloride solution into the leveling bottle J and raise the bottle to fill F with the solution, allow excess of solution to flow out of H. Turn G to connect gas burette with the absorber and lower the leveling bottle to fill tubes D, E, I and the inlet of the tap G, close the tap immediately. Eliminate any gas and ammonia-ammonium chloride solution in the gas burette through H by raising the leveling bottle and turning the tap. Attach a reducing valve (specially intend to be used for oxygen) to the metal gas cylinder and connect a rubber tube to the outlet of the valve. Open the cylinder valve slightly with care and then open the reducing valve to let the oxygen spurt out of the cylinder for 1 minute. Adjust the gas flow until it becomes weaker.

Connect the other end of the rubber tube to H and fill the gas burette with the gas being examined. Close G and disconnect the rubber tube from H, allow to stand for a few minutes. Turn G to connect with H and adjust the leveling bottle (keep the solution level slightly lighter than that in the gas burette in order to prevent the inlet of air from outside) so that the liquid level in the gas burette reaches the 100 ml graduation. Turn G to connect gas burette to the absorber and raise the leveling bottle to introduce the gas into absorber A. Close G when the saturated sodium chloride solution flows through tube I and filled up tube D. Shake absorber A carefully and thoroughly for 5-10 minutes. Turn G to connect the gas burette to the absorber when the absorption of gas is nearly completed (residual gas is nitrogen or other nonabsorbable gases). Lower the leveling bottle to transfer the remaining gas into the gas burette. The tap is closed when the ammonia-ammonium chloride solution filled up absorber A and passed through D, E and I.

Adjust the liquid surface of the leveling bottle after about 5 minutes to equilibrate the pressure of the gas in the gas burette with the atmosphere pressure. Read the level of the

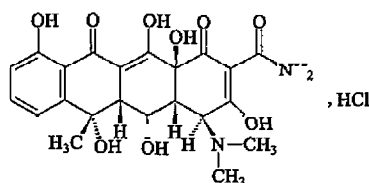
liquid meniscus on the graduated part of the burette and calculate the content of O_2 in the gas.

Repeat the above procedure, beginning at the words "Turn G to connect gas burette to the absorber and raise the leveling bottle..." until the volume of the residual gas is constant (the difference between two operations is not more than 0.05 ml) so as to check the completeness of oxygen absorption. Before the checking or determination, keep the metal gas cylinder under room temperature for not less than 6 hours.

Category For the prevention and treatment of oxygen deficiency.

Storage Preserve in a pressure-resistant metal cylinder, stored at a temperature below 36°C .

Oxytetracycline Hydrochloride



$C_{22}H_{24}N_2O_9 \cdot HCl$ 496.90

[2058-46-0]

Oxytetracycline Hydrochloride is 4-(dimethylamino)-1,4,4a,5,5a,6,11,12a-octahydro-3,5,6,10,12,12a-hexahydroxy-6-methyl-1,11-dioxo-2-naphthacenecarboxamide monohydrochloride. It contains not less than 88.0% of $C_{22}H_{24}N_2O_9$, calculated on the anhydrous basis.

Description A yellow crystalline powder; odourless; taste, slightly bitter; slightly hygroscopic. Darkens on exposure to sunlight and decomposes in alkaline solutions. Freely soluble in water; sparingly soluble in ethanol; insoluble in chloroform or ether.

Specific optical rotation -188° to -200° , in a solution of 10 mg per ml in hydrochloric acid solution (9 \rightarrow 1000), measured on standing for 1 hour, protected from light (Appendix VI E).

Identification (1) To about 0.5 mg add 2 ml of sulfuric acid; a deep red colour is produced; then add 1 ml of water, the colour changes to yellow.

(2) Carry out the method for thin-layer chromatography (Appendix V B). Apply separately to the plate* 1 μ l each of five solutions in methanol containing (1) 1 mg per ml of the substance being examined, (2) 1 mg per ml of oxytetracycline hydrochloride CRS, (3) 1 mg per ml of chlortetracycline hydrochloride CRS, (4) 1 mg per ml of tetracycline hydrochloride CRS, (5) 1 mg each of oxytetracycline hydrochloride CRS, chlortetracycline hydrochloride CRS and tetracycline hydrochloride CRS per ml. Mix 200 ml of acetone-chloroform-ethyl acetate (1:2:2) with 5 ml of 4% disodium edetate solution (pH 7.0) as the mobile phase. After developing and removal of the plate, dry it in air, expose to the vapour of ammonia and examine under an ultraviolet light (365 nm), three clearly separated spots are obtained with solution (5). The position and intensity of fluorescence of the principal spot in the chromatogram obtained with solution (1) correspond to the principal spot obtained with solution (2).

(3) The retention time of the principal peak of the substance being examined in the chromatogram obtained in the Assay is identical with that of the principal peak obtained in the

chromatogram of the reference solution.

(4) The light absorption of a solution of 20 μ g per ml in potassium chloride solution [Dilute 250 ml of 0.2 mol/L potassium chloride solution and 53 ml of 0.2 mol/L hydrochloric acid solution to 1000 ml with water] exhibits a maximum at 353 nm (Appendix IV A), the absorbance is 0.54-0.58.

(5) The aqueous solution yields the reactions characteristic of chlorides (Appendix III).

(2) or (3) may be used alternatively.

Acidity A solution of 10 mg per ml in water, pH 2.3-2.9 (Appendix VI H).

Light-absorbing impurities The absorbance of a solution of 2.0 mg per ml in a mixture of 1 volume of hydrochloric acid solution (0.1 mol/L) and 99 volumes of methanol, at 430 nm, measured within 1 hour, is not greater than 0.50; the absorbance of a solution of 10 mg per ml in the same solvent at 490 nm, measured within 1 hour, is not greater than 0.20 (Appendix IV A).

Related substances Dissolve a quantity of the substance being examined, accurately weighted, in a small volume of 0.1 mol/L hydrochloric acid solution, and dilute to 0.15 mg per ml with water, mix well as the test solution. Dissolve a quantity of the substance being examined, accurately weighted, dilute to 3 μ g per ml with 0.01 mol/L hydrochloric acid solution as reference solution. Carry out the method as described under Assay. Inject 20 μ l of the reference solution into the column, adjust the attenuation so that the principal peak height in the chromatogram is 10% of the full scale of the chart. Inject 20 μ l of the test solution and reference solution respectively into the column, and record the chromatogram for twice the retention time of the principal peak. The sum of the areas of all peaks other than the principal peak in the chromatogram obtained with the test solution is not greater than that of the principal peak in the chromatogram obtained with the reference solution (2.0%).

Water Not more than 2.0% (Appendix VIII M, method 1 A).

Assay Carry out the method for high performance liquid chromatography (Appendix V D), using a column packed with octadecylsilane bonded silica gel (pH adaptive value is greater than 8), and a mixture of 0.05 mol/L ammonium oxalate solution-dimethylformamide -0.2 mol/L diammonium hydrogen phosphate solution (75:20:5) as the mobile phase. Adjust the pH to 8.0 ± 0.2 with ammonia TS. The flow rate is 0.8 ml per minute. The temperature of the column is 35°C . Detection wavelength is 280 nm and the number of the theoretical plates of the column is not less than 2500, calculated with reference to the peak of oxytetracycline. The resolution factor between the peaks of oxytetracycline and adjacent peaks complies the related requirements.

Procedure Dissolve about 25 mg of the substance being examined, accurately weighed, in a 50 ml volumetric flask with 5 ml of 0.1 mol/L hydrochloric acid solution, and dilute to volume with water. Mix well, transfer 10 ml, accurately measured, to a 50 ml volumetric flask, and dilute to volume with 0.1 mol/L hydrochloric acid solution, mix well. Inject 20 μ l of the resulting solution into the column. Repeat the operation, using 25 mg of oxytetracycline RS instead of the substance being examined. Calculate the content of $C_{22}H_{24}N_2O_9$ by the external standard method. The flow sequence is oxytetracycline, metacycline and tetracycline, following the peak of the solvent.

Category Tetracycline Antibiotic.

Storage Preserve in tightly closed containers, protected

from light and stored in a dry place.

Preparation Oxytetracycline Hydrochloride Tablets

* Preparation of chromatographic plate Use a mixture of 4% solution of disodium edetate (adjusted to pH 7.0 with concentrated ammonia solution)-glycerol (95:5) as adhesive and slurry a mixture of dried kieselguhr-adhesive (1 g:3 ml) as the coating substance. Spread the plate with a layer of about 0.4 mm, allow it to dry at room temperature and then heat at 105°C for one hour.

Oxytetracycline Hydrochloride Tablets

Oxytetracycline Hydrochloride Tablets contain not less than 90.0% and not more than 110.0% of the labelled amount of oxytetracycline ($C_{22}H_{24}N_2O_9$).

Description Yellow tablets or sugar coated tablets with yellow core.

Identification Extract a quantity of the powdered tablets equivalent to about 25 mg of oxytetracycline hydrochloride with 25 ml of warm ethanol for 20 minutes, filter and evaporate the filtrate to dryness on a water bath. The residue complies with tests for Identification described under Oxytetracycline Hydrochloride.

Related substances Weigh accurately a quantity of powder obtained in weight variation equivalent to about 30 mg of oxytetracycline, in a 200 ml volumetric flask, add 20 ml of 0.1 mol/L hydrochloric acid solution, dissolve and dilute with water to volume, mix well and filter. Discard the initial filtrate, the successive filtrate is used as the test solution. Transfer accurately 20 ml of successive filtrate, in a 100 ml volumetric flask, and dilute with 0.1 mol/L hydrochloric acid solution to volume as reference solution. Carry out the method as described under Oxytetracycline Hydrochloride.

Other requirements Comply with the general requirements for tablets (Appendix I A).

Assay Dissolve a quantity of the mixed contents obtained in weight variation equivalent to 100 mg of Oxytetracycline, accurately weighed, in a 200 ml volumetric flask with 20 ml of 0.1 mol/L hydrochloric acid solution, and dilute to volume with water. Mix well, filter. Transfer 10 ml of the successive filtrate, accurately measured to a 50 ml volumetric flask, and dilute to volume with 0.1 mol/L hydrochloric acid solution, mix well. Carry out the Assay described under Oxytetracycline Hydrochloride.

Category As described under Oxytetracycline Hydrochloride.

Strength Calculated as $C_{22}H_{24}N_2O_9$
(1) 0.125 g (2) 0.25 g

Storage Preserve in tightly closed containers, protected from light and stored in a dry place.

Oxytocin Injection

Oxytocin Injection is a sterile solution of Oxytocin in Water for Injection, which is obtained from the posterior lobe of the pituitary of pork or cattle or prepared by synthesis. It contains not less than 91% and not more than 116% of the labelled potency of oxytocin.

Description A colourless, clear or almost clear liquid.

Identification (1) Carry out the biological assay of oxytocin (Appendix XII F), causes contraction of the muscle of the uterus.

(2) Carry out the method for high performance liquid chromatography (Appendix V D), using a column packed with octadecylsilane bonded silica gel and a mixture of sodium dihydrogen phosphate solution (0.1 mol/L)-acetonitrile (82:18) as the mobile phase with a flow rate of 0.8 ml per minute. Detection wavelength is 220 nm. Dilute the substance being examined with 0.9% sodium chloride solution (solution 1) and dissolve the synthetic Oxytocin RS in 0.9% sodium chloride solution (solution 2) to produce the solutions of 5 Units or 10 Units per ml respectively. Inject separately 20 µl of the same concentration of solution (1) and solution (2) into the column. The retention time of the two principal peaks is concordant with each other.

pH value 3.0-4.5 (Appendix VI H).

Vasopressor substances Comply with the test for vasopressor substances (Appendix XI F), using a solution of 2 Units per ml in sterile Sodium Chloride Solution.

Bacterial endotoxin Carry out the test for bacterial endotoxin (Appendix XI E); not more than 2.5 EU per unit.

Other requirements Comply with the general requirements for injections (Appendix I B).

Assay Carry out the biological assay of oxytocin (Appendix XII F), it complies with the requirement for potency.

Category Uterine stimulant.

Strength (1) 0.5 ml : 2.5 Units (2) 1 ml : 5 Units
(3) 1 ml : 10 Units

Storage Preserve in tightly closed containers, stored in a cool and dark place.

Pancreatin

[8049-47-6]

Pancreatin is an enzyme mixture extracted from the pancreases of pig, sheep or cattle. It contains not less than 600 Units of protease, 7000 Units of amylase and 4000 Units of lipase per g, calculated on the dried basis. It may be diluted with lactose, sucrose or pancreatin of lower activity if necessary.

Description An almost white to slightly yellow powder; odour slight but not moldy; hygroscopic. The aqueous solution is inactivated by acids or on boiling.

Fat To 1 g add 10 ml of ether in a stoppered conical flask, allow to stand for about 2 hours with frequent swirling. Filter the solution through an ether-moistened filter paper. Treat the residue with 10 ml of ether as described above and wash with 5 ml of ether. Combine the filtrate and washing in an evaporating dish previously dried to constant weight. Evaporate ether and dry at 105°C for 2 hours. The residue is not more than 20 mg.

Loss on drying When dried at 105°C for 4 hours, loses not more than 5.0% of its weight (Appendix VIII L).

Enzyme activity (1) *Protease Reference solution* Dissolve an accurately weighed quantity of tyrosine CRS, in 0.2 mol/L hydrochloric acid solution to produce a solution of 50 µg per ml.

Test solution Triturate about 0.1 g of the substance being examined, accurately weighed, with a small quantity of cold calcium chloride solution (dissolve 1.47 g of calcium chloride in 500 ml of water, adjust to pH 6.0-6.2 with 0.1 mol/L hydrochloric acid solution or 0.1 mol/L sodium hydroxide solution, cool it below 5°C before use). Pulverize well, and transfer the mixture to a 100 ml volumetric flask, add calcium chloride solution to volume and shake well. Dilute 10 ml of the solution, accurately measured, to 50 ml volumetric flask with borate BS (pH 7.5)* to produce a solution containing about 0.12 Unit of protease per ml.

Procedure To each of 3 test tubes add accurately 1.0 ml of test solution and 2.0 ml of borate BS (pH 7.5), warm in a 40°C water bath for 10 minutes. Add accurately to each tube 5.0 ml of casein solution [add 13 ml of 0.1 mol/L sodium hydroxide solution and 40 ml of water to 1.5 g of casein CRS, heat in a 60°C water bath to dissolve casein and cool, dilute with water to 100 ml and adjust the pH to 8.0 with 0.1 mol/L sodium hydroxide solution or 0.1 mol/L hydrochloric acid solution. Warm in a 40°C water bath before use], mix well. Place the tubes in a 40°C ± 0.5°C water bath for exact 30 minutes. Add to each tube 5.0 ml of 5% trichloroacetic acid, shake well and filter. Discard the initial filtrate and use the successive filtrate for the assay. To another test tube add 1.0 ml of test solution, accurately measured, and 2.0 ml of borate BS (pH 7.5), warm in a 40°C water bath for 10 minutes, add accurately 5 ml of 5% trichloroacetic acid solution and mix well. Allow the reaction to proceed in a 40°C ± 0.5°C water bath for exact 30 minutes. Add immediately 5.0 ml of casein solution, accurately measured, shake well and filter, using the successive filtrate as the blank. Measure the absorbances at 275 nm (Appendix IV A), calculate the average absorbance (A) of the 3 solutions. Measure the absorbance of the reference solution (As) at 275 nm, using 0.2 mol/L hydrochloric acid solution as blank. Calculate the activity of

$$\text{Activity of protease (Unit per g)} = \frac{\bar{A}}{A_s} \times \frac{W_s}{181.19} \times \frac{13}{30} \times \frac{n}{W}$$

Where W_s is Weight of tyrosine per ml in the reference solution (µg);
 W is Weight of the substance being examined (g);
 n is Dilution factor of the substance being examined (500).

Under the above mentioned conditions, the amount of peptides and amino acids produced per minute when casein is hydrolyzed by 1 Unit of protease is equivalent to 1 micromole of tyrosine.

The concentration of the test solution must be altered if the value of \bar{A} is outside the range of 0.15-0.60.

(2) *Amylase Test solution* Triturate an accurately weighed quantity of the substance being examined with a small quantity of cold phosphate BS (pH 6.8)*, add phosphate BS to produce a solution containing 10-20 Units of amylase per ml.

Procedure To 25 ml of 1% potato starch solution (add 10 ml of water to 1.0 g of potato starch, previously dried at 105°C for 2 hours, shake well. Slowly pour the suspension with stirring into 100 ml of boiling water and continue to boil for 20 minutes, cool, add water to produce 100 ml) in a 250 ml glass-stoppered conical flask add 10 ml of phosphate BS (pH 6.8), 1 ml of 1.2% sodium chloride solution and 20 ml of water, warm in a 40°C water bath for 10 minutes, add accurately 1.0 ml of test solution and mix well. Allow the reaction to proceed in a 40°C ± 0.5°C water bath for exact 10 minutes. Add 2 ml of 1 mol/L hydrochloric acid solution and mix well, cool the solution to room temperature. Add accurately 10.0 ml of iodine (0.05 mol/L) VS and add dropwise 45 ml of 0.1 mol/L sodium hydroxide solution with shaking. Allow to stand in the dark for 20 minutes, add 4 ml of 0.1 mol/L sulfuric acid solution (1→4) and titrate with sodium thiosulfate (0.1 mol/L) VS to colourless. To 25 ml of 1% potato starch solution in another glass-stoppered conical flask add 10 ml of phosphate BS (pH 6.8), 1 ml of 1.2% sodium chloride solution and 20 ml of water, warm in a 40°C ± 0.5°C water bath for 10 minutes. Cool to room temperature, add 2 ml of 1 mol/L hydrochloric acid solution and mix well, then add 1.0 ml of test solution and mix well. Add accurately 10.0 ml of iodine (0.05 mol/L) VS and add dropwise 45 ml of 0.1 mol/L sodium hydroxide solution with shaking. Allow to stand in the dark for 20 minutes, add 4 ml of sulfuric acid solution (1→4) and titrate with sodium thiosulfate (0.1 mol/L) VS to colourless (as blank). Each ml of iodine (0.05 mol/L) VS is equivalent to 9.008 mg of anhydrous glucose. Calculate the activity of amylase as follows:

$$\text{Activity of amylase (Unit per g)} = \frac{(B-A) F}{10} \times \frac{9.008 \times 1000}{180.16} \times \frac{n}{W}$$

Where A is Volume of sodium thiosulfate VS consumed in the titration of the substance being examined (ml);
 B is Volume of sodium thiosulfate VS consumed in the titration of the blank (ml);
 F is Concentration factor of the sodium thiosulfate VS, mol/L;
 W is Weight of the substance being examined (g);
 n is Dilution factor of the substance being examined (200).

Under the above mentioned conditions, 1 micromole of glucose is produced per minute when starch is hydrolyzed by 1 Unit of amylase.

The concentration of the test solution must be altered if

(3) **Lipase Test solution** Triturate an accurately weighed quantity of the substance being examined with a small quantity of cold trometamol BS (pH 7.1)^{***}, add the buffer solution to produce a solution containing 8-16 Units of lipase per ml.

Procedure Transfer 25 ml of olive oil emulsion (triturate 4 ml of olive oil with 7.5 g of acacia and gradually add water with constant trituration to produce 100 ml, agitate the mixture in a tissue blender twice at a speed of 8000 rpm, each for 3 minutes. Examine the emulsion under a microscope, 90% of the particles is less than 3 μ m in diameter and none of the particle is above 10 μ m in diameter), 2 ml of 8% taurocholate solution and 10 ml of water to a 100 ml beaker, adjust to pH 9.0 with 0.1 mol/L sodium hydroxide solution. Warm in a 37°C \pm 0.1°C water bath for 10 minutes and adjust to pH 9.0 again, add accurately 1.0 ml of test solution and allow the reaction to proceed in 37°C \pm 0.1°C water bath for exact 10 minutes. Titrate with sodium hydroxide (0.1 mol/L) VS to keep the reaction mixture at pH 9.0, calculate the volume of sodium hydroxide (0.1 mol/L) VS consumed. Boil 1.0 ml of test solution in a water bath for 15-30 minutes and proceed in the same manner as described above as a blank titration. Calculate the activity of lipase as follows:

$$\text{Activity of lipase (Unit per g)} = \frac{(A-B) M \times 1000}{10} \times \frac{n}{W}$$

Where A is Volume of sodium hydroxide VS consumed in the titration of the substance being examined (ml);

B is Volume of sodium hydroxide VS consumed in the titration of the blank (ml);

M is Concentration of sodium hydroxide VS (mol/L);

W is Weight of the substance being examined (g);

n is Dilution factor of the substance being examined (50).

Under the above mentioned conditions, 1 micromole of fatty acids is produced per minute when olive oil is hydrolyzed by 1 Unit of lipase.

The concentration of the test solution must be altered if the average consumption of sodium hydroxide VS (0.1 mol/L) per minute is outside 0.08-0.16 ml.

Category Digestive.

Storage Preserve in tightly closed containers, protected from light and stored in a dry place.

Preparation (1) Pancreatin Enteric-coated capsules

(2) Pancreatin Enteric-coated Tablets

* Borate BS (pH 7.5): Dissolve 2.85 g of borax, 10.5 g of boric acid and 2.5 g of sodium chloride in water to produce 1000 ml, adjust the pH to 7.5 \pm 0.1. Cool the solution to a temperature below 5°C before use.

** Phosphate BS (pH 6.8): Dissolve 13.61 g of potassium dihydrogen phosphate and 35.80 g of disodium hydrogen phosphate in water to produce 1000 ml, adjust the pH to 6.8. Cool the solution to a temperature below 5°C before use.

*** Trometamol BS (pH 7.1): Dissolve 606 mg of trometamol in 45.7 ml of 0.1 mol/L hydrochloric acid, add water to produce 100 ml, mix well and adjust the pH to 7.1. Cool the solution to a temperature below 5°C before use.

Pancreatin Enteric-coated Capsules

Pancreatin Enteric-coated Capsules contain not less than 540 Units of protease, not less than 6300 Units of amylase and not less than 3400 Units of lipase per g, calculated with reference to the labelled amount of pancreatin.

Description Enteric-coated capsules containing almost white to slightly yellow powder.

Loss on drying When dried at 105°C for 4 hours, loses not more than 7.0% of its weight (Appendix VIII L), using the mixed contents of the capsules.

Microbial limit Comply with the test for microbial limit (Appendix XI J) except that number of bacterial is not more than 10000 and that of fungus is not more than 100 per g.

Other requirements Comply with the general requirements for capsules (Appendix I E).

Activity of enzyme Protease Weigh accurately a quantity of the mixed contents in the test for weight variation of contents equivalent to about 0.45 g of pancreatin to a mortar, triturate with a small quantity of calcium chloride solution (as described under Pancreatin), previously cooled to a temperature below 5°C. Transfer the resulting solution to a 100 ml volumetric flask, add calcium chloride solution to volume, mix well. Measure accurately a quantity of liquid, dilute with borate BS (as described under Pancreatin), previously cooled to a temperature below 5°C to produce a solution of about 0.12 Units of trypsin per ml. Carry out the method described under Pancreatin.

Amylase Weigh accurately a quantity of the mixed contents in the test for weight variation of contents equivalent to about 0.45 g of pancreatin to a mortar, triturate with a small quantity of phosphate BS (as described under Pancreatin), previously cooled to a temperature below 5°C, dilute with the same phosphate BS to produce a solution of 10-12 Units of amylase per ml. Carry out the method described under Pancreatin.

Lipase Weigh accurately a quantity of the mixed contents in the test for weight variation of contents to a mortar, triturate with a small quantity of trometamol BS (as described under Pancreatin), previously cooled to a temperature below 5°C, dilute with the same BS to produce a solution of 8-16 Units of lipase per ml. Carry out the method described under Pancreatin.

Category As described under Pancreatin.

Strength 0.15 g

Storage Preserve in tightly closed containers, stored in a dry place and protected from light.

Pancreatin Enteric-coated Tablets

Pancreatin Enteric-coated Tablets contain not less than 540 Units of protease, not less than 6300 Units of amylase and not less than 3400 Units of lipase per gram, calculated with reference to the labelled amount of pancreatin.

Description Enteric-coated tablets with white to pale yellow core

Microbial limit Comply with the test for Microbial limit (Appendix XI J) except that number of bacterial is not more than 10000 and that of fungus is not more than 100 per g.

Other requirements Comply with the general requirements for tablets (Appendix I A).

Activity of enzyme *Protease* Pulverize finely 5 (0.3 g) or 3 (0.5 g) tablets with the coating removed, triturate with a small quantity of calcium chloride solution, previously cooled to a temperature below 5°C. Add calcium chloride solution to produce 200 ml, shake thoroughly. Measure accurately a quantity of the liquid, dilute with borate BS, previously cooled to a temperature below 5°C to produce a solution containing 0.12 Units of protease per ml. Carry out the method described under Pancreatin.

Amylase Pulverize finely 5 (0.3 g) or 3 (0.5 g) tablets with the coating removed, triturate with a small quantity of phosphate BS, previously cooled to a temperature below 5°C, dilute with phosphate BS to produce a solution containing 10-12 Units of amylase per ml. Carry out the method described under Pancreatin.

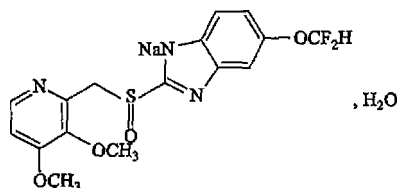
Lipase Pulverize finely 5 (0.3 g) or 3 (0.5 g) tablets with the coating removed, triturate with a small quantity of trometamol BS (as described under pancreatin), previously cooled to a temperature 5°C, dilute with the same BS to produce a solution containing 8-16 Units of lipase per ml. Carry out the method described under Pancreatin.

Category As described under Pancreatin.

Strength (1) 0.3 g (2) 0.5 g

Storage Preserve in tightly closed containers, protected from light and stored in a dry place.

Pantoprazole Sodium



$C_{16}H_{14}F_2N_3NaO_4S \cdot H_2O$ 423.38

Pantoprazole Sodium is 5-difluoromethoxy-2-[[(3,4-dimethoxy-2-pyridinyl) methyl] sulfinyl]-1H-benzimidazole sodium, monohydrate. It contains not less than 98.0% and not more than 102.0% of $C_{16}H_{14}F_2N_3NaO_4S$, calculated on anhydrous basis.

Description A white or almost white crystalline powder. Freely soluble in water or methanol; practically insoluble in chloroform or ether.

Identification (1) Dissolve 10 mg in 20 ml of water to 2 ml of the resulting solution add 5 drops of dilute hydrochloric acid, then add 1 ml of silicotungstic acid TS dropwise, a white curdy precipitate is produced.

(2) The light absorption of a solution of 15 µg per ml in ethanol exhibits a maximum at 292 nm, and a minimum at 250 nm (Appendix IV A).

(3) The infrared absorption spectrum (Appendix IV C) is concordant with the reference spectrum of pantoprazole sodium (Appendix XVI).

(4) Yields the reactions characteristic of sodium salts

Alkalinity An aqueous solution of 20 mg per ml, pH 9.5-11.0 (Appendix VI H).

Clarity and colour of solution Dissolve 0.20 g in 10 ml of water, the solution is clear and colourless; any colour produced is not more intense than that of reference solution Y_2 (Appendix IX A, method 1).

Related substances Protect from light throughout the procedure. Dissolve a quantity of the substance being examined with mobile phase to produce a solution of 0.2 mg per ml as test solution. Measure accurately 1 ml of the test solution, to a 100 ml volumetric flask, dilute to volume with mobile phase, mix well as reference solution. Carry out the method as described under the Assay. Inject 20 µl of the reference solution into the column, adjust the attenuation so that the principal peak height in the chromatogram is 10%-20% full scale of the chart. Inject separately 20 µl each of the test solution and the reference solution into the column, and record the chromatogram for triple the retention time of the principal peak. The sum of the areas of the secondary peaks is not greater than 4/5 of the area (for injection) or not greater than the area (for oral administration) of the principal peak in the chromatogram obtained with the reference solution.

Toluene Transfer 50 mg, accurately weighed, to a 10 ml headspace vial, add 5 ml of 10% dimethylformamide solution, accurately measured, close tightly as test preparation. Dissolve a quantity of toluene, accurately weighed, in 10% dimethylformamide solution to produce a solution of 0.5 µg per ml, transfer 5 ml of the solution, accurately measured, to a 10 ml headspace vial and close tightly as reference preparation. Heat the vials in a water bath maintained at 60°C for 40 minutes separately. Carry out the method for gas chromatography (Appendix V E), using a column packed with porous polymer beads of divinyl-ethylvinylbenzene as the stationary phase, and maintain the column temperature at 180°C. Inject separately 1 ml each of the test preparation and reference preparation into the column. The content of toluene is not more than 0.089%.

Acetone Transfer 0.10 g, accurately weighed, to a 10 ml volumetric flask, dilute with water to volume, mix well as test preparation. Dissolve a quantity of acetone, accurately weighed, in water to produce a solution of 10 µg per ml as reference preparation. Complies with the test for Residue so vent Appendix VIII P, method 3, using a column packed with porous polymer beads of divinyl-ethylvinylbenzene as the stationary phase and maintain the column temperature at 150°C. Inject separately 1 µl each of the test preparation and the reference preparation into the column. The content of acetone complies with the requirement.

Water 4.0%-6.0% (Appendix VIII M, method 1).

Heavy metals Carry out the limit test for heavy metals (Appendix VIII H, method 2); not more than 0.002%, using 1.0 g.

Assay Carry out the method for high performance liquid chromatography (Appendix V D), using a column packed with octadecylsilane bonded silica gel and a mixture of phosphate buffer solution (dissolve 1.12 g of disodium hydrogen phosphate and 0.18 g of sodium dihydrogen phosphate in water, and dilute to 1000 ml, mix well, and adjust to pH 7.6)-acetonitrile (70 : 30) as the mobile phase. The detection wavelength is 288 nm. The number of the theoretical plate of the column is not less than 2500, calculated with reference to the peak of pantoprazole.

Procedure Protect from light throughout the procedure. Dissolve a quantity of the substance being examined, weigh

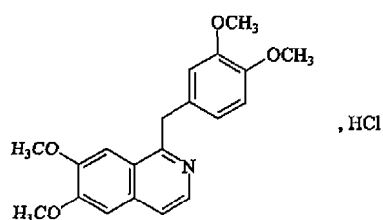
accurately, in mobile phase to produce a solution of about 60 µg per ml. Inject 20 µl into the column and record the chromatogram. Repeat the operation using Pantoprazole Sodium CRS instead of the substance being examined. Calculate the content of $C_{18}H_{14}F_2N_3NaO_4S$ with respect to the peak area obtained in the chromatogram by the external standard method.

Category Digestive system medicine.

Storage Preserve in tightly closed containers, stored in a cool place and dark place.

Preparation Pantoprazole Sodium for Injection

Papaverine Hydrochloride



$C_{20}H_{21}NO_4 \cdot HCl$ 375.85

[61-25-6]

Papaverine Hydrochloride is 1-[(3,4-dimethoxyphenyl)methyl]-6,7-dimethoxyisoquinoline Hydrochloride. It contains not less than 99.0% of $C_{20}H_{21}NO_4 \cdot HCl$, calculated on the dried basis.

Description A white crystalline powder; odourless. Soluble in chloroform; sparingly soluble in water; slightly soluble in ethanol; practically insoluble in ether.

Identification (1) Dissolve 0.1 g in 10 ml of water, heat to about 50°C. Add a slight excess of ammonium hydroxide TS dropwise to make alkaline and stir to precipitate. Allow to stand for 5 minutes, filter, wash the precipitate with small quantities of water and dry at 105°C for 1 hour. It melts at 146-148°C (Appendix VI C).

(2) Dissolve 10 mg in 10 ml of water, add 3 drops of dilute hydrochloric acid and 5 drops of potassium ferricyanide TS; a pale yellow precipitate is produced (distinction from other opium alkaloids).

(3) Dissolve 5 mg in 1 ml of formaldehyde-sulfuric acid TS, a colourless or pale yellow solution is produced, which gradually changes to deep rose and finally becomes violet (morphine and its esters develop purple or violet colour immediately).

(4) The infrared absorption spectrum (Appendix IV C) is concordant with the reference spectrum of Papaverine Hydrochloride (Appendix XVI).

(5) Yields the reactions characteristic of chlorides (Appendix III).

Acidity Dissolve 0.20 g in 10 ml of water, pH 3.0-4.0 (Appendix VI H).

Colour of solution Dissolve 0.2 g in 10 ml of freshly boiled and cold water. Any colour produced is not more intense than that of the reference solution OY₂ (Appendix IX A, method 1).

Related substances Carry out the method for thin-layer chromatography (Appendix V B), using silica gel GF₂₅₄ as the coating substance and a mixture of toluene-ethyl acetate-diethylamine (70 : 20 : 12) as the mobile phase. Apply

mixture of equal volumes of ethanol and water containing (1) 50 mg per ml, (2) 0.50 mg per ml of the substance being examined. After developing and removal of the plate, dry in air until the diethylamine is volatilized and examine under ultraviolet light (254 nm). No spot other than the principal spot in the chromatogram obtained with solution (1) is more intense than the principal spot obtained with solution (2).

Readily carbonisable substances Dissolve 50 mg in 2 ml of sulfuric acid. Any colour produced is not more intense than that of an equal volume of reference solution [dilute 2 ml of potassium permanganate solution (0.02 mol/L) with water to 1000 ml].

Loss on drying When dried to constant weight at 105°C, loses not more than 1.0% of its weight (Appendix VIII L).

Residue on ignition Not more than 0.1% (Appendix VII N).

Assay Dissolve about 0.3 g, accurately weighed, in 10 ml of glacial acetic acid and 6 ml of mercuric acetate TS. Add 1 drop of crystal violet IS and titrate with perchloric acid (0.1 mol/L) VS, until the colour changes to green. Perform a blank determination and make any necessary correction. Each ml of perchloric acid (0.1 mol/L) VS is equivalent to 37.58 mg of $C_{20}H_{21}NO_4 \cdot HCl$.

Category Vasodilator.

Storage Preserve in tightly closed containers, protected from light.

Preparation (1) Papaverine Hydrochloride Injection
(2) Papaverine Hydrochloride Tablets

Papaverine Hydrochloride Injection

Papaverine Hydrochloride Injection is a sterile solution of Papaverine Hydrochloride in Water for Injection. It contains not less than 95.0% and not more than 105.0% of the labelled amount of $C_{20}H_{21}NO_4 \cdot HCl$.

Description A clear, colourless or slightly orange yellow liquid.

Identification Evaporate 5 ml to dryness on a water bath, the residue complies with the tests (1), (2), (3) and (5) for Identification described under Papaverine Hydrochloride.

pH value 2.5-4.0 (Appendix VI H).

Colour Not more intense than the colour of the reference solution OY₅ (Appendix IX A, method 1).

Other requirements Complies with the general requirements for injections (Appendix I B).

Assay Measure accurately 10 ml, evaporate to dryness on a water bath, dry at 105°C for 1 hour and allow to cool. Dissolve the residue in 10 ml of glacial acetic acid and 6 ml of mercuric acetate TS, add 1 drop of crystal violet IS, titrate with perchloric acid (0.1 mol/L) VS, until the colour changes to green. Perform a blank determination and make any necessary correction. Each ml of perchloric acid (0.1 mol/L) VS is equivalent to 37.58 mg of $C_{20}H_{21}NO_4 \cdot HCl$.

Category As described under Papaverine Hydrochloride.

Strength 1 ml : 30 mg

Storage Preserve in well closed containers, protected from light.

Papaverine Hydrochloride Tablets

Papaverine Hydrochloride Tablets contain not less than 93.0% and not more than 107.0% of the base, calculated as the hydrochloride ($C_{20}H_{21}NO_4 \cdot HCl$).

Description White tablets.

Identification Shake to dissolve a quantity of the powdered tablets equivalent to about 60 mg of papaverine hydrochloride in 10 ml of water, filter, the filtrate complies with tests (2), (3) and (5) for Identification described under Papaverine Hydrochloride.

Dissolution Carry out the dissolution test (Appendix X C, method 1), using 900 ml of water as the dissolution medium, adjust the rotational speed of the basket to 100 rpm. Withdraw a quantity of the solution after exact 30 minutes and filter. Dilute the successive filtrate with 0.1 mol/L hydrochloric acid solution to produce a solution of 2.4 µg per ml. Measure the absorbance of the resulting solution at 250 nm (Appendix IV A), calculate the dissolution of $C_{20}H_{21}NO_4 \cdot HCl$ from each tablet, taking 1830 as the value of A (1%, 1 cm). Not less than 75% of the labelled amount is dissolved.

Content uniformity Comply with the requirements (Appendix X E). Triturate 1 tablet with a quantity of water and transfer to a 250 ml volumetric flask with 50 ml of water in portions, add 3 ml of hydrochloric acid, shake for 15 minutes, dilute with water to volume and mix well, filter. Transfer 1 ml of the successive filtrate, accurately measured, to a 50 ml volumetric flask, dilute with water to volume and mix well. Measure the absorbance of the resulting solution at 250 nm (Appendix IV A), calculate the content of $C_{20}H_{21}NO_4 \cdot HCl$, taking 1830 as the value of A (1%, 1 cm).

Other requirements Comply with the general requirements for tablets (Appendix I A).

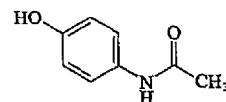
Assay Weigh accurately and powder 20 tablets. Transfer an accurately weighed quantity of the powdered tablets equivalent to about 0.12 g of papaverine hydrochloride to a separator, add 20 ml of water, mix well, add 7.5 ml of ammonia TS. Extract with 6 portions of chloroform (30 ml, 15 ml, 10 ml, 10 ml, 10 ml, 10 ml), wash each chloroform extract with the same 10 ml of water. Filter through absorbent cotton moistened by chloroform, wash twice the filter with each of 10 ml chloroform, combine the filtrate and washings, evaporate to dryness on a water bath. To the residue add 5 ml of dehydrated ethanol, evaporate to dryness, add another 5 ml of dehydrated ethanol, evaporate until no characteristic odour of ethanol is perceptible, then dry it at 105°C for half an hour. Shake to dissolve the residue in 10 ml of glacial acetic acid, add 1 drop of crystal violet IS, titrate with perchloric acid (0.05 mol/L) VS until the colour changes to green. Perform a blank determination and make any necessary correction. Each ml of perchloric acid (0.05 mol/L) VS is equivalent to 18.79 mg of $C_{20}H_{21}NO_4 \cdot HCl$.

Category As described under Papaverine Hydrochloride.

Strength 30 mg

Storage Preserve in tightly closed containers, protected from light.

Paracetamol



$C_8H_9NO_2$ 151.16

[103-90-2]

Paracetamol is 4'-hydroxyacetyl phenyl amine. It contains not less than 98.0% and not more than 102.0% of $C_8H_9NO_2$, calculated on the dried basis.

Description A white crystalline powder or crystal; odourless; taste, slightly bitter. Very soluble in hot water or ethanol; soluble in acetone; sparingly soluble in water.

Melting range 168-172°C (Appendix VI C).

Identification (1) To the aqueous solution add ferric chloride TS, a bluish-violet colour is produced.

(2) Heat about 0.1 g with 5 ml of dilute hydrochloric acid in a water bath for 40 minutes and cool. To 0.5 ml of the solution add 5 drops of sodium nitrite TS, mix well; dilute with 3 ml of water, add 2 ml of alkaline β-naphthol TS and shake; a red colour is produced.

(3) The infrared absorption spectrum (Appendix IV C) is concordant with the reference spectrum of paracetamol (Appendix XVI).

Acidity Dissolve 0.10 g in 10 ml of water, pH 5.5-6.5 (Appendix VI H).

Clarity and colour of ethanol solution A solution of 1.0 g in 10 ml of ethanol is clear and colourless. Any opalescence produced is not more pronounced than that of reference suspension I (Appendix IX B); any colour produced is not more intense than that of the reference solution BR₂ or OR₂ (Appendix IX A, method 1).

Chlorides Dissolve 2.0 g in 100 ml of water by heating, cool and filter. Carry out the limit test for chlorides (Appendix VIII A), using 25 ml of the filtrate. Any opalescence produced is not more intense than that of a reference using 5.0 ml of sodium chloride standard solution (0.01%).

Sulfates Carry out the limit test for sulfates (Appendix VIII B), using 25 ml of the filtrate obtained in the test for chlorides. Any opalescence produced is not more intense than that of a reference using 1.0 ml of potassium sulfate standard solution (0.02%).

Related substances Place 1.0 g of the finely powdered substance in a centrifugal tube or a test tube with stopper and shake for 30 minutes with 5 ml of ether. Centrifuge or allow to stand until the solution is clear. The supernatant solution is used as test solution. Prepare a reference solution by dissolving 1.0 mg of *p*-chloroacetanilide in 1 ml of ethanol and dilute to 50 µg per ml with ether. Carry out the method for thin-layer chromatography (Appendix V B), using silica gel GF₂₅₄ as the coating substance and chloroform-acetone-toluene (13 : 5 : 2) as the mobile phase. Apply separately to the plate (1) 200 µl of the test solution, (2) 40 µl of the reference solution. After developing and removal of the plate, dry in air and examine under an ultraviolet light (254 nm). Any spot, other than the principal spot, in the chromatogram obtained with solution

solution (2).

4-Aminophenol Dissolve 1.0 g in 20 ml of methanol solution (1→2), add 1 ml of alkaline sodium nitroprusside TS, mix well and allow to stand for 30 minutes. Any colour produced is not more intense than that of a reference prepared in the same manner using a mixture of 1.0 g of paracetamol CRS and 50 µg of 4-aminophenol (0.005%).

Loss on drying When dried to constant weight at 105°C, loses not more than 0.5% of its weight (Appendix VIII L).

Residue on ignition Not more than 0.1% (Appendix VIII N).

Heavy metals Dissolve 1.0 g in 20 ml of water by heating in a water bath, cool and filter. To the filtrate add 2 ml of acetate BS (pH 3.5) and a quantity of water to produce 25 ml, carry out the limit test for heavy metals (Appendix VIII H, method 1); not more than 0.001%.

Assay Dissolve about 40 mg, accurately weighed, in 50 ml of 0.4% sodium hydroxide solution in a 250 ml volumetric flask, dilute with water to volume and mix well. Transfer 5 ml, accurately measured, to a 100 ml volumetric flask, add 10 ml of 0.4% sodium hydroxide solution and then dilute with water to volume, mix well. Measure the absorbance of the resulting solution at 257 nm (Appendix IV A). Calculate the content of $C_8H_9NO_2$, taking 715 as the value of A (1%, 1 cm).

Category Analgesic and antipyretic agent.

Storage Preserve in tightly closed containers.

Preparation (1) Paracetamol Capsules
(2) Paracetamol Chewable Tablets
(3) Paracetamol Drops
(4) Paracetamol Effervescent Tablets
(5) Paracetamol Gel
(6) Paracetamol Granules
(7) Paracetamol Injection
(8) Paracetamol Suppositories
(9) Paracetamol Tablets

Paracetamol and Caffeine Tablets

Paracetamol and Caffeine Tablets contain not less than 90.0% and not more than 110.0% of the labelled amount of paracetamol ($C_8H_9NO_2$) and caffeine ($C_8H_{10}N_4O_2$).

Description Pale yellow or yellow tablets or film coated tablets.

Identification The retention time of two principal peaks in the chromatogram of the test solution obtained under the Assay corresponds with that of the principal peaks in the chromatogram of the reference solution.

Dissolution Carry out the dissolution test (Appendix X C, method 2), using 900 ml of water as the dissolution medium, adjust the rotational speed of the paddle to 100 rpm. Withdraw 20 ml of the solution after exact 30 minutes and filter. Measure accurately 10 ml of the successive filtrate and 5 ml of internal standard solution as described under the Assay, into a 50 ml volumetric flask, dilute with a mixture of methanol-glacial acetic acid (95 : 5) to volume, mix well, as test solution. Carry out the method as described under Assay. Calculate separately the dissolution of $C_8H_9NO_2$ and $C_8H_{10}N_4O_2$ from each tablet. Not less than 75% of the labelled amount is dissolved.

Other requirements Comply with the general requirements

Assay Carry out the method for high performance liquid chromatography (Appendix V D), using a column packed with octadecylsilane bonded silica gel, and a mixture of methanol-water-glacial acetic acid (28 : 69 : 3) as the mobile phase. Detection wavelength is 275 nm. The resolution factors between the peaks of paracetamol, caffeine and internal standard comply with the related requirements.

Internal standard solution Dissolve a quantity of benzoic acid with methanol to produce a solution of 3.5 mg per ml.

Procedure Weigh accurately and powder 20 tablets. Weigh accurately a quantity of the powder, equivalent to about 0.25 g of paracetamol, into a 100 ml volumetric flask, add about 75 ml of a mixture of methanol-glacial acetic acid (95 : 5), shake 30 minutes to dissolve paracetamol and caffeine, dilute with the mixture to volume, shake thoroughly and filter. Measure accurately 2 ml of the successive filtrate and 5 ml of internal standard solution into a 50 ml volumetric flask, dilute with the mixture of methanol-glacial acetic acid (95 : 5) to volume, mix well as test solution. Prepare a solution of 2.5 mg of paracetamol CRS and 0.3 mg of caffeine CRS per ml in a mixture of methanol-glacial acetic acid (95 : 5). Measure accurately 2 ml of the resulting solution and 5 ml of internal standard solution into a 50 ml volumetric flask, dilute with a mixture of methanol-glacial acetic acid (95 : 5) to volume, mix well as reference solution. Inject separately 10 µl each of the test solution and the reference solution into the column and record the chromatogram. Calculate the content of $C_8H_9NO_2$ and $C_8H_{10}N_4O_2$ with respect to the peak area obtained in the chromatogram by internal standard method.

Category Analgesic and antipyretic agent.

Strength (1) paracetamol 250 mg, caffeine 32.5 mg
(2) paracetamol 500 mg, caffeine 65 mg

Storage Preserve in tightly closed containers, protected from light.

Paracetamol Capsules

Paracetamol Capsules contain not less than 95.0% and not more than 105.0% of the labelled amount of Paracetamol ($C_8H_9NO_2$).

Identification Triturate a quantity of the contents, equivalent to about 0.5 g of paracetamol with 20 ml of ethanol in portions to dissolve paracetamol. Filter, combine the filtrates and evaporate to dryness; the residue complies with the test (1) and (2) for Identification described under Paracetamol.

Loss on drying When dried to constant weight at 105°C, loses not more than 0.5% of its weight (Appendix VIII L).

Dissolution Carry out the dissolution test (Appendix XI C, method 2), using 24 ml dilution hydrochloric acid diluted with water to produce 1000 ml as the dissolution medium, adjust the rotational speed of the paddle to 50 rpm. At 45 minutes, carry out the Dissolution as described under paracetamol tablets beginning at the words "to withdraw 5 ml...". Not less than 80% of the labelled amount is dissolved.

Other requirements Comply with the general requirements for capsules (Appendix I 'E').

Assay Weigh accurately a quantity of the mixed contents obtained in the test for weight variation of contents equivalent to about 40 mg of paracetamol in a 250 ml

solution and 50 ml of water, shake, then dilute with water to volume, mix well. Filter, discard the initial filtrate. Measure accurately 5 ml of the successive filtrate, carry out the Assay as described under paracetamol beginning at the words "to a 100 ml of volumetric flask. . .".

Category As described under Paracetamol.

Strength 0.3 g

Storage Preserve in tightly closed containers.

Paracetamol Chewable Tablets

Paracetamol Chewable Tablets contain not less than 90.0% and not more than 110.0% of the labelled amount of paracetamol ($C_8H_9NO_2$).

Description Tablets with colouring agents, taste, sweet.

Identification Triturate a quantity of the powdered tablets equivalent to about 0.5 g of paracetamol with 20 ml of ethanol in portions to dissolve paracetamol. Filter, combine the filtrates and evaporate to dryness, the residue complies with the tests (1) and (2) for Identification described under Paracetamol.

4-Aminophenol Carry out the method for high performance liquid chromatography (Appendix V D), using a column packed with octadecylsilane bonded silica gel and 0.05 mol/L ammonium acetate solution-methanol (85 : 15) as the mobile phase. Detection wavelength is 257 nm and the number of theoretical plates of column is not less than 5000, calculated with reference to the peak of paracetamol. The resolution factor between the peaks of paracetamol and 4-aminophenol complies with the related requirements.

Procedure Weigh accurately a quantity of the powder equivalent to about 100 mg of paracetamol in a 10 ml volumetric flask, add a quantity of mobile phase and shake to dissolve paracetamol, dilute with mobile phase to volume and mix well. Filter and use the successive filtrate as the test solution (prepared before used). Prepare a reference solution of 10 µg of 4-aminophenol CRS per ml with mobile phase. Inject 10 µl of the reference solution into the column. Adjust the attenuation so that the principal peak height in the chromatogram is 10% full scale of the chart. Inject 10 µl each of the test solution and reference solution into column, record the chromatogram. Calculate the content of 4-aminophenol with respect to the peak area by the external standard method. It is not more than 0.1% of the labelled amount of paracetamol.

Other requirements Comply with the general requirements for tablets except disintegration test (Appendix I A).

Assay Weigh accurately and powder 10 tablets. To an accurately weighed quantity equivalent to about 40 mg of paracetamol in a 250 ml volumetric flask, add 50 ml of 0.4% sodium hydroxide solution and 50 ml of water, shake to dissolve paracetamol, dilute with water to volume and mix well. Filter and transfer accurately 5 ml of the successive filtrate, carry out the Assay as described under paracetamol beginning at the words "to a 100 ml of volumetric flask. . .".

Category As described under paracetamol.

Strength (1) 80 mg (2) 160 mg

Storage Preserve in tightly containers, stored in a cool place and protected from light.

Paracetamol Drops

Paracetamol drops contain not less than 90.0% and not more than 110.0% of the labelled amount of paracetamol ($C_8H_9NO_2$).

Description A clear liquid with colouring agents.

Identification (1) To 20 ml, add 20 ml of chloroform, shake and allow it to separate. To evaporate the chloroform layer to dryness, the residue complies with the tests (2) for Identification described under Paracetamol.

(2) The retention time of principal peak in the substance being examined in the chromatogram obtained in the Assay is identical with that principal peak in the chromatogram of the reference solution.

4-Aminophenol Dissolve a quantity of the substance being examined in water to produce a solution of 2 mg of paracetamol per ml, mix well as the test solution (prepared before used). Prepare a reference solution of 2 µg of 4-aminophenol CRS per ml with water. Carry out the method as described under Assay. Inject 10 µl of the reference solution into the column. Adjust the attenuation so that the principal peak height in the chromatogram is 10% full scale of the chart. Inject separately 10 µl of the test solution and reference solution into column, record the chromatogram. Calculate the content of 4-aminophenol with respect to the peak area by the external standard method. It is not more than 0.1% of the labelled amount of paracetamol.

Relative density 1.070-1.150 (Appendix VI A).

pH value 4.5-6.5 (Appendix VI H).

Other requirements Comply with the general requirements for oral solutions (Appendix I O).

Assay Carry out the method for high performance liquid chromatography (Appendix V D), using a column packed with octadecylsilane bonded silica gel and a mixture of 0.05 mol/L ammonium acetate solution-methanol (85 : 15) as the mobile phase. Detection wavelength is 257 nm and the number of theoretical plates of column is not less than 5000, calculated with reference to the peak of paracetamol. The resolution factor between the peaks of paracetamol and internal standard complies with the related requirements.

Internal standard solution Dissolve a quantity of theophylline in water to produce a solution of 1.0 mg per ml, mix well.

Procedure Dissolve a quantity of the substance being examined, accurately measured, in water to produce a solution of 0.6 mg of paracetamol per ml as the test solution. Transfer 5 ml each of the test solution and the internal standard solution, both measured accurately in a 50 ml volumetric flask, dilute with water to volume and mix well. Inject 10 µl into the column, record the chromatogram. Repeat the operation, using paracetamol CRS instead of substance being examined. Calculate the content of $C_8H_9NO_2$.

Category As described under paracetamol.

Strength (1) 10 ml : 1 g (2) 15 ml : 1.5 g
(3) 16 ml : 1.6 g

Storage Preserve in tightly closed containers and protected from light.

Paracetamol Effervescent Tablets

Paracetamol Effervescent Tablets contain not less than 93.0% and not more than 107.0% of the labelled amount of paracetamol ($C_8H_9NO_2$).

Description White or pale yellow tablets, the surface with some yellow points.

Identification (1) Triturate a quantity of the powdered tablets equivalent to about 0.5 g of paracetamol with 20 ml of ethanol in portions to dissolve paracetamol. Filter, combine the filtrates and evaporate to dryness, the residue complies with the tests (2) for Identification described under Paracetamol.

(2) The retention time of principal peak in the substance being examined in the chromatogram obtained in the Assay is identical with that principal peak in the chromatogram of the reference solution.

Acidity Disintegrate 1 tablet in 100 ml of water at 15–25°C, pH 4.5–6.0 (Appendix VI H).

4-Aminophenol Weigh accurately a quantity of the powder equivalent to about 25 mg of paracetamol in a 50 ml volumetric flask, add a quantity of mobile phase and shake to dissolve paracetamol, dilute with mobile phase to volume and mix well. Filter and use the successive filtrate as the test solution (prepared before used). Prepare a reference solution of 0.5 µg of 4-aminophenol CRS per ml with mobile phase. Carry out the method as described under Assay. Inject 10 µl of the reference solution into the column. Adjust the attenuation so that the principal peak height in the chromatogram is 10% full scale of the chart. And then inject 10 µl each of the test solution and reference solution into column, record the chromatogram. Calculate the content of 4-aminophenol with respect to the peak area by the external standard method. It is not more than 0.1% of the labelled amount of paracetamol.

Other requirements Comply with the general requirements for tablets except friability test (Appendix I A).

Assay Carry out the method for high performance liquid chromatography (Appendix V D), using a column packed with octadecylsilane bonded silica gel and a mixture of phosphate BS (pH 4.5) [dissolve 15.04 g sodium dihydrogen phosphate ($NaH_2PO_4 \cdot 2H_2O$) and 0.0627 g disodium hydrogen phosphate in 1000 ml of water, adjust pH to 4.5]–methanol (80 : 20) as the mobile phase. Detection wavelength is 254 nm and the number of theoretical plates of column is not less than 5000, calculated with reference to the peak of paracetamol. The resolution factor between the peaks of paracetamol and 4-aminophenol complies with the related requirements.

Procedure Weigh accurately and powder 10 tablets. To an accurately weighed quantity equivalent to about 25 mg of paracetamol in a 50 ml volumetric flask, dilute with the mobile phase to volume, mix well. Filter and transfer accurately 10 ml the successive filtrate into a 50 ml volumetric flask, dilute with the mobile phase to volume and mix well. Inject 10 µl into the column, record the chromatogram. Repeat the operation, using paracetamol CRS instead of substance being examined. Calculate the content of $C_8H_9NO_2$.

Category As described under paracetamol.

Strength (1) 0.1 g (2) 0.5 g

Storage Store in tightly closed containers.

Paracetamol Gel

Paracetamol Gel contain not less than 90.0% and not more than 110.0% of the labelled amount of paracetamol ($C_8H_9NO_2$).

Description Pale yellow transparent and semisolid gel; taste, sweet.

Identification (1) To a quantity of the mixed contents equivalent to about 50 mg of paracetamol, add 10 ml of water and heat in a warm water bath with shaking to dissolve paracetamol. Filter and add ferric chloride TS to the filtrate, a blue colour is produced.

(2) The light absorption of the test solution obtained in the Assay exhibits a maximum at 248 nm (Appendix IV A).

Acidity Dissolve 1.0 g in 20 ml of water, heat to dissolve paracetamol, cool, pH 4.0–5.5 (Appendix VI H).

Other requirements Comply with the general requirements for gel (Appendix I U).

Assay Carry out the method for high performance liquid chromatography (Appendix V D), using a column packed with octadecylsilane bonded silica gel and methanol–water–phosphoric acid (22 : 78 : 0.1) as the mobile phase. Detection wavelength is 248 nm and the number of theoretical plates of column is not less than 1000, calculated with reference to the peak of paracetamol.

Procedure Weigh accurately a quantity of the mixed contents obtained in the test for weight variation of contents, equivalent to about 20 mg of paracetamol, to a 100 ml volumetric flask, add a quantity of water, heat in a warm water bath with shaking to dissolve paracetamol, cool to room temperature, dilute with water to volume, mix well. Filter and transfer accurately 3 ml the successive filtrate into a 50 ml volumetric flask, dilute with methanol to volume and mix well, as the test solution. Inject 10 µl into the column, record the chromatogram. Repeat the operation, using a solution of 12 µg per ml of paracetamol CRS in methanol. Calculate the content of $C_8H_9NO_2$.

Category As described under paracetamol.

Strength 5 g : 0.12 g

Storage Preserve in tightly containers and protected from light.

Paracetamol Granules

Paracetamol Granules contain not less than 95.0% and not more than 105.0% of the labelled amount of paracetamol ($C_8H_9NO_2$).

Description white or almost white granules; taste, sweet.

Identification Triturate a quantity of the granules equivalent to about 0.5 g of paracetamol with 20 ml of ethanol in portions to dissolve paracetamol. Filter, combine the filtrates and evaporate to dryness, the residue complies with the tests (1) and (2) for Identification described under Paracetamol.

4-Aminophenol Carry out the method for high performance liquid chromatography (Appendix V D), using a column packed with octadecylsilane bonded silica gel and 0.05 mol/L

mobile phase. Detection wavelength is 257 nm and the number of theoretical plates of column is not less than 5000, calculated with reference to the peak of paracetamol. The resolution factor between the peaks of paracetamol and 4-aminophenol complies with the related requirements.

Procedure Weigh accurately a quantity of the mixed contents in the test for weight variation of contents equivalent to about 100 mg of paracetamol in a 10 ml volumetric flask, add a quantity of mobile phase and shake to dissolve paracetamol, dilute with mobile phase to volume and shake well. Filter and use the successive filtrate as the test solution (Prepared before used). Prepare a reference solution of 10 µg of 4-aminophenol CRS per ml in mobile phase. Inject 10 µl of the reference solution into the column. Adjust the attenuation so that the principal peak height in the chromatogram is 10% full scale of the chart. Inject 10 µl each of the test solution and reference solution into column, record the chromatogram. Calculate the content of 4-aminophenol with respect to the peak area by the external standard method. It is not more than 0.1% of the labelled amount of paracetamol.

Dissolution Carry out the dissolution test (Appendix X C, method 2), using 24 ml dilution hydrochloric acid diluted with water to produce 1000 ml as the dissolution medium, adjust the rotational speed of the paddle to 50 rpm. Withdraw 10 ml of the solution after exact 30 minutes and filter. Dilute a quantity of successive filtrate with 0.04% sodium hydroxide to produce a solution of 8 µg of paracetamol per ml, mix well. Measure the absorbance of the resulting solution at 257 nm (Appendix IV A). Calculate the dissolution of $C_8H_9NO_2$ from each container, taking 715 as the value of A (1%, 1 cm). Not less than 80% of the labelled amount is dissolved.

Other requirements Comply with the general requirements for granules (Appendix I N).

Assay Weigh accurately a quantity of the mixed contents obtained in the test for weight variation of contents equivalent to about 40 mg of paracetamol in a 250 ml volumetric flask, add 50 ml of 0.4% sodium hydroxide solution and 50 ml of water, shake, then dilute with water to volume and mix well. Filter and transfer accurately 5 ml of the successive filtrate, carry out the Assay as described under paracetamol beginning at the words "to a 100 ml of volumetric flask..."

Category As described under paracetamol.

Strength (1) 0.1 g (2) 0.16 g (3) 0.25 g (4) 0.5 g

Storage Preserve in tightly closed containers, stored in a cool place.

Paracetamol Injection

Paracetamol Injection is a sterile solution of Paracetamol in Water for Injection. It contains not less than 95.0% and not more than 105.0% of the labelled amount of paracetamol ($C_8H_9NO_2$). It may contain a sufficient quantity of stabilizers and auxiliary solubilizer.

Description A colourless or almost colourless slightly viscous clear liquid.

Identification Complies with the Tests (1) and (2) for Identification described under paracetamol.

pH value 4.5-6.5 (Appendix VI H)

for injections (Appendix I B).

Assay To a quantity of the injection add 0.01 mol/L sodium hydroxide to produce a solution of 6 µg per ml, measure the absorbance at 257 nm (Appendix VI A). Calculate the content of $C_8H_9NO_2$, taking 715 as the value of A (1%, 1 cm).

Category As described under Paracetamol.

Strength (1) 1 ml : 0.075 g (2) 2 ml : 0.25 g

Storage Preserve in well closed containers, protected from light.

Paracetamol Suppositories

Paracetamol Suppositories contain not less than 90.0% and not more than 110.0% of the labelled amount of paracetamol ($C_8H_9NO_2$).

Description Creamy-white to faint yellow suppositories.

Identification (1) To a quantity of suppositories equivalent to about 0.3 g of paracetamol add 20 ml of water, melt by heating on a water bath at 60°C, shake for 5 minutes, cool in an ice bath and filter. Measure 5 ml of the filtrate, add 1 drop of ferric chloride TS; a bluish-violet precipitate is produced.

(2) To 5 ml of the filtrate obtained in test (1) for Identification add 5.0 ml of the dilute hydrochloric acid, heat on a water bath for 30 minutes, cool, add dropwise a few drops of sodium nitrite TS and alkaline 2-naphthol TS; a precipitate coloured from orange yellow to scarlet red is produced.

(3) To 3 ml of the filtrate obtained in test (1) for identification add 1.5 ml of hydrochloric acid, boil for 3 minutes, add water to about 10 ml, cool, no precipitate is produced, add 1 drop of 0.01667 mol/L potassium dichromate solution, a violet colour is produced gradually which do not change to red colour.

Other requirements Comply with the general requirements for suppositories (Appendix I D).

Assay Weigh accurately and cut 10 suppositories to chips, mix well. Weigh accurately a quantity equivalent to about 0.25 g of paracetamol in a 250 ml volumetric flask. Add 80 ml of 0.01 mol/L sodium hydroxide solution about 60°C, shake for 10 minutes. Allow to cool to room temperature, dilute with 0.01 mol/L sodium hydroxide solution to volume, allow to stand on a cold water bath for 1 hour and filter. Discard the initial filtrate, measure accurately 10 ml of the successive filtrate at room temperature to a 100 ml volumetric flask, dilute with 0.01 mol/L sodium hydroxide solution to volume and mix well. Measure accurately 5 ml to a 50 ml volumetric flask, dilute to volume and mix well. Measure the absorbance of the resulting solution at 257 nm (Appendix IV A), calculate the content of $C_8H_9NO_2$, taking 715 as the value of A (1%, 1 cm).

Category As described under Paracetamol.

Strength (1) 0.15 g (2) 0.3 g (3) 0.6 g

Storage Preserve in tightly closed containers, stored in a cool place.

Paracetamol Tablets

and not more than 105.0% of the labelled amount of paracetamol ($C_8H_9NO_2$).

Description White tablets, film coated or glutin coated tablets with white core.

Identification Triturate a quantity of powdered tablets equivalent to about 0.5 g of paracetamol with 20 ml of ethanol in portions to dissolve paracetamol. Filter, combine the filtrates and evaporate to dryness, the residue complies with the tests (1) and (2) for Identification described under Paracetamol.

Dissolution Carry out the dissolution test (Appendix X C, method 1) using 24 ml of dilute hydrochloric acid diluted to 1000 ml with water as the dissolution medium, adjust the rotational speed of the basket to 100 rpm. Withdraw 5 ml of the solution after exact 30 minutes and filter. Discard the initial filtrate, measure accurately 1 ml of the successive filtrate and dilute with 0.04% sodium hydroxide solution to 50 ml, mix well. Measure the absorbance of the resulting solution at 257 nm (Appendix IV A). Calculate the dissolution of $C_8H_9NO_2$ from each tablet, taking 715 as the value of A (1%, 1 cm). Not less than 80% of the labelled amount is dissolved.

Other requirements Comply with the general requirements for tablets (Appendix I A).

Assay Weigh accurately and powder 10 tablets. To an accurately weighed quantity equivalent to about 40 mg of paracetamol in a 250 ml volumetric flask add 50 ml of 0.4% sodium hydroxide solution and 50 ml of water, shake for 15 minutes, dilute with water to volume and mix well. Filter and discard the initial filtrate. Transfer accurately 5 ml of the successive filtrate to a 100 ml volumetric flask and carry out the Assay described under Paracetamol, beginning at the words "add 100 ml of...".

Category As described under Paracetamol.

strength (1) 0.1 g (2) 0.3 g (3) 0.5 g

Storage Preserve in tightly closed containers.

Paracetamol and Codeine Phosphate Tablets (I)

Paracetamol and Codeine Phosphate Tablets contain not less than 475 mg and not more than 525 mg of Paracetamol ($C_8H_9NO_2$), and not less than 7.56 mg and not more than 9.24 mg of Codeine Phosphate ($C_{18}H_{21}NO_3 \cdot H_3PO_4 \cdot 1\frac{1}{2} H_2O$) in each tablet.

Formula	Paracetamol	500 g
	Codeine Phosphate	8.4 g
	Excipients	a quantity
	to make	1000 tablets

Description White tablets.

Identification (1) To about 0.1 g of the powdered tablets add 10 ml of water, shake to dissolve Paracetamol. Filter, and add ferric chloride TS to the filtrate; a bluish purple colour is produced.

(2) To about 0.1 g of the powdered tablets add 5 ml of dilute hydrochloric acid, heat on a water bath for 30 minutes, allow to cool. To 0.5 ml of the above solution add

of water, add 2 ml of alkaline β -naphthol TS and mix well, a red colour is produced.

(3) To about 0.5 g of the powdered tablets add 5 ml of water, shake to dissolve Codeine Phosphate. Filter and transfer the filtrate to a separator, add dropwise of ammonia TS to make the filtrate alkaline. Add 10 ml of chloroform and mix well, evaporate the chloroform layer on a water bath to dryness. To the residue add 0.5 ml of sulfuric acid containing 2.5 mg of selenic acid, a green colour is produced which turns to blue gradually.

Content uniformity Comply with the requirements of content uniformity (Appendix X E). Triturate 1 tablet in a mortar and transfer to a 250 ml volumetric flask with water in portions. Carry out the method as described under Assay, beginning at the words "add 200 ml of water...".

Dissolution Carry out the dissolution test (Appendix X C method 1), using 900 ml of water as the dissolution medium, adjust the rotational speed of the basket at 100 rpm. Withdraw a quantity of the solution after exact 30 minutes and filter through a membrane filter. The successive filtrate is used as the test solution. Prepare the reference solution as described under the Assay. Measure 20 μ l of each of the two solutions, carry out the method in the Assay. Calculate the dissolution from each tablet. Not less than 80% of the labelled amount is dissolved.

Other requirements Comply with the general requirements for tablets (Appendix I A).

Assay Carry out the method for high performance liquid chromatography (Appendix V D), using a column packed with octadecylsilane bonded silica gel and a mixture of 0.05 mol/L potassium dihydrogen phosphate solution-methanol-tetrahydrofuran (50 : 10 : 4) as the mobile phase. Detection wavelength is 280 nm and the number of the theoretical plates of the column is not less than 2000, calculated with reference to the peak of Codeine Phosphate. The resolution factor between the peaks of Paracetamol and Codeine Phosphate complies with the related requirements.

Procedure Weigh accurately and powder 20 tablets. To a quantity accurately weighed, equivalent to about 8.4 mg of Codeine Phosphate and 500 mg of Paracetamol, add 200 ml of water in a 250 ml volumetric flask, sonicate for 10 minutes, add water to volume, shake thoroughly. Filter through a membrane filter. Inject 10 μ l of the successive filtrate into the column, accurately measured, record the chromatogram. Dissolve a quantity of Codeine Phosphate CRS and Paracetamol CRS in water, accurately weighed, to produce a solution of 0.03 mg of Codeine Phosphate and 2 mg of Paracetamol per ml, repeat the operation. Calculate the content of Paracetamol and Codeine Phosphate respectively with respect to the peak areas obtained in the chromatogram by the external standard method. The coefficient 1.068 is multiplied in the calculation of the content of Codeine Phosphate.

Category Analgetic.

Storage Preserve in tightly closed container, protected from light.

Paracetamol and Codeine Phosphate Tablets (II)

Paracetamol and Codeine Phosphate Tablets contain not less than 270 mg and not more than 330 mg of Paracetamol ($C_8H_9NO_2$), and not less than

Phosphate ($C_{18}H_{21}NO_3 \cdot H_3PO_4 \cdot 1\frac{1}{2} H_2O$) in each tablet.

Formula	Paracetamol	300 g
	Codeine Phosphate	15 g
	Excipients	a quantity
	to make	1000 tablets

Description White tablets.

Identification (1) To about 0.1 g of the powdered tablets add 10 ml of water, shake to dissolve Paracetamol. Filter, and add ferric chloride TS to the filtrate; a purple colour is produced.

(2) To about 0.5 g of the powdered tablets add 5 ml of water, shake to dissolve Codeine Phosphate. Filter, and transfer the filtrate to a separator, add dropwise of ammonia TS to make the filtrate alkaline. Add 10 ml of chloroform and mix well, evaporate the chloroform layer on a water bath to dryness. To the residue add 0.5 ml of sulfuric acid containing 2.5 mg of selenic acid, a green colour is produced which turns to blue gradually.

(3) To about 0.2 g of the powdered tablets in a conical flask with stopper add 25 ml of methanol, shake to dissolve Paracetamol CRS and Codeine Phosphate. Filter, and use the successive filtrate as the test solution. Dissolve Paracetamol CRS and Codeine Phosphate CRS in methanol to produce a solution containing 6 mg of Paracetamol and 0.3 mg of Codeine Phosphate per ml as the reference solution. Carry out the method for thin-layer chromatography (Appendix V B), using silica gel GF₂₅₄ as the coating substance and a mixture of ethyl acetate-methanol-concentrated ammonia solution (85 : 10 : 5) as the mobile phase. Apply separately to the plate 5 µl of each of the above two solutions. After developing and removal of the plate, dry in air, and examine under ultraviolet light (254 nm). The two principal dark spots in the chromatogram obtained with the test solution correspond in position to the principal spots obtained with the reference solution. Then spray with oil-soluble bi-ortho-nitric TS, the spot in the chromatogram obtained with the test solution corresponds in position and colour to the spot of Codeine Phosphate obtained with the reference solution.

Content uniformity *Codeine Phosphate* Comply with the requirements for content uniformity (Appendix X E). Triturate 1 tablet with water in a beaker and transfer to a 50 ml volumetric flask with water in portions, sonicate for 10 minutes, dilute with water to volume, shake thoroughly and filter through a membrane filter of not more than 0.45 µm. Measure accurately 5 ml of the successive filtrate to a 25 ml volumetric flask, dilute with the mobile phase to volume and mix well, used as the test solution. Weigh accurately 15 mg of Codeine Phosphate CRS, in a 50 ml volumetric flask, add water to dissolve Codeine Phosphate and dilute to volume, shake thoroughly. Measure accurately 5 ml to a 25 ml volumetric flask, and dilute with the mobile phase to volume and mix well, use as the reference solution. Carry out the method in the Assay and calculate the content of Codeine Phosphate.

Dissolution Carry out the dissolution test (Appendix X C method 1), using 900 ml of water as the dissolution medium, adjust the rotational speed of the basket at 100 rpm. Withdraw a quantity of the solution after exact 30 minutes and filter through a membrane filter. The successive filtrate is used as the test solution. Prepare the reference solution as described under the Assay. Measure 20 µl of each of the two solutions, carry out the method in the Assay.

Other requirements Comply with the general requirements for tablets (Appendix I A).

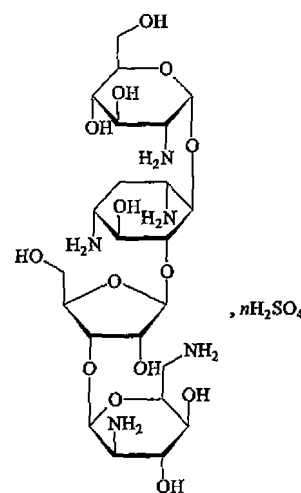
Assay Carry out the method for high performance liquid chromatography (Appendix V D), using a column packed with octadecylsilane bonded silica gel and a mixture of 0.05 mol/L potassium dihydrogen phosphate solution-methanol-tetrahydrofuran (800 : 100 : 37.5) as the mobile phase (adjust to pH 4.0 with phosphoric acid). Detection wavelength is 280 nm and the number of the theoretical plates of the column is not less than 2500, calculated with reference to the peak of Codeine Phosphate. The resolution factor between the peaks of Paracetamol and Codeine Phosphate complies with the related requirements.

Procedure Weigh accurately and powder 20 tablets. To a quantity accurately weighed, equivalent to about 15 mg of Codeine Phosphate and 300 mg of Paracetamol, add 200 ml of water in a 250 ml volumetric flask, sonicate for 10 minutes, add water to volume, shake thoroughly. Filter through a membrane filter. Inject 10 µl of the successive filtrate into the column, accurately measured, record the chromatogram. Dissolve a quantity of Codeine Phosphate CRS and Paracetamol CRS in water, accurately weighed, to produce a solution of 0.06 mg of Codeine Phosphate and 1.2 mg of Paracetamol per ml, repeat the operation. Calculate the content of Paracetamol and Codeine Phosphate respectively with respect to the peak areas obtained in the chromatogram by the external standard method. The coefficient 1.068 is multiplied in the calculation of the content of Codeine Phosphate.

Category Analgetic.

Storage Preserve in tightly closed container, protected from light.

Paromomycin Sulfate



$C_{23}H_{45}N_5O_{14} \cdot nH_2SO_4$

[1263-89-4]

Paromomycin Sulfate is O-2-amino-2-deoxy-α-D-glucopyranosyl-(1 → 4)-O-[O-2,6-diamino-2,6-dideoxy-β-L-idopyranosyl-(1 → 3)-β-D-ribofuranosyl-(1 → 5)]-2-deoxy-D-streptamine sulfate. It has a potency of not less than 700 Paromomycin Units per mg, calculated on the dried basis.

Description A white to pale yellow powder; odourless;

Freely soluble in water, insoluble in methanol, ethanol, acetone, chloroform or ether.

Specific optical rotation $+50^{\circ}$ to $+55^{\circ}$, in a solution of 50 mg per ml in water (Appendix VI E).

Identification (1) Carry out the method for thin-layer chromatography (Appendix V B), using silica gel H as the coating substance and a mixture of 50% methanol containing 1.5% of sodium chloride-concentrated ammonia solution (100 : 8) as the mobile phase. Apply separately to the plate 1 μ l each of two solutions in water containing (1) 20 mg per ml of the substance being examined and (2) 20 mg of paromomycin RS per ml. After developing and removal of the plate, allow it to dry in air, then heat at 105°C , allow to cool and spray with a solution of ninhydrin in aqueous solution of pyridine diluted with water (dissolve 0.5 g of ninhydrin in 100 ml of 40% pyridine in water). The colour and position of the principal spot in the chromatogram obtained with solution (1) correspond to that of the principal spot obtained with solution (2).

(2) The infrared absorption spectrum (Appendix IV C) is concordant with the reference spectrum of paromomycin Sulfate (Appendix XVI).

(3) The aqueous solution yields the reactions characteristic of sulfates (Appendix III).

Acidity or alkalinity Dissolve a quantity in water to produce a solution of 50 mg per ml, pH 5.0-7.5 (Appendix VI H).

Loss on drying When dried to constant weight at 105°C , loses not more than 7.0% of its weight (Appendix VIII L).

Assay Dissolve an accurately weighed quantity in sterile water to produce a solution of 1000 Units per ml and carry out the Microbiological Assay of Antibiotics (Appendix XI A). 1000 Paromomycin Units are equivalent to 1 mg Paromomycin.

Category Aminoglycoside antibiotic.

Storage Preserve in tightly closed containers, protected from light and stored in a dry place.

Preparation Paromomycin Sulfate Tablets

Paromomycin Sulfate Tablets

Paromomycin Sulfate Tablets contain not less than 90.0% and not more than 110.0% of the labelled potency of paromomycin.

Description White to slight yellow tablets or sugar coated tablets with white to slight yellow core.

Identification To a quantity of the powdered tablets (with sugar coating removed) add water to produce a suspension containing 20 mg of Paromomycin per ml, shake thoroughly and filter. The filtrate complies with tests for Identification described under Paromomycin sulfate.

Other requirements Comply with the general requirements for tablets (Appendix I A), except that the plain tablets disintegrate within 30 minutes.

Assay Weigh accurately and powder 10 tablets or 4 sugar coated tablets. To a quantity of the powder equivalent to about 0.25 g of paromomycin add sterile water to produce a suspension of 1000 Unit per ml, shake thoroughly and allow to stand. Measure accurately a quantity of the supernatant liquid and carry out the Assay described under Paromomycin Sulfate.

Category As described under Paromomycin Sulfate.

Strength (1) 0.1 g (100000 Units)

(2) 0.25 g (250000 Units)

Storage Preserve in tightly closed containers, protected from light and stored in a dry place.

Paroxetine Hydrochloride Tablets

Paroxetine hydrochloride tablets contain not less than 93.0% and not more than 107.0% of the labelled amount of paroxetine ($\text{C}_{19}\text{H}_{20}\text{FNO}_3$).

Description Coated tablets with white core.

Identification The retention time of principal peak of the paroxetine hydrochloride in the substance being examined in the chromatogram obtained in the Assay is identical with that of the principal peak of paroxetine hydrochloride CRS in the chromatogram of the reference solution.

Dissolution Carry out the dissolution test (Appendix X C, method 2). Using hydrochloric acid solution (9 \rightarrow 1000) 1000 ml as dissolution medium, adjust the rotational speed of the paddle to 50 rpm. Withdraw 20 ml of the solution after exact 45 minutes and filter. Dissolve about 23 mg of paroxetine hydrochloride CRS, accurately weighed, in dissolution medium in a 100 ml volumetric flask, add a quantity of dissolution medium and ultrasonicate to dissolve it, dilute with dissolution medium to the volume, mix well. Measure accurately 5 ml in a 50 ml volumetric flask, dilute with dissolution medium to the volume, mix well, as the reference solution. Inject 20 μ l each of above two solutions into the column, carry out the procedure as described under the Assay. Detection wavelength is 293 nm. Calculate the dissolution of $\text{C}_{19}\text{H}_{20}\text{FNO}_3$ from each tablet, not less than 75% of the labelled amount is dissolved.

Other requirements Comply with the general requirements for tablets (Appendix I A).

Assay Carry out the method for high performance liquid chromatography (Appendix V D). Using a column packed with cyano bonded silica gel and a mixture of phosphate BS (dissolve 4.9 g of phosphoric acid in 800 ml of water, adjust pH value to 6.0 with 0.1 mol/L sodium hydroxide, dilute with water to 1000 ml)-acetonitrile (1 : 1) as the mobile phase. Detection wavelength is 295 nm. The number of theoretical plates of the column is not less than 2000, calculated with reference to the peak of paroxetine hydrochloride.

Procedure Transfer 10 tablets into a 250 ml volumetric flask, add 70 ml of water and 5 ml of 0.01 mol/L hydrochloric acid solution, ultrasonicate for 15 minutes and shake occasionally, cool to room temperature, dilute with iso-propanol to the volume, mix well, filter. Measure accurately 10 ml the successive filtrate to a 100 ml volumetric flask, dilute with iso-propanol-water (70 : 30) to the volume, mix well. Inject 20 μ l of the solution and record the chromatogram. Dissolve a quantity of paroxetine hydrochloride CRS equivalent to about 20 mg of paroxetine, weighed accurately, in a 250 ml volumetric flask, add 10 ml of 0.01 mol/L hydrochloric acid solution and a quantity of iso-propanol-water (70 : 30), shake well, dilute with iso-propanol-water (70 : 30) to the volume, mix well. Measure in the same manner. Calculate the content of $\text{C}_{19}\text{H}_{20}\text{FNO}_3$.

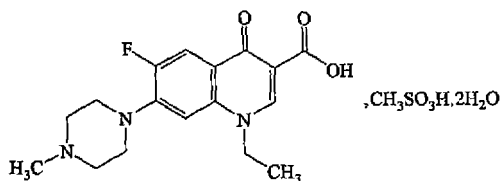
Category Antidepressant.

Strength Calculated as $\text{C}_{19}\text{H}_{20}\text{FNO}_3$
0.20 mg

Storage Preserve in tightly closed containers, protected

from light.

Pefloxacin Mesylate



$C_{17}H_{20}FN_3O_3 \cdot CH_3O_3S \cdot 2H_2O$ 465.49

Pefloxacin mesylate is 1-ethyl-6-fluoro-7-(4-methylpiperazin-1-yl)-4-oxo-1,4-dihydroquinoline-3-carboxylic acid methanesulphonate dihydrate. It contains not less than 76.4% of $C_{17}H_{20}FN_3O_3$, calculated on the anhydrous basis.

Description A white or slight yellow crystalline powder. Freely soluble in water, very slightly soluble in ethanol, sparingly soluble in chloroform.

Identification (1) Weigh about 30 mg, add 0.2 g of sodium hydroxide and add a few droplets of water. After dissolved, vaporize slowly to dryness on an alcohol lamp and char. Add a few droplets of water and 3-4 ml of 2 mol/L hydrochloride solution and heat slowly. The vapor of sulfur dioxide is produced and change the wet potassium iodate-starch indicator paper (Immerse the paper into a mixture solution containing 5% potassium iodate solution and starch indicator solution and stand to dry) to blue.

(2) The retention time of the principal peak of the substance being examined in the chromatogram obtained in the Assay is identical with the principal peak in the chromatogram of pefloxacin mesylate CRS.

(3) The infrared absorption spectrum (Appendix IV C) is concordant with the reference spectrum of pefloxacin mesylate (Appendix XVI).

Acidity Dissolve a quantity in water to produce a solution of 10 mg per ml, pH 3.5-4.5.

Clarity and colour of solution To 5 portions each of 0.5 g add 5 ml water to dissolve. The solutions are clear and colourless; any opalescence produced is not more pronounced than that of reference suspension II (Appendix IX B). Any colour produced (for injection) is not more intense than that of reference solution YG₅ (Appendix IX A, method 1).

Related substances Protected from light throughout the procedure. Carry out the method described under Assay. Inject 20 μ l of the reference solution into the column. Adjust the attenuation so that the peak height of pefloxacin in the chromatogram is about 20%-25% of full scale of the chart. Dissolve a quantity of the substance being examined in water to produce a solution of 0.2 mg of pefloxacin per ml as test solution. Transfer 1 ml of test solution, measured accurately, to a 100 ml volumetric flask, dilute with water to volume and mix well as reference solution. Inject separately 20 μ l of the test solution and the reference solution respectively into column and record the chromatogram for three times the retention time of the pefloxacin peak. The sum of the areas of all peaks other than the principal peak is not greater than area of the pefloxacin peak in the chromatogram obtained with the reference solution (1.0%).

Not less than 99.0% dissolved in a mixture solution of

method 1 A).

Residue on ignition Not more than 0.2% (Appendix VIII N), using 1.0 g in a platinum crucible.

Heavy metals Carry out the limit test for heavy metals (Appendix VIII H, method 2), using the residue obtained in the test for Residue on Ignition; not more than 0.002%.

Bacteria endotoxin Carry out the test for bacterial endotoxin (Appendix XI E); less than 0.75 EU per mg of pefloxacin (for injection).

Assay Protected from light throughout the procedure. Carry out the method for high performance liquid chromatography (Appendix V D), using a column packed with octadecylsilane bonded silica gel and a mixture of 0.04 mol/L potassium dihydrogen phosphate-0.05 mol/L tetrabutylammonium bromide-acetonitrile (80:8:9) as the mobile phase. Detection wavelength is 277 nm and the number of theoretical plates of the column is not less than 2000, calculated with reference to the peak of pefloxacin. The resolution factor between the peak of pefloxacin and adjacent peaks complies with the requirements.

Procedure Dissolve a quantity, accurately weighed, in the mobile phase and dilute to produce a solution of 20 μ g of pefloxacin per ml and mix well. Measure accurately 20 μ l of the solution into the column and record the chromatogram. Repeat the operation, using pefloxacin CRS instead of the substance being examined, calculate the content of $C_{17}H_{20}FN_3O_3$.

Category Quinolone antibiotic.

Storage Preserve in tightly closed containers, protected from light, stored in a dry place.

Preparation (1) Pefloxacin Mesylate Tablets
(2) Pefloxacin Mesylate Injections
(3) Pefloxacin Mesylate Capsules
(4) Pefloxacin Mesylate for Injection

Pefloxacin Mesylate Capsules

Pefloxacin Mesylate Capsules contain not less than 93.0% and not more than 107.0% of the labelled amount of pefloxacin ($C_{17}H_{20}FN_3O_3$).

Description Capsules containing white or slight yellow powder.

Identification (1) Dissolve a quantity of the content in 10 ml water and filter. Evaporate a quantity of successive filtrate on a water bath to dryness. Weigh about 30 mg of residue, comply with the identification (1) of Pefloxacin Mesylate.

(2) The retention time of the principal peak of the substance being examined in the chromatogram obtained in the Assay is identical with the principal peak in the chromatogram of pefloxacin CRS.

Dissolution Carry out the dissolution test (Appendix X C, method 2), using 1000 ml of 0.1 mol/L hydrochloride acid solution as the dissolution medium, adjust the rotational speed of the paddle to 50 rpm. Withdraw 10 ml of the solution after exact 45 minutes and filter. Dilute an accurately measured quantity of the successive filtrate with 0.1 mol/L hydrochloride acid to produce a solution of 4 μ g of pefloxacin per ml. Dissolve a quantity of pefloxacin CRS in 0.1 mol/L hydrochloride acid solution to produce a solution of 4 μ g per ml. Measure the absorbance of the resulting solutions at 277 nm (Appendix IV A). Calculate the Not less

than 80% of the labelled amount is dissolved.

Other requirements Comply with the general requirements for capsules (Appendix I E).

Assay Transfer an accurately weighed quantity of the mixed contents of capsules obtained in the test for weight variation of contents, equivalent to about 100 mg of pefloxacin to a 200 ml volumetric flask, add a quantity of 0.1 mol/L hydrochloric acid to dissolve pefloxacin mesylate, and dilute to volume, mix well and filter. Measure accurately 5 ml of the successive filtrate to a 100 ml volumetric flask, dilute with the mobile phase to volume and mix well. Inject 20 μ l to the column and proceed as described under Pefloxacin Mesylate.

Category As described under Pefloxacin Mesylate

Strength Calculated as $C_{17}H_{20}FN_3O_3$
(1) 0.1 g (2) 0.2 g

Storage Preserve in tightly closed containers, protected from light, stored in a dry place.

Pefloxacin Mesylate for Injection

Pefloxacin Mesylate for Injection is sterile lyophilized preparation of pefloxacin mesylate. It contains not less than 90.0% and not more than 110.0% of the labelled amount of pefloxacin ($C_{17}H_{20}FN_3O_3$).

Description A white or slight yellow lyophilized mass or powder.

Identification (1) Comply with the identification (1) of Pefloxacin Mesylate, using 30 mg.

(2) The retention time of the principal peak of the substance being examined in the chromatogram obtained in the Assay is identical with the principal peak in the chromatogram of pefloxacin CRS.

Acidity Dissolve a quantity in water to produce a solution of 10 mg per ml, pH 3.0-4.5 (Appendix VI H).

Clarity and colour of solution To each of 5 container add 5 ml of water. The solutions are clear and colourless; any opalescence produced is not more pronounced than that of reference suspension I (Appendix IX B); any colour produced is not more intense than that of reference solution YG₅ (Appendix IX A, method 1).

Related substances Carry out the method described under Pefloxacin Mesylate. Dissolve a quantity of the substance being examined, measured accurately, in water to produce a solution containing 0.2 mg of pefloxacin per ml as the test solution. Transfer 1 ml of the test solution, measured accurately, to a 100 ml volumetric flask, dilute with water to volume and mix well as the reference solution. Inject accurately 20 μ l of the test solution and the reference solution respectively into column. The sum of the areas of all peaks other than the principal peak is not greater than the area of the pefloxacin peak in the chromatogram obtained with the reference solution (1.0%).

Loss on drying When dried 6 hours at 105°C, loses not more than 3.0% of its weight (Appendix VIII L).

Bacterial endotoxin Carry out the test for bacterial endotoxin (Appendix XI E): less than 0.75 EU per mg of pefloxacin.

Sterility Complies with the test for sterility (Appendix XI H, membrane filtration method), transfer each portion to at least 500 ml of 0.9% sterile water, after dissolving in a

quantity of sterile water.

Other requirements Comply with the general requirements for Injections (Appendix I B).

Assay Measure accurately a quantity of the mixed contents obtained in the test for weight variation of contents. Add water to produce a solution of 20 μ g per ml of pefloxacin and proceed as described under Pefloxacin Mesylate.

Category As described under Pefloxacin Mesylate.

Strength Calculated as $C_{17}H_{20}FN_3O_3$
0.2 g

Storage Preserve in tightly closed containers, protected from light.

Pefloxacin Mesylate Injection

Pefloxacin Mesylate Injection is sterile solution of pefloxacin mesylate. It contains not less than 90.0% and not more than 110.0% of the labelled amount of pefloxacin ($C_{17}H_{20}FN_3O_3$).

Description Clear, colourless to slight yellow or slight yellow-greenish liquid.

Identification (1) Heat 1 ml on a water bath to dryness. Complies with the Identification (1) described under Pefloxacin Mesylate, using 30 mg of the residue.

(2) The retention time of the principal peak of the substance being examined in the chromatogram obtained in the Assay is identical with the principal peak in the chromatogram of pefloxacin CRS.

pH value 3.0-5.0 (Appendix VI H).

Colour of solution The solutions is not more intense than that of reference solution YG₅ (Appendix IX A, method 1).

Related substances Carry out the method described under Pefloxacin Mesylate. Transfer a quantity of the substance being examined, measured accurately, in water to produce a solution of 0.2 mg of pefloxacin per ml as the test solution. Transfer 1 ml of the test solution, measured accurately, to a 100 ml volumetric flask, dilute with water to volume and mix well as the reference solution. Inject separately 20 μ l of the test solution and the reference solution respectively into column. The sum of the areas of all peaks other than the principal peak is not greater than the area of the pefloxacin peak in the chromatogram obtained with the reference solution (1.0%).

Bacterial endotoxin Carry out the test for bacterial endotoxin (Appendix XI E): less than 0.75 EU per mg of pefloxacin.

Sterility Complies with the test for sterility (Appendix XI H, membrane filtration method), transfer each portion to 500 ml of 0.9% sterile sodium chloride solution.

Other requirements Comply with the general requirements for Injections (Appendix I B).

Assay Dilute a quantity of the substance being examined with water to produce a solution of 20 μ g per ml of pefloxacin and proceed as described under Pefloxacin Mesylate.

Category As described under Pefloxacin Mesylate.

Strength Calculated as $C_{17}H_{20}FN_3O_3$
(1) 2 ml : 0.2 g (2) 5 ml : 0.4 g

Storage Preserve in well closed containers, protected from light.

Pefloxacin Mesylate Tablets

Pefloxacin Mesylate Tablets contain not less than 93.0% and not more than 107.0% of the labelled amount of pefloxacin ($C_{17}H_{20}FN_3O_3$).

Description White or slight yellow tablets or film coated tablets with white or slight yellow core.

Identification (1) Dissolve a quantity of the powdered tablets in 10 ml water and filter. Evaporate a quantity of successive filtrate on a water bath to dryness. Weigh about 30 mg of residue and comply with the Identification (1) of Pefloxacin Mesylate.

(2) The retention time of the principal peak of the substance being examined in the chromatogram obtained in the Assay is identical with the principal peak in the chromatogram of pefloxacin CRS.

Dissolution Carry out the dissolution test (Appendix X C, method 2), using 1000 ml of 0.1 mol/L hydrochloride acid solution as the dissolution medium, adjust the rotational speed of the paddle to 50 rpm. Withdraw 10 ml of the solution after exact 45 minutes and filter. Dilute an accurately measured quantity of the successive filtrate with 0.1 mol/L hydrochloride acid solution to produce a solution of 4 μ g of pefloxacin per ml. Dissolve a quantity of pefloxacin CRS in 0.1 mol/L hydrochloride acid solution to produce a solution of 4 μ g of pefloxacin per ml. Measure the absorbance of the resulting solutions at 277 nm (Appendix IV A). Calculate the dissolution of $C_{17}H_{20}FN_3O_3$ from each tablet. Not less than 75% of the labelled amount is dissolved.

Other requirements Comply with the general requirements for tablets (Appendix I A).

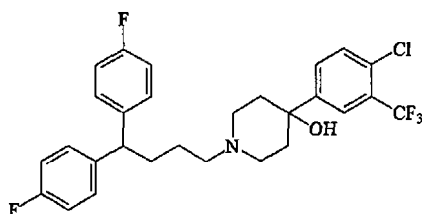
Assay Weigh accurately and powder finely 10 tablets with coating removed. Dissolve an accurately weighed quantity of powder equivalent to about 100 mg of pefloxacin with 0.1 mol/L hydrochloride acid in a 200 ml volumetric flask and dilute to volume, mix well and filter. Measure accurately a quantity of the successive filtrate to produce a solution of 20 μ g per ml of pefloxacin as the test solution. Dissolve about 25 mg of pefloxacin CRS, weighed accurately, in 0.1 mol/L hydrochloric acid in 50 ml volumetric flask, and dilute to volume. Mix well, dilute a quantity of the solution in water to produce a solution of 20 μ g of pefloxacin per ml, as the reference solution. Proceed as described under Pefloxacin Mesylate.

Category As described under Pefloxacin Mesylate.

Strength Calculated as $C_{17}H_{20}FN_3O_3$
(1) 0.1 g (2) 0.2 g

Storage Preserve in tightly closed containers, protected from light, stored in a dry place.

Penfluridol



Penfluridol is 1-[4,4-bis (4-fluorophenyl) butyl]-4-[4-chloro-3-(trifluoro-methyl) phenyl]-4-piperidinol. It contains not less than 99.0% of $C_{28}H_{27}ClF_5NO$, calculated on the dried basis.

Description A white or almost white crystalline powder; odourless; tasteless.

Freely soluble in methanol, ethanol or chloroform; practically insoluble in water.

Melting point 105-108°C (Appendix VI C).

Identification (1) Dissolve 5-10 mg in 1 ml of ethanol, add 1 ml of a mixture of carbon disulfide-benzene (1 : 3) and 0.5 ml of silver nitrate TS; a pale yellow precipitate is produced which changes to greyish-black gradually.

(2) The light absorption of a 0.1 mg per ml solution in ethanol exhibits maxima at 267 and 273 nm; minima at 240 and 270 nm (Appendix IV A).

(3) The infrared absorption spectrum (Appendix IV C) is concordant with the reference spectrum of penfluridol (Appendix XVI).

Fluorides To 0.40 g add 50 ml of water, shake for 5 minutes and filter. Transfer 25 ml of filtrate to a 50 ml Nessler cylinder, allow to cool below 15°C, add 2.0 ml of acidic zirconyl alizarin TS, dilute with water to volume, mix well. Allow it to stand for 1 hour at a temperature below 15°C and protect from light. The colour of the solution is not more intense than that of a reference solution (dilute 4.0 ml of 0.0022% sodium fluoride solution with water to 25 ml) treated in the same manner (0.02%).

Related substances Carry out the method for thin-layer chromatography (Appendix V B), using silica gel G as the coating substance and a mixture of ethyl acetate-benzene-concentrated ammonia solution (8 : 3 : 2) as the mobile phase. Apply separately to the plate 10 μ l each of two solutions in ethanol containing (1) 20 mg per ml, (2) 0.20 mg per ml of the substance being examined. After developing and removal of the plate, dry in air and then at 60°C for 15 minutes, expose to iodine vapour and examine immediately. Not more than 3 secondary spots are obtained with solution (1). Any spot, other than the principal spot obtained with solution (1) is not more intense than the principal spot obtained with solution (2).

Loss on drying When dried to constant weight at 80°C, loses not more than 0.5% of its weight (Appendix VIII L).

Residue on ignition Not more than 0.1% (Appendix VIII N).

Assay Dissolve about 0.1 g, accurately weighed, in 30 ml of ethanol. Carry out the method for potentiometric titration (Appendix VII A), titrate with hydrochloric acid (0.025 mol/L) VS to pH 5.1. Perform a blank determination and make any necessary correction. Each ml of hydrochloric acid (0.025 mol/L) VS is equivalent to 13.10 mg of $C_{28}H_{27}ClF_5NO$.

Category Antipsychotic agent.

Storage Preserve in tightly closed containers, protected from light.

Preparation Penfluridol Tablets

Penfluridol Tablets

Penfluridol Tablets contain not less than 90.0% and not more than 110.0% of the labelled amount of penfluridol ($C_{28}H_{27}ClF_5NO$).

Description Sugar coated white tablets with a white or almost white core.

Identification (1) To a quantity of the powdered tablets equivalent to about 20 mg of penfluridol add 4 ml of ethanol, shake to dissolve penfluridol and filter. The filtrate complies with test (1) for Identification described under Penfluridol. (2) Extract a quantity of the powdered tablets equivalent to 0.1 mg of penfluridol per ml with ethanol and filter. The filtrate complies with test (2) for Identification described under Penfluridol.

Other requirements Comply with the general requirements for tablets (Appendix I A).

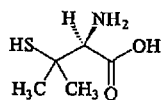
Assay Add a quantity of ethanol to 10 tablets (for 20 mg strength) or 20 tablets (for 10 mg strength) in a 50 ml volumetric flask, with sugar coating removed, shake to dissolve penfluridol, dilute with ethanol to volume and mix well. Filter, discard the initial filtrate and measure accurately 25 ml of the successive filtrate. Complete the Assay described under Penfluridol, beginning at the words "Carry out the method for potentiometric titration...". Each ml of hydrochloric acid (0.025 mol/L) VS is equivalent to 13.10 mg of $C_{28}H_{27}ClF_5NO$.

Category As described under Penfluridol.

Strength (1) 10 mg (2) 20 mg

Storage Preserve in tightly closed containers.

Penicillamine



$C_5H_{11}NO_2S$ 149.21

[52-67-5]

Penicillamine is D-3-mercaptovaline. It contains not less than 95.0% of $C_5H_{11}NO_2S$, calculated on the dried basis.

Description A white or almost white crystalline powder. Freely soluble in water; slightly soluble in ethanol; insoluble in chloroform or ether.

Specific optical rotation -61.0° to -65.0° , in a solution of 50 mg per ml in 1 mol/L sodium hydroxide solution (Appendix VI E).

Identification (1) Dissolve the substance being examined and penicillamine CRS in water to produce two solutions of 2.5 mg per ml, respectively. Carry out the method for thin-layer chromatography (Appendix V B), using silica gel G as the coating substance and a mixture of *n*-butanol-glacial acetic acid-water (72 : 18 : 18) as the mobile phase. Apply separately to the plate 2 μ l each of the two solutions. After developing and removal of the plate, dry it at $105^\circ C$ for 10 minutes and expose it in iodine vapour for 5 to 10 minutes. The colour and position of the principal spot in the chromatogram obtained with the solution of substance being examined corresponds to that of the principal spot obtained with the solution of penicillamine CRS.

(2) Dissolve about 40 mg in 4 ml of water, add 2 ml of phosphotungstic acid TS (1 \rightarrow 10), allow to stand for a few minutes, a deep blue colour is produced.

(3) Dissolve about 0.5 ml in 5 ml of acetone containing 0.5 ml of hydrochloric acid. Cool in ice bath and rub the tube

wash the precipitate with acetone and dry in air. The 1% solution of precipitate in water is dextrorotatory.

Acidity An aqueous solution of 10 mg per ml, pH 4.0-6.0 (Appendix VI H).

Loss on drying When dried in vacuum over phosphorous pentoxide to constant weight at $60^\circ C$, loses not more than 0.5% of its weight (Appendix VIII L).

Penicillin Carry out the method for Microbiological assay of antibiotics (Appendix XI A).

Preparation of culture medium Mix 6.0 g of peptone, 4.0 g of pancreatin digested casein, 3.0 g of yeast, 1.5 g of beef extract, 1.0 g of glucose, 15.0 g of agar and 1000 ml of water. Adjust the pH of the solution so that the final pH of the sterilized medium is 6.5-6.7. Sterilize the medium at $115^\circ C$ for 30 minutes.

Preparation of inoculum Prepare *Sarcina lutea* inoculum as directed in *Sarcina lutea* [CMCC(B)28001].

Preparation of reference solution Dilute an accurately weighed quantity of penicillin CRS with sterile phosphate BS (pH 6.0) to produce a solution of 0.02 unit per ml.

Preparation of test solution Weigh accurately 1 g to a separator, add 9 ml of water to dissolve. Add 10 ml of ether and 1 ml of phosphate BS (pH 2.5), shake for 1 minute, separate the aqueous layer to another separator, extract with 10 ml each of ether for 2 times. Combine the ether extracts, add 9 ml of water and 1 ml of phosphate BS (pH 2.5), shake for 30 seconds and discard the aqueous layer (this procedure must be completed within 6-7 minutes). Extract the ether layer with 10 ml of sterile phosphate BS (pH 6.0) for 3 minutes, separate 5 ml of the aqueous layer as test solution (1). Add 0.1 ml of penicillinase to the remaining aqueous solution and allow to stand at $36-37^\circ C$ for 1 hour as test solution (2).

Procedure Use not less 4 petri dishes, add 10 ml of culture medium to the bottom and add 5 ml of culture medium to the bacteria layer in each dish. Place 6 stainless steel cylinders, fill two of the diagonal cylinders on each plate with reference solution, test solution (1) and test solution (2) respectively, incubate the dishes at $29-30^\circ C$ for 24 hours. Measure the diameter of the inhibition zones. The mean diameter of the inhibition zone of test solution (1) is not more than the mean diameter of the inhibition zone of reference solution and no inhibition zone is produced with test solution (2) (0.2 unit/g).

Assay Dissolve about 150 mg, accurately weighed, in 100 ml of acetate BS (5.4 g of sodium acetate in a 100 ml volumetric flask, add 50 ml of water to dissolve, and adjust to pH 4.6, dilute to volume with water and mix well). Carry out the method for potentiometric titration (Appendix VII A), using platinum electrode as indicating electrode and mercury-mercurous sulfate electrode as reference electrode. Titrate slowly with mercuric nitrate (0.05 mol/L) VS, calculate the quantity of titrant at the end point by internal insertion method. Each ml of mercuric nitrate (0.05 mol/L) VS is equivalent to 7.461 mg of $C_5H_{11}NO_2S$.

Category Antidote of heavy metals.

Storage Preserve in tightly closed containers.

Preparation Penicillamine Tablets

Penicillamine Tablets

Penicillamine Tablets contain not less than 95.0% of

and not more than 110.0% of the labelled amount of penicillamine ($C_5H_{11}NO_2S$).

Description Sugar coated tablets with white core.

Identification Remove the sugar coating and powder the tablets. Weigh a quantity of the powder equivalent to about 250 mg of penicillamine, add 25 ml of water, stir and filter. The filtrate complies with test (1) and (2) for Identification described under Penicillamine.

Other requirements Comply with the general requirements for tablets (Appendix I A).

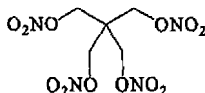
Assay Weigh accurately and powder 10 tablets. Weigh accurately a quantity of the powder equivalent to about 0.15 g of penicillamine, carry out the method for Assay described under Penicillamine.

Category As described under Penicillamine.

Strength 0.125 g

Storage Preserve in tightly closed containers.

Powdered Pentaerithrityl Tetranitrate



$C_5H_8N_4O_{12}$ 316.14

[78-11-5]

Pentaerithrityl Tetranitrate Powder is a mixture of 1 part of pentaerithrityl tetranitrate, 3 parts of lactose and 1 part of starch. It contains not less than 18.5% and not more than 21.5% of $C_5H_8N_4O_{12}$.

Description A white power; odourless.

Identification (1) Stir a quantity equivalent to about 50 mg of pentaerithrityl tetranitrate with 25 ml of dehydrated acetone (dry acetone with anhydrous sodium carbonate and distil) to dissolve pentaerithrityl tetranitrate, and filter. Transfer the filtrate to an evaporating dish, expel acetone on a warm water bath. The residue melt at 139-143°C (Appendix VI C) (pentaerithrityl tetranitrate has explosive property, suitable protective mask should be used in operation. Dissolve the remaining residue in acetone, dispose by burning in a porcelain dish).

(2) Transfer about 10 mg of the residue obtained from test (1) to a mixture of 3 ml of sulfuric acid and 1 ml of water, cool, add 3 ml of ferrous sulfate TS along the wall of test tube, a brown ring is produced at the junction of the liquids.

Assay Reference solution Dissolve 127.9 mg of potassium nitrate previously dried to constant weight at 105°C, accurately weighed, in a 200 ml volumetric flask with 3 ml of water, dilute with glacial acetic acid to volume and mix well. Measure accurately 5 ml of the solution to a 10 ml volumetric flask, dilute with glacial acetic acid to volume and mix well (each ml is equivalent to 0.25 mg of $C_5H_8N_4O_{12}$).

Test solution Weigh accurately a quantity equivalent to about 25 mg of pentaerithrityl tetranitrate to a 100 ml volumetric flask, add 75 ml of glacial acetic acid, heat on a water bath for 20 minutes, cool, add glacial acetic acid to volume, mix well and filter, using the filtrate.

Procedure Transfer 2 ml each of the two solutions, accurately measured, to two 50 ml volumetric flasks separately. Add accurately 2 ml of phenoldisulfonic acid TS

25 ml of water and cool, then add gradually 8 ml of concentrated ammonia solution to alkalinize the solution, cool to room temperature, add water to volume and mix well. Measure the absorbance of the resulting solutions at 405 nm (Appendix IV A). Calculate the content of $C_5H_8N_4O_{12}$.

Category Vasodilator.

Storage Preserve in tightly closed containers, protected from light, stored in a cool place.

Preparation Pentaerithrityl Tetranitrate Tablets

Pentaerithrityl Tetranitrate Tablets

Pentaerithrityl Tetranitrate Tablets contain not less than 90.0% and not more than 110.0% of the labelled amount of pentaerithrityl tetranitrate ($C_5H_8N_4O_{12}$).

Description White tablets.

Identification (1) Stir a quantity of the powdered tablets equivalent to about 50 mg of pentaerithrityl tetranitrate with about 25 ml of dehydrated acetone (dry acetone with anhydrous sodium carbonate and distil), and filter. Transfer the filtrate to an evaporating dish, expel acetone on a warm water bath. The residue melt at 139-143°C (Appendix VI C) (pentaerithrityl tetranitrate has explosive property, suitable protective mask should be used in operation. Dissolve the remaining residue in acetone, dispose by burning in a porcelain dish).

(2) Transfer about 10 mg of the residue obtained from test (1) to a mixture of 3 ml of sulfuric acid and 1 ml of water, cool, add 3 ml of ferrous sulfate TS along the wall of test tube, a brown ring is produced at the junction of the liquids.

Content uniformity Comply with the requirements (Appendix X E). Triturate 1 tablet with glacial acetic acid in a mortar, transfer to a 50 ml volumetric flask with glacial acetic acid in portions under a ventilation hood. Heat on a water bath for about 20 minutes, shake to dissolve pentaerithrityl tetranitrate and cool, dilute to volume and mix well. Filter, use the successive filtrate as test solution, carry out the Assay as described under Powdered Pentaerithrityl Tetranitrate. Calculate the content of $C_5H_8N_4O_{12}$.

Other requirements Comply with the general requirements for tablets (Appendix I A).

Assay Weigh accurately and powder 20 tablets. Triturate an accurately weighed quantity of the powder equivalent to about 25 mg of pentaerithrityl tetranitrate to a 100 ml volumetric flask. Add about 75 ml of glacial acetic acid, heat on a water bath for 20 minutes, allow to cool, add glacial acetic acid to volume. Use the successive filtrate as test solution, carry out the Assay described under Powdered Pentaerithrityl Tetranitrate, calculate the content of $C_5H_8N_4O_{12}$.

Category, Storage As described under Powdered Pentaerithrityl Tetranitrate.

Strength 10 mg

Pentagastrin

$C_{37}H_{49}N_7O_9S$ 767.9

[5534-95-2]

Pentagastrin is *N*-Carboxy- β -alaninyl-L-tryptophyl-L-methionyl-L-aspartylphenyl-L-alaninamide-*N*-

and not more than 103.0% of $C_{37}H_{49}N_7O_9S$, calculated on the dried basis.

Description A white or almost white powder; odourless. Soluble in dimethylformamide; slightly soluble in ethanol; insoluble in water; soluble in dilute ammonia solution.

Specific optical rotation -25.0° to -29.0° , in a solution of 10 mg per ml in dimethylformamide (Appendix VI E).

Identification (1) The light absorption of the solution obtained in the Assay, in the range of 230-350 nm (Appendix IV A), exhibits two maxima at 280 nm and 288 nm, and an inflection at 275 nm.

(2) Carry out the method for thin-layer chromatography (Appendix V B), using silica G as the coating substance and the upper layer of a mixture of butanol-water-isobutyric acid-glacial acetic acid (50 : 50 : 5 : 7) as the mobile phase. Apply separately to the plate 3 μ l each of the following solutions. For solution (1) shake about 5 mg of pentagastrin with 0.5 ml of hydrochloride acid solution (1 \rightarrow 2), transfer to an ampoule, seal and hydrolysis at 150°C for 30 minutes. Transfer the hydrolysate to a small beaker, evaporate to dryness on a water bath, dissolve the residue in 0.1 ml of water as test solution. Solution (2) contains 2.5 mg of methionine CRS per ml in water. Solution (3) contains 2.5 mg of tryptophan CRS per ml in water. Solution (4) contains 2.5 mg of phenylalanine CRS per ml in water. Solution (5) contains 2.5 mg of aspartic acid CRS per ml in water. Solution (6) contains 2.5 mg of β -alanine CRS in water. Solution (7) contains the same concentration of each of the reference substances specified in solution (2) to solution (6). Develop the plate for three times in one direction. During each development allow the mobile phase to ascend about 15 cm above the line of application, dry the plate in the air and develop again in the same manner with the developing path being slightly longer than the previous. After developing and removal of the plate, dry in air, spray with ninhydrin TS (To 0.1 g of ninhydrin add 0.2 ml of water, 0.4 ml of glacial acetic acid, 1 ml of trimethylpyridine and a quantity of ethanol to 20 ml) and heat at 70-80°C for 15 minutes. There are five spots in the chromatogram obtained with solution (7). The colour and position of the spots in the chromatogram obtained with solution (1) correspond to the principal spots obtained with solution (2) to solution (6).

Absorbance ratio Measure the light absorption of solution obtained in the assay and the ratio of the absorbance at 280 nm to that at 288 nm is 1.12-1.22.

Loss on drying When dried in vacuum over phosphorous pentoxide for 24 hours, loses not more than 0.5% of its weight (Appendix VIII L).

The relative proportions of the amino acids To a quantity of pentagastrin add a quantity of hydrochloride acid solution (1 \rightarrow 2), hydrolysis at 110°C for 24 hours, determine hydrolysate by means of an amino-acid autoanalyzer, the relative proportions of amino acids is 1.

Related substances Carry out the method for thin-layer chromatography (Appendix V B), using silica gel G as the coating substance and a mixture of ether-glacial acetic acid-water (10 : 2 : 1) as the mobile phase. Apply separately to the plate 10 μ l each of two solutions in a mixture of methanol-concentrated ammonia solution (24 : 1) containing (1) 5 mg per ml (2) 0.1 mg per ml of the substance being examined. After developing and removal of the plate, allow it to dry in air, heat at 100°C for 2 minutes, spray with *p*-dimethylaminobenzaldehyde solution (Dissolve 1 g of *p*-dimethylaminobenzaldehyde in a quantity of a mixture of methanol-hydrochloric acid (3 : 1)) and heat at 100°C until

chromatogram other than the principal spot obtained with solution (1) is not more intense than the principal spot obtained with solution (2) (2.0%).

Assay Dissolve an accurately weighed quantity of pentagastrin in 0.01 mol/L ammonia solution to produce a solution of about 50 μ g per ml, measure the absorbance at 280 nm (Appendix IV A). Calculate the content of $C_{37}H_{49}N_7O_9S$, taking 70 as the value of A (1%, 1 cm).

Category Diagnostic agent.

Storage Preserve in tightly closed containers, protected from light.

Preparation Pentagastrin Injection

Pentagastrin Injection

Pentagastrin Injection is a sterile solution of Pentagastrin in Water for Injection. It contains not less than 90.0% and not more than 110.0% of the labelled amount of pentagastrin ($C_{37}H_{49}N_7O_9S$).

Description A clear, colourless liquid.

Identification Complies with the tests for Identification described under pentagastrin.

pH value 7.0-8.0 (Appendix VI H).

Related substances Carry out the method for thin-layer chromatography (Appendix V B), using silica gel G as the coating substance and a mixture of ether-glacial acetic acid-water (10 : 2 : 1) as the mobile phase. Apply separately to the plate 5 μ l each of two solutions in water containing (1) 0.25 mg per ml and (2) 50 μ g per ml of the substance being examined. Carry out the procedure as described under Pentagastrin beginning at the words "After developing and removal of the plate...".

Pyrogens Complies with the test for pyrogens (Appendix XI D), using 1.5 ml of a solution of 250 μ g per ml in Water for Injections per kg of rabbit's weight.

Other requirements Complies with the general requirements for injections (Appendix I B).

Assay Dilute an accurately measured quantity of the test solution equivalent to about 0.75 mg of pentagastrin with 0.01 mol/L ammonia solution to produce a solution of about 50 μ g per ml. Carry out the procedure as described under Pentagastrin. Calculate the content of $C_{37}H_{49}N_7O_9S$.

Category As described under Pentagastrin.

Strength 2 ml : 400 μ g

Storage Preserve in tightly closed containers, stored in a cool place and protected from light.

Pentetate Acid and Stannous Chloride for Injection

Pentetate Acid and Stannous Chloride for Injection is a sterile, lyophilized mixture of pentetate acid, stannous chloride and sodium chloride. It contains not less than 90.0% and not more than 110.0% of the labelled amount of pentetate acid ($C_{14}H_{23}N_3O_{10}$).

Description A white lyophilized powder.

Identification (1) To 10 ml of water, add one drop each of ferric chloride TS and ammonium thiocyanate TS, mix well, a red solution is obtained. Apply 2 ml of the solution to the substance being examined, the red colour disappears.

(2) Dissolve the content of one container in 0.5 ml of Sodium Chloride Injection, apply one drop of the solution to a strip of ammonium phosphomolybdate TP, a blue colour is produced.

Clarity and colour of solution Dissolve the content of one container in 5 ml of Sodium Chloride Injection, the solution is clear and colourless.

Stannous ion Dissolve the content of each of 5 containers separately in 3 ml of 1 mol/L hydrochloric acid solution saturated with nitrogen. Carry out the method for potentiometric titration (Appendix VII A) under a current of nitrogen, titrate with potassium iodate (0.001667 mol/L) VS. Not less than 0.02 ml is consumed for each container. Repeat the test with another 5 containers if one of them fails, all the containers in the second test must comply with the requirement.

Acidity or alkalinity pH 4.0–7.5 (Appendix VI H), using the solution obtained in the test for Clarity and colour of solution.

Bacterial endotoxin Dissolve each container in 5 ml of water BET and dilute with water BET to at least 30 times. Carry out the test for bacterial endotoxin (Appendix XI E); less than 75 EU per container.

Other requirements Complies with the general requirements for injections (Appendix I B).

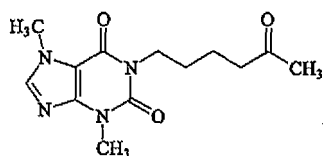
Assay Dissolve the content of each of 20 containers separately in 5 ml of water, combine all the solutions to a 250 ml conical flask, add 10 ml of ammonia-ammonium chloride buffer solution (to 20 g of ammonium chloride add 72 ml of concentrated ammonia solution, dilute with water to 1000 ml), mix well. Add a quantity of eriochrome black T IS, titrate with Zinc (0.05 mol/L) VS until a purplish red colour is obtained. Each ml of Zinc (0.05 mol/L) VS is equivalent to 19.67 mg of $C_{14}H_{23}N_4O_3$.

Category Used for the preparation of Technetium [^{99m}Tc] Pentetate Injection.

Strength 2.1 mg of pentetate acid and 0.13 mg stannous chloride dihydrate ($\text{SnCl}_2 \cdot 2\text{H}_2\text{O}$)

Storage Preserved in tightly closed containers, stored in a dark place at 2–8°C.

Pentoxifylline



$C_{13}H_{18}N_4O_3$ 278.31

[6493-05-6]

Pentoxifylline is 3,7-dihydro-3,7-dimethyl-1-(5-oxohexyl)-1*H*-purine-2,6-dione. It contains not less than 97.0% and not more than 103.0% of $C_{13}H_{18}N_4O_3$, calculated on the dried basis.

Description A white powder or granules; odour, slightly characteristic; taste, bitter.

Freely soluble in chloroform; soluble in water, ethanol or benzene; slightly soluble in ether.

Identification (1) To 10 mg add 1 ml of hydrochloric acid and 0.1 g of potassium chlorate, evaporate on a water bath to dryness, the residue reacts with ammonia vapour to produce a purple colour, which disappears on the addition of a few drops of sodium hydroxide TS.

(2) Dissolve 10 mg in 5 ml of water, add 1 ml of dilute sulfuric acid, and then add a few drops of iodine TS, a brown precipitate is produced.

(3) The infrared absorption spectrum (Appendix IV C) is concordant with the reference spectrum of pentoxifylline (Appendix XVI).

Clarity of benzene solution Dissolve 0.5 g in 1 ml of benzene in a dry test tube, warm gently in a water bath to dissolve pentoxifylline, the solution is clear.

Bromides Dissolve 0.50 g in 10 ml of water, add 0.5 ml of dilute nitric acid and 1 ml of silver nitrate TS, heat to boil, cool and dilute with water to 25 ml, mix well, the colour and turbidity produced is not more intense than that of a reference solution, using 11.0 ml of potassium bromide standard solution (0.01 mg Br per ml) prepared in same manner.

Loss on drying When dried to constant weight at 80°C, loses not more than 0.5% (Appendix VIII L).

Residue on ignition Not more than 0.1% (Appendix VIII N).

Heavy metals Dissolve 1.0 g in 2 ml of dilute acetic acid and a quantity of water to 25 ml. Carry out the limit test for heavy metals (Appendix VIII H, method 1); not more than 0.002%.

Assay Dissolve an accurately weighed quantity in water to produce a solution of 10 µg per ml, measure the absorbance at 274 nm (Appendix IV A), calculate the content of $C_{13}H_{18}N_4O_3$, taking 365 as the value of *A* (1%, 1 cm).

Category Vasodilator.

Storage Preserve in tightly closed containers, protected from light.

Preparation (1) Pentoxifylline Enteric-coated Tablets
(2) Pentoxifylline Injection
(3) Pentoxifylline Sustained-release Tablets

Pentoxifylline Enteric-Coated Tablets

Pentoxifylline Enteric-Coated Tablets contain not less than 93.0% and not more than 107.0% of the labelled amount of pentoxifylline ($C_{13}H_{18}N_4O_3$).

Description Enteric-coated tablets with white core.

Identification To a quantity of pulverized tablets equivalent to 50 mg of pentoxifylline add 10 ml of chloroform, shake thoroughly, filter and evaporate the filtrate on a water bath to dryness, the residue complies with tests (1) and (2) for Identification described under Pentoxifylline.

Other requirements Comply with the general requirements for tablets (Appendix I A).

Assay Weigh accurately and powder 10 tablets with enteric-coated film removed. Dissolve a quantity of the powder equivalent to 0.1 g of pentoxifylline, accurately weighed, in a 100 ml volumetric flask with 70 ml of water, keep warm in a water bath and shake, cool, dilute with water to volume, mix well and filter. Discard the initial filtrate, measure accurately a quantity of successive filtrate, dilute with water to produce a solution of 10 µg per ml. Measure the absorbance of the resulting solution at 274 nm (Appendix IV A), calculate the content of $C_{13}H_{18}N_4O_3$, taking 365 as the value of *A* (1%, 1 cm).

Category, Storage As described under Pentoxifylline.

Strength 0.1 g

Pentoxifylline Injection

Pentoxifylline Injection is a sterile solution of pentoxifylline in Water for Injection. It contains not less than 90.0% and not more than 110.0% of the labelled amount of pentoxifylline ($C_{13}H_{18}N_4O_3$).

Description A clear, colourless liquid.

Identification (1) To a quantity equivalent to about 10 mg of pentoxifylline add 1 ml of hydrochloric acid and 0.1 g of potassium chlorate, evaporate to dryness on a water bath. The residue reacts with ammonia vapour to produce a purple colour, which disappears on the addition of a few drops of sodium hydroxide TS.

(2) Dilute a quantity equivalent to about 10 mg of pentoxifylline with 5 ml of water, add 1 ml of dilute sulfuric acid, and a few drops of iodine TS; a brown precipitate is produced.

(3) The light absorption of the solution obtained in Assay exhibits a maximum at 274 nm and a minimum at 246 nm.

pH value 4.0-6.5 (Appendix VI H).

Pyrogens Complies with the test for pyrogens (Appendix XI D), using 20 mg per kg of rabbit's weight, injected slowly.

Other requirements Complies with the general requirements for injections (Appendix I B).

Assay Dilute an accurately measured quantity with water to produce a solution of 10 µg per ml. Measure the absorbance of the resulting solution at 274 nm (Appendix IV A), calculate the content of $C_{13}H_{18}N_4O_3$, taking 365 as the value of A (1%, 1 cm).

Category As described under pentoxifylline.

Storage Preserve in well closed containers, protected from light.

Strength (1) 2 ml : 0.1 g (2) 5 ml : 0.1 g

Pentoxifylline Sustained-release Tablets

Pentoxifylline Sustained-release Tablets contain not less than 93.0% and not more than 107.0% of the labelled amount of pentoxifylline ($C_{13}H_{18}N_4O_3$).

Description Film coated tablets with white or almost white core.

Identification To a quantity of powdered tablets with coating removed (equivalent to about 50 mg of pentoxifylline), add 10 ml of chloroform, shake and centrifuge, evaporate the chloroform solution to dryness. The residue complies with tests for identification (1), (2) described under Pentoxifylline.

Drug release Carry out the method for dissolution test (Appendix X D, method 1), using the apparatus described under Dissolution test (Appendix X C, method 2) and 900 ml of hydrochloric acid solution (9 → 1000) as the dissolution medium, adjust the rotational speed of the basket to 50 rpm. Withdraw 10 ml of the solution at exact 2, 6, 12 and 16 hours respectively, filter and supply 10 ml of the

medium accordingly to the vessel immediately. Transfer separately 3 ml, 1 ml, 1 ml and 1 ml of the successive filtrate to different 25 ml volumetric flask, accurately measured, and dilute with the dissolution medium to volume and mix well. Measure the absorbance of the resulting solutions at 274 nm (Appendix IV A), calculate the content of $C_{13}H_{18}N_4O_3$ dissolved from each tablet at 2, 6, 12 and 16 hours separately, taking 351 as the value of A (1%, 1 cm). The dissolution of pentoxifylline complies with the requirement; the quantity dissolved of each tablet is not less than 10%-30%, 30%-55%, 50%-85% and over 75% of the labelled amount of $C_{13}H_{18}N_4O_3$ at 2, 6, 12 and 16 hours respectively.

Other requirements Comply with the general requirements for tablets (Appendix I A).

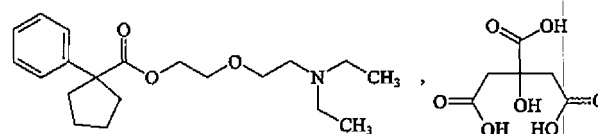
Assay Weigh accurately and powder 10 tablets with film coating removed. Triturate an accurately weighed quantity of powder equivalent to about 0.4 g of pentoxifylline into a 200 ml volumetric flask, add 100 ml of water. Keep the temperature in a warm water bath with constant shaking to dissolve pentoxifylline, cool to room temperature, dilute with water to volume and shake well. Filter and measure accurately a quantity of the successive filtrate and dilute with water to produce a solution of 10 µg per ml. Measure the absorbance of the solution at 274 nm (Appendix IV A). Calculate the content of $C_{13}H_{18}N_4O_3$, taking 365 as the value of A (1%, 1 cm).

Category As described under Pentoxifylline.

Strength 0.4 g

Storage Preserve in tightly closed containers, protected from light.

Pentoxifyverine Citrate



$C_{20}H_{31}NO_3 \cdot C_6H_8O_7$ 525.60

[23142-01-0]

Pentoxifyverine Citrate is 2-(2-Diethylaminoethoxy) ethyl-1-phenylcyclopentane-1-carboxylate citrate. It contains not less than 98.5% of $C_{20}H_{31}NO_3 \cdot C_6H_8O_7$, calculated on the dried basis.

Description A white or almost white crystalline powder or granule; odourless; taste; bitter. Freely soluble in water; soluble in ethanol; sparingly soluble in chloroform; practically insoluble in ether.

Melting range 88-93°C (Appendix VI C).

Determined in a capillary tube sealed under reduced pressure.

Identification (1) Dissolve about 20 mg in 2 ml of water, add 4 drops of dilute hydrochloric acid and a few drops of potassium ferrocyanide TS, a yellowish-white precipitate is produced.

(2) Dissolve about 20 mg in 10 ml of water, add 2 drops of dilute hydrochloric acid and a few drops of potassium dichromate TS, a yellow precipitate is produced.

(3) The infrared absorption spectrum (Appendix IV C) is concordant with the reference spectrum of pentoxifyverine citrate (Appendix XVI).

(4) The aqueous solution yields the reactions characteristic

of citrates (Appendix III).

Clarity of solution Dissolve with shaking 0.5 g in 5 ml of water. Any opalescence produced is not more pronounced than that of reference suspension III (Appendix IX B).

Related substances Carry out the method for thin-layer chromatography (Appendix V B), using silica gel G as the coating substance and a mixture of ethyl acetate-methanol-concentrate ammonia solution (27 : 2.5 : 0.6) as the mobile phase. Apply separately to the plate 5 μ l of each of two solutions in ethanol containing (1) 30 mg per ml, (2) 0.3 mg per ml of the substance being examined. After developing and removal of the plate, dry in air, spray with potassium iodobismuthate TS and examine immediately. Not more than 3 secondary spots are obtained with solution (1). Any spot, other than the principal spot obtained with solution (1) is not more intense than the principal spot obtained with solution (2).

Loss on drying When dried in vacuum over phosphorus pentoxide to constant weight, loses not more than 1.0% of its weight (Appendix VIII L).

Residue on ignition Not more than 0.1% (Appendix VIII N), using 1.0 g.

Heavy metals Carry out the limit test for heavy metals (Appendix VIII H, method 2) using the residue obtained in Residue on ignition; not more than 0.0015%.

Assay Dissolve about 0.4 g, accurately weighed, in 10 ml of glacial acetic acid, add 1 drop of crystal violet IS, titrate with perchloric acid (0.1 mol/L) VS until the solution becomes blue. Perform a blank determination and make any necessary correction. Each ml perchloric acid (0.1 mol/L) VS is equivalent to 52.56 mg of $C_{20}H_{31}NO_3 \cdot C_6H_8O_7$.

Category Antitussive.

Storage Preserve in tightly closed containers, stored in a dry place.

Preparation (1) Pentoxyverine Citrate Pills
(2) Pentoxyverine Citrate Tablets

Pentoxyverine Citrate Pills

Pentoxyverine Citrate Pills contain not less than 90.0% and not more than 110.0% of the labelled amount of pentoxyverine citrate ($C_{20}H_{31}NO_3 \cdot C_6H_8O_7$).

Description White pills.

Identification Add 5 ml of water to 4 pills, heat gently to dissolve pentoxyverine citrate, cool and filter, the filtrate complies with the tests for Identification (1), (2), (4) described under Pentoxyverine Citrate.

Other requirements Comply with the general requirements for pills (Appendix I H) except that the disintegration time is within 60 minutes.

Assay Dissolve 10 pills in 20 ml of chloroform, add 10 ml of glacial acetic acid and 1 drop of crystal violet IS, titrate with perchloric acid (0.1 mol/L) VS until the solution turns to blue. Perform a blank determination and make any necessary correction. Each ml of perchloric acid (0.1 mol/L) VS is equivalent to 52.56 mg of $C_{20}H_{31}NO_3 \cdot C_6H_8O_7$.

Category As described under Pentoxyverine Citrate.

Strength 25 mg

dry place.

Pentoxyverine Citrate Tablets

Pentoxyverine Citrate Tablets contain not less than 90.0% and not more than 110.0% of the labelled amount of pentoxyverine citrate ($C_{20}H_{31}NO_3 \cdot C_6H_8O_7$).

Description Sugar coated tablets with white core.

Identification (1) Remove the coating, powder finely and to a quantity equivalent to about 0.10 g of pentoxyverine citrate add 50 ml of water to dissolve pentoxyverine citrate, filter. The filtrate complies with test (1), (2) for Identification described under Pentoxyverine Citrate. (2) The fine powder yields the reaction characteristic of citrate (Appendix III).

Other requirements Comply with the general requirements for tablets (Appendix I A).

Assay Remove the coating of 50 tablets and weigh accurately. Powder finely and weigh accurately a quantity equivalent to about 0.5 g of pentoxyverine citrate to a separator, add 15 ml of water, shake to dissolve pentoxyverine citrate, add 3 ml of 20% sodium hydroxide solution and mix well. Extract with 50 ml of chloroform, measured accurately, shake for 15 minutes and allow to stand. Separate the chloroform layer and filter through a piece of dry filter paper. Discard the initial filtrate and measure accurately 25 ml of the successive filtrate to a conical flask. Add 20 ml of glacial acetic acid, 3 ml of acetic anhydride and 1 drop of crystal violet IS. Titrate with perchloric acid (0.1 mol/L) VS until the solution becomes blue. Perform a blank determination and make any necessary correction. Each ml of perchloric acid (0.1 mol/L) VS is equivalent to 52.56 mg of $C_{20}H_{31}NO_3 \cdot C_6H_8O_7$.

Category As described under Pentoxyverine Citrate.

Strength 25 mg

Storage Preserve in tightly closed containers, stored in a dry place.

Pepsin

Pepsin is a protease extracted from the gastric mucosa of pigs, sheep or cattle. It contains not less than 3800 Units per g.

Description A white to slight yellow powder; odour, slight but moldy; hygroscopic. The aqueous solution exhibits acidic reaction.

Identification To aqueous solution add the solutions of tannic acid, gallic acid or heavy metals salts, a precipitate is produced.

Loss on drying When dried at 100°C for 4 hours, loses not more than 5.0% of weight (Appendix VIII L).

Assay Reference solution Weigh accurately a quantity of tyrosine, add hydrochloric acid solution [dilute 65 ml of 1 mol/L hydrochloric acid solution with water to produce 1000 ml] to produce a solution of about 0.5 mg per ml.

Test solution Weigh accurately a quantity of the substance being examined, add the above hydrochloric acid solution to produce a solution of about 0.2-0.4 Units per ml.

Procedure Add accurately 1 ml of the reference solution to each of three test tubes and add accurately 1 ml of test solution to each of another three test tubes. Place the six test tubes in a water bath maintained at $37^{\circ}\text{C} \pm 0.5^{\circ}\text{C}$ for 5 minutes, then to each add accurately 5 ml of hemoglobin TS, previously heated to $37^{\circ}\text{C} \pm 0.5^{\circ}\text{C}$, mix well and allow the reaction to proceed in a $37^{\circ}\text{C} \pm 0.5^{\circ}\text{C}$ water bath for exactly 10 minutes. Add immediately 5 ml of 5% trichloroacetic acid solution and mix well. Filter, and collect the successive filtrate for use. To each of another two test tubes add accurately 5 ml of hemoglobin TS, place the two test tubes in a water bath maintained at $37^{\circ}\text{C} \pm 0.5^{\circ}\text{C}$ for 10 minutes, then to each tube add accurately 5 ml of 5% trichloroacetic acid solution. Add 1 ml of test solution to one test tube and add 1 ml of above mentioned diluted hydrochloric acid solution to another test tube, mix well, filter, use the successive filtrates separately as the blanks for test solution and reference solution respectively. Measure the absorbances of resulting solutions at 275 nm (Appendix IV A). Calculate the protease activity as follows:

$$\text{Units of protease activity per g} = \frac{\bar{A} \times W_s \times n}{\bar{A}_s \times W \times 10 \times 181.19}$$

Where \bar{A} is the average absorbance of test solution;
 \bar{A}_s is average absorbance of reference solution;
 W_s is the quantity of tyrosine (μg) in 1 ml of reference solution;
 W is the weight of substance being examined (g);
 n is the dilution factor.

One Unit of protease activity is defined as the amount of protease which hydrolyzed hemoglobin to produce 1 μmol of tyrosine per minute under the specified conditions.

Category Digestant.

Storage Preserve in tightly closed containers, stored in a dry place.

Preparation (1) Saccharated Pepsin (2) Pepsin Granules (3) Pepsin Tablets

Pepsin Granules

Pepsin Granules contains not less than 480 Units of pepsin activity.

Description Almost white to yellow granules; odour, characteristic of fruit; taste, sweet; hygroscopic.

Identification Triturate a quantity with water to dissolve pepsin and filter, the filtrate complies with the test for Identification described under Pepsin.

Acidity Dissolve 1 g in 20 ml of water, pH 3.0-4.0 (Appendix VI H).

Loss on drying When dried at 100°C for 4 hours, loses not more than 5.0% of its weight (Appendix VIII L).

Microbial limit Comply with the test for microbial limit described under Pepsin Tablets.

Other requirements Comply with the general requirements for granules (Appendix I N).

Assay Dissolve a quantity of the mixed contents obtained in the test for weight variation of contents equivalent to about 240 Units of pepsin, accurately weighed, in hydrochloric acid solution (as described under Pepsin) to produce a solution of about 0.2-0.4 Units per ml, as the test solution, carry out the Assay described under Pepsin.

Category As described under Pepsin.

Strength 480 Units

Storage Preserve in tightly closed containers, stored in a dry place.

Pepsin Tablets

Pepsin Tablets contains not less than 120 Units of pepsin activity.

Description Sugar-coated tablets with slight yellow core.

Identification Triturate a quantity with water to dissolve pepsin and filter, the filtrate complies with the test for Identification described under Pepsin.

Microbial limit Comply with test for microbial limit (Appendix XI J), except that number of bacterial is not more than 5000 and that of fungus is not more than 100 per g.

Other requirements Comply with the general requirements for tablets (Appendix I H) except that the disintegration time is within 30 minutes.

Assay Triturate 5 tablets with a small quantity of hydrochloric acid solution (as described under Pepsin) in a mortar, transfer to a 250 ml volumetric flask, add the above hydrochloric acid solution to volume and mix well. Dilute a quantity of the resulting solution, accurately measured, with the above hydrochloric acid solution to produce a solution of 0.2-0.4 Units per ml as the test solution, carry out the Assay described under Pepsin.

Category As described under Pepsin.

Strength 120 Units

Storage Preserve in tightly closed containers, stored in a cool and dark place.

Saccharated Pepsin

Saccharated Pepsin is obtained by diluting pepsin with lactose, glucose or sucrose. It contains not less than 120 or 1200 Units of pepsin activity per g.

Description A white to pale yellow powder; taste, sweet; odour, not moldy; hygroscopic. The aqueous solution exhibits acidic reaction.

Identification The aqueous solution complies with the test for Identification described under Pepsin.

Loss on drying When dried at 100°C for 4 hours, loses not more than 5.0% of its weight (Appendix VIII L).

Microbial limit Complies with the test for Microbial limit described under Pepsin Tablets.

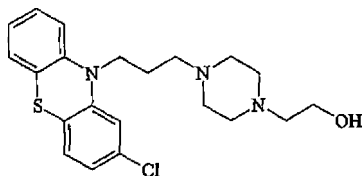
Assay Carry out the Assay described under Pepsin.

Category As described under Pepsin

Strength (1) 1 g : 120 Units (2) 1 g : 1200 Units

Storage Preserve in tightly closed containers, stored in a dry place.

Perphenazine



$C_{21}H_{26}ClN_3OS$ 403.97

[58-39-9]

Perphenazine is 4-[3-(2-chloro-10*H*-phenothiazin-10-yl)propyl]-1-piperazineethanol. It contains not less than 98.5% of $C_{21}H_{26}ClN_3OS$, calculated on the dried basis.

Description A white to pale yellow crystalline powder; almost odourless; taste, slight bitter.

Very soluble in chloroform; soluble in ethanol; practically insoluble in water; soluble in dilute hydrochloric acid.

Melting range 94-100°C (Appendix VI C).

Identification (1) Heat 5 mg in 1 ml of hydrochloric acid and 1 ml of water to 80°C, add a few drops of hydrogen peroxide TS; a deep red colour is produced, fading gradually on standing.

(2) The light absorption of a solution of 7 µg per ml in dehydrated ethanol exhibits a maximum at 258 nm. The absorbance is about 0.65 (Appendix IV A).

(3) The infrared absorption spectrum (Appendix IV C) is concordant with the reference spectrum of perphenazine (Appendix XVI).

Clarity and colour of methanol solution Dissolve 0.20 g in 10 ml of methanol, the solution is clear; any colour produced is not more intense than that of a reference solution Y_2 (Appendix IX A, method 1).

Related substances Protect from light throughout the procedure. Dissolve an accurately weighed quantity in ethanol to produce a solution of 5 mg per ml as the test solution. Measure accurately a quantity of the test solution, add ethanol to produce three reference solutions containing (1) 0.075 mg per ml, (2) 0.05 mg per ml and (3) 0.025 mg per ml. Carry out the thin-layer chromatography (Appendix V B), using silica gel G as the coating substance and a mixture of *n*-butanol-water-concentrated ammonia TS (85 : 14 : 1) as the mobile phase. Apply separately to the same plate 10 µl each of the above four solutions. After developing (allow the mobile phase ascends 15 cm above the line of application) and removal of the plate, dry in air and examine under ultraviolet light (254 nm). The total related substance other than the principal spot obtained in the chromatogram of the test solution are not greater than 3.0% in comparison with the principal spot in the chromatograms of the reference solution (1), (2) and (3), respectively.

Loss on drying When dried in vacuum over phosphorus pentoxide to constant weight, loses not more than 0.5% of its weight (Appendix VIII L).

Residue on ignition Not more than 0.1% (Appendix VIII N).

Assay Dissolve about 0.15 g, accurately weighed, in 20 ml of glacial acetic acid, add 1 drop of crystal violet IS, titrate with perchloric acid (0.1 mol/L) VS until the colour changes to bluish-green. Perform a blank determination and make any necessary correction. Each ml of perchloric acid

Category Antipsychotic agent.

Storage Preserve in tightly closed containers, protected from light.

Preparation (1) Perphenazine Injection
(2) Perphenazine Tablets

Perphenazine Injection

Perphenazine Injection is a sterile solution of Perphenazine in Water for Injection. It contains not less than 93.0% and not more than 107.0% of the labelled amount of perphenazine ($C_{21}H_{26}ClN_3OS$).

Description A clear, colourless to slight yellow liquid.

Identification (1) Heat 1 ml with 1 ml of hydrochloric acid and 1 ml of water to 80°C, add a few drops of hydrogen peroxide solution, a deep red colour is produced, fading gradually on standing.

(2) Evaporate 1 ml in an evaporating dish on a water bath to dryness, allow to cool. Dissolve the residue in 5 ml of sulfuric acid, a cherry red colour is produced, turning to deep red on standing. Heat a part of the sulfuric acid solution, it changes to fuchsin colour. Add a few drops of 0.1 mol/L potassium dichromate solution to another part of the sulfuric acid solution, the colour changes to deep red, then reddish brown finally to brownish green.

pH value 3.0-5.0 (Appendix VI H).

Other requirements Complies with the general requirements for injections (Appendix I B).

Assay To an accurately measured quantity of the injection, equivalent to about 125 mg of perphenazine into a separator add 2 ml of sodium hydroxide TS to make alkaline. Extract with each 20 ml of chloroform for 4 times, combine the extracts, filter with dry filter paper containing 5 g of anhydrous sodium sulfate. Evaporate the filtrate on water bath to dryness. Dissolve the residue in 10 ml of glacial acetic acid, add 1 drop of crystal violet IS and titrate with perchloric acid (0.1 mol/L) VS. Perform a blank determination and make any necessary correction. Each ml of perchloric acid (0.1 mol/L) VS is equivalent to 20.20 mg of $C_{21}H_{26}ClN_3OS$.

Category As described under perphenazine.

Strength 1 ml : 5 mg

Storage Preserve in well closed containers, protected from light.

Perphenazine Tablets

Perphenazine Tablets contain not less than 93.0% and not more than 107.0% of the labelled amount of perphenazine ($C_{21}H_{26}ClN_3OS$).

Description Sugar-coated or film coated tablets with white core.

Identification Shake a quantity of the powdered tablets equivalent to about 5 mg of perphenazine with 2 ml of chloroform, filter and evaporate the filtrate to dryness. The residue complies with test (1) for Identification described under Perphenazine.

(2) Protect from light throughout the operation. The light

exhibits a maximum at 258 nm (Appendix IV A).

Related substances Protect from light throughout the procedure. Pulverize some tablets removed the coating and weigh accurately a quantity of the powdered tablets equivalent to about 20 mg of perphenazine. Triturate it with ethanol and transfer to a 10 ml volumetric flask, shake thoroughly and add ethanol to volume, mix well and filter. The successive filtrate is used as the test solution. Measure accurately various quantities to produce four reference solutions in ethanol containing (1) 0.1 mg per ml, (2) 0.075 mg per ml, (3) 0.05 mg per ml and (4) 0.025 mg per ml. Carry out the thin-layer chromatography (Appendix V B), using silica gel GF₂₅₄ as the coating substance and a mixture of *n*-butanol-water-concentrated ammonia TS (85 : 14 : 1) as the mobile phase. Apply separately to the same plate 25 μ l each of above five solutions. After developing (allow the mobile phase ascends 15 cm above the line of application), remove the plate and dry in air, examine under ultraviolet light (254 nm). The total related substances other than the principal spot in the chromatogram of the obtained test solution is not greater than 3.5% in comparison with the principal spot in the chromatograms of four reference solutions.

Content uniformity Protect from light throughout the procedure. Comply with the requirements (Appendix X E). Grind finely 1 tablet in a mortar, with sugar coating removed, then moisten with 5 drops of water, add a quantity of hydrochloride acid-ethanol solution [To 500 ml of ethanol add 10 ml of hydrochloride acid, dilute it with water to 1000 ml, mix well] and mix well. Transfer the mixture to a 50 ml volumetric flask with a quantity of hydrochloride acid-ethanol solution, shake thoroughly to dissolve perphenazine, add hydrochloride acid-ethanol solution to volume, mix well. Filter, measure accurately a quantity of the successive filtrate and add hydrochloride acid-ethanol solution to produce a solution of 4 μ g per ml, as the test solution. Dissolve an accurately weighed quantity of perphenazine CRS in the hydrochloride acid-ethanol solution to produce a solution of 4 μ g per ml as reference solution. Measure the absorbances of the solutions at 258 nm (Appendix IV A), calculate the content of C₂₁H₂₆ClN₃OS.

Dissolution Protect from light throughout the procedure. Comply with dissolution test (Appendix X C, method 2), using 500 ml (in case of 4 mg/tablet is tested, using 1000 ml) of 0.3% solution of polysorbate-80 as the dissolution medium, adjust the rotational speed of the paddle to 100 rpm. Withdraw some solution after exactly 45 minutes and filter. The successive filtrate is used as test solution. Dissolve an accurately weighed quantity of perphenazine CRS in dehydrated ethanol to produce a solution of 0.4 mg per ml, measure accurately 5 ml to 500 ml volumetric flask and add dissolution medium to volume, mix well and filter, the successive filtrate is used as reference solution. Measure separately absorbances of the above two solutions at 259 nm (Appendix IV A). Calculate the dissolution of C₂₁H₂₆ClN₃OS from each tablet. Not less than 75% of the labelled amount is dissolved.

Other requirements Comply with the general requirements for tablets (Appendix I A).

Assay Protect from light throughout the procedure. Weigh accurately and powder 20 tablets with sugar coating removed. Transfer an accurately weighed quantity of the powdered tablets equivalent to about 10 mg of perphenazine to a 100 ml volumetric flask, add about 70 ml of hydrochloride acid-ethanol solution. Shake thoroughly to dissolve perphenazine, dilute with above solution to volume, mix well and filter. Measure accurately 5 ml of the successive

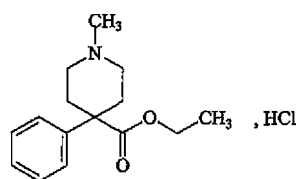
ethanol solution to volume, mix well, the resulting solution is used as test solution. Dissolve an accurately weighed quantity of perphenazine CRS in the hydrochloride acid-ethanol solution to produce a solution of 5 μ g per ml as reference solution. Measure separately the absorbances of above two solutions at 258 nm (Appendix IV A). Calculate the content of C₂₁H₂₆ClN₃OS.

Category As described under Perphenazine.

Strength (1) 2 mg (2) 4 mg

Storage Preserve in tightly closed containers, protected from light.

Pethidine Hydrochloride



C₁₅H₂₁NO₂ · HCl 283.80

[50-13-5]

Pethidine Hydrochloride is 1-methyl-4-phenyl-4-piperidinecarboxylic acid ethyl ester hydrochloride. It contains not less than 99.0% of C₁₅H₂₁NO₂ · HCl, calculated on the dried basis.

Description A white crystalline powder; odourless or almost odourless.

Freely soluble in water or ethanol; soluble in chloroform; practically insoluble in ether.

Melting range 186-190°C (Appendix VI C).

Identification (1) Dissolve 50 mg in 5 ml of ethanol, add 5 ml of trinitrophenol ethanolic solution (1→30) and shake; a yellow crystalline precipitate is produced. Allow to stand, filter, wash the precipitate with water and dry at 105°C for 2 hours. It melts at 188-191°C (Appendix VI C).

(2) Dissolve 50 mg in 5 ml of water, add 2 ml of sodium carbonate TS, shake; oily droplets are produced.

(3) The infrared absorption spectrum (Appendix IV C) is concordant with the reference spectrum of pethidine hydrochloride (Appendix XVI).

(4) The aqueous solution yields the reactions characteristic of chlorides (Appendix III).

Acidity Dissolve 0.30 g in 10 ml of water, pH 4.5-5.5 (Appendix VI H).

Clarity and colour of solution A solution of 0.10 g in 5 ml of water is clear and almost colourless.

Related substances Weigh about 1.0 g to a separator, add 5 ml of sodium hydroxide TS and 10 ml of ether, shake and allow to stand. Discard the aqueous layer and evaporate the ether extract to dryness at room temperature. Dissolve the residue in 2 ml of ethanol as the test solution. Measure accurately 0.5 ml to a 50 ml volumetric flask, dilute with ethanol to volume and mix well as the reference solution. Carry out the thin-layer chromatography (Appendix V B), using kieselguhr G as the coating substance with phenoxetol as the stationary phase [preparation: develop the plate coated with kieselguhr G in the mobile phase of acetone-phenoxetol (9 : 1). The mobile phase ascends a three fourths of the distance, remove the plate and dry in air].

diethylamine (100 : 8 : 1) to a separator, shake and allow to separate, use the supernatant liquid as the mobile phase. Apply separately to the same plate 5 μ l each of the above two solutions, after developing and removal of the plate, dry in air, spray with 0.2% dichlorofluorescein solution in methanol, allow it to dry in air and examine immediately under ultraviolet light (365 nm). Any spot, other than the principal spot in the chromatogram, obtained with the test solution is not more than two spots and not more intense than the principal spot obtained with the reference solution.

Loss on drying When dried to constant weight at 105°C, loses not more than 1.0% of its weight (Appendix VIII L).

Residue on ignition Not more than 0.1% (Appendix VIII N).

Assay Dissolve about 0.25 g, accurately weighed, in 10 ml of glacial acetic acid and 5 ml of mercuric acetate TS, add 1 drop of crystal violet IS, titrate with perchloric acid (0.1 mol/L) VS until the colour changes to bluish-green. Perform a blank determination and make any necessary correction. Each ml of perchloric acid (0.1 mol/L) VS is equivalent to 28.38 mg of $C_{15}H_{21}NO_2 \cdot HCl$.

Category Analgesic.

Storage Preserve in tightly closed containers.

Preparation (1) Pethidine Hydrochloride Injection
(2) Pethidine Hydrochloride Tablets

Pethidine Hydrochloride Injection

Pethidine Hydrochloride Injection is a sterile solution of Pethidine Hydrochloride in Water for Injection. It contains not less than 95.0% and not more than 105.0% of the labelled amount of pethidine hydrochloride ($C_{15}H_{21}NO_2 \cdot HCl$).

Description A clear and colourless liquid.

Identification (1) Dilute 1 ml with water to 5 ml, add 2 ml of sodium carbonate TS, shake, oily droplets are produced. Extract the oily droplets twice with ether, each of 10 ml, combine the ether extracts and filter. Add 5 drops of hydrochloric acid to the filtrate, evaporate the ether. The residue when dried at 105°C for 1 hour, melts at 182-187°C (Appendix VI C).

(2) Yields the reactions characteristic of chlorides (Appendix III).

pH value 4.0-6.0 (Appendix VI H).

Related substances Carry out the test for Related substances described under Pethidine hydrochloride, using 2 ml, beginning at the words "to a separator...". The results comply with the requirements.

Other requirements Complies with the general requirements for injections (Appendix I B).

Assay Measure accurately 5 ml of pethidine hydrochloride injection, add 10 ml of water and 3 ml of sodium hydroxide TS and mix well. Extract five times with chloroform (20 ml, 20 ml, 20 ml, 20 ml, 10 ml) and wash the combined extracts with 10 ml of water. Extract the washing with 10 ml chloroform, combine all of the extracts and filter through anhydrous sodium sulfate into conical flask. Wash the anhydrous sodium sulfate with 5 ml of chloroform and combine the washing to the filtrate. Evaporate the filtrate to dryness under vacuum, add 10 ml of glacial acetic acid and 1 ml of crystal violet TS, titrate with perchloric acid (0.1

a blank determination and make any necessary correction. Each ml of perchloric acid (0.1 mol/L) VS is equivalent to 28.38 mg of $C_{15}H_{21}NO_2 \cdot HCl$.

Category As described under Pethidine Hydrochloride.

Strength (1) 1 ml : 50 mg (2) 2 ml : 100 mg

Storage Preserve in tightly closed containers.

Pethidine Hydrochloride Tablets

Pethidine Hydrochloride Tablets contain not less than 95.0% and not more than 105.0% of the labelled amount of pethidine hydrochloride ($C_{15}H_{21}NO_2 \cdot HCl$).

Description White tablets or film coated tablets.

Identification (1) Dissolve a quantity of the powdered tablets equivalent to 50 mg of pethidine hydrochloride in 5 ml of ethanol and filter. The filtrate complies with test (1) for Identification described under Pethidine Hydrochloride.

(2) Dissolve a quantity of the powdered tablets, equivalent to 0.1 g of pethidine hydrochloride in 10 ml of water and filter. The filtrate complies with tests (2) and (4) for Identification described under Pethidine Hydrochloride.

Content uniformity Comply with the requirements (Appendix X E). Put 1 tablet in a 50 ml (for strength 25 mg) or 100 ml (for strength 50 mg) volumetric flask add a quantity of water, shake thoroughly, dilute to volume with water, mix well and filter. Measure the absorbance of the successive filtrate at 257 nm (Appendix IV A), calculate the content of $C_{15}H_{21}NO_2 \cdot HCl$.

Dissolution Carry out the dissolution test (Appendix XI C method 3), using 100 ml of water as the dissolution medium, adjust the rotational speed of the paddle to 100 rpm. Pour 1 tablet (for strength 50 mg) or two tablets (for strength 25 mg) into each cup. Withdraw 10 ml of the solution after exactly 40 minutes and filter. Measure the absorbance of the successive filtrate at 257 nm (Appendix IV A). Dissolve an accurately weighted quantity of pethidine hydrochloride CRS in water, and dilute to produce a solution of 0.5 mg pre ml. Measure in the same way as the test solution. Calculate the dissolution of $C_{15}H_{21}NO_2 \cdot HCl$ from each tablet. Not less than 80% of the labelled amount is dissolved.

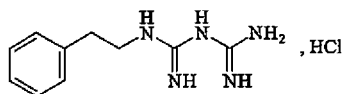
Other requirements Comply with the general requirements for tablets (Appendix I A).

Assay Weigh accurately and powder 30 tablets (for strength 25 mg) or 20 tablets (for strength 50 mg) with coating removed. Weigh accurately a quantity of the powder equivalent to 250 mg of pethidine hydrochloride to a separator, dissolve pethidine hydrochloride in 15 ml of water, add 3 ml of sodium hydroxide TS and mix well. Extract five times with chloroform (20 ml, 20 ml, 20 ml, 20 ml, 10 ml) and wash the combined extracts with 10 ml of water. Extract the washing with 10 ml chloroform, combine all of the extracts and filter through anhydrous sodium sulfate into conical flask. Wash the anhydrous sodium sulfate with 5 ml of chloroform and combine the washing to the filtrate. Evaporate the filtrate to dryness under vacuum, add 10 ml of glacial acetic acid and 1 drop of crystal violet IS, titrate with perchloric acid (0.1 mol/L) VS until the colour changes to blue-green. Perform a blank determination and make any necessary correction. Each ml of perchloric acid (0.1 mol/L) VS is equivalent to 28.38 mg of $C_{15}H_{21}NO_2 \cdot HCl$.

Category As described under Pethidine Hydrochloride.

Strength (1) 25 mg (2) 50 mg

Phenformin Hydrochloride



$C_{10}H_{15}N_5 \cdot HCl$ 241.72

[834-28-6]

Phenformin Hydrochloride is 1-(2-phenylethyl)-biguanidine hydrochloride. It contains not less than 99.0% of $C_{10}H_{15}N_5 \cdot HCl$.

Description A white crystal or crystalline powder; odourless; taste, bitter.

Freely soluble in water; soluble in ethanol; practically insoluble in chloroform or ether.

Melting range 174-178°C (Appendix VI C).

Identification (1) To 2 ml of the aqueous solution (1→20) add 2 drops of ammonium cupric sulfate TS; a violet-red precipitate is produced.

(2) The light absorption of a solution of 10 µg per ml in water exhibits a maximum at 234 nm and the absorbance is about 0.60 (Appendix VI A).

(3) The aqueous solution yields the reactions characteristic of chlorides (Appendix III).

(4) The infrared absorption spectrum (Appendix IV C) is concordant with the reference spectrum of phenformin hydrochloride (Appendix XVI).

Acidity Dissolve 0.20 g in 10 ml of water, pH 6.0-7.0 (Appendix VI H).

Related biguanides Dissolve 1.0 g in methanol in a 10 ml volumetric flask, dilute to volume and mix well. Carry out the method for descending paper chromatography (Appendix V A), using three strips of chromatographic paper 7.5 cm×50 cm in size as absorbent and ethyl acetate-ethanol-water (6 : 3 : 1) as the mobile phase. Apply separately 0.2 ml each of the solution accurately measured to two strips and 0.2 ml of methanol to another strip as blank. Keep the diameter of the spots at 0.5-1 cm. Place the three strips in the tank and allow elution to proceed until the solvent fronts travel to within 7 cm of the lower end of the paper. After removal of the strips, dry them in the air and spray one of the treated strips with a solution prepared as follows: Mix 1 ml each of 10% potassium ferric anide solution, 10% sodium nitro-russide solution and 10% sodium hydroxide solution, allow to stand for 15 minutes, add 10 ml of water and 12 ml of acetone, mix well. The related biguanides occur as red bands with a R_f value of about 0.1. Cut the corresponding position of the second treated strip and the blank strip with an area extending for 1 cm in all directions. Cut into pieces and extract separately with 20 ml of methanol, accurately measured. Measure the absorbance of the resulting solutions at 232 nm (Appendix IV A), the absorbance of related biguanides is not greater than 0.48.

Residue on ignition Not more than 0.1% (Appendix VIII N).

Assay Dissolve about 0.1 g, accurately weighed, in 30 ml of glacial acetic acid and 5 ml of mercuric acetate TS. Carry out the method for potentiometric titration (Appendix VII A), titrate with perchloric acid (0.1 mol/L) VS. Perform a blank determination and make any necessary correction. Each ml of perchloric acid (0.1 mol/L) VS is equivalent to 12.09 mg of $C_{10}H_{15}N_5 \cdot HCl$.

Category Hypoglycemic agent.

Storage Preserve in tightly closed containers.

Preparation Phenformin Hydrochloride Tablets

Phenformin Hydrochloride Tablets

Phenformin Hydrochloride Tablets contain not less than 90.0% and not more than 110.0% of the labelled amount of phenformin hydrochloride ($C_{10}H_{15}N_5 \cdot HCl$).

Description White tablets.

Identification (1) Pulverize 20 tablets, add 10 ml of water and shake to dissolve phenformin hydrochloride, filter. The filtrate complies with tests (1) and (4) for Identification described under Phenformin Hydrochloride.

(2) To 2 ml of the filtrate obtained in test (1) add potassium dichromate TS, a yellow precipitate is produced immediately, which is dissolved on adding dilute nitric acid.

(3) Add ammoniated nickel nitrate TS to 2 ml of the filtrate obtained in test (1), a pale yellow precipitate is produced immediately and changes to yellow on standing.

Other requirements Comply with the general requirements for tablets (Appendix I A).

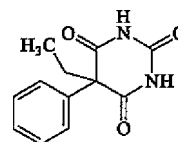
Assay Weigh accurately and powder 20 tablets. To an accurately weighed quantity equivalent to 0.1 g of phenformin hydrochloride in a 250 ml kjeldahl flask add 2 g of potassium sulfate (or anhydrous sodium sulfate) and 0.2 g of powdered cupric sulfate. Then add slowly 10 ml of sulfuric acid along the inner wall of the flask, boil the mixture briskly until a clear, green solution is obtained. Continue the heating for 30 minutes and allow to cool. Dissolve the reaction mixture in water and transfer the solution to a 200 ml volumetric flask, dilute to volume with water and mix well. Measure accurately 5 ml, carry out the method for determination of nitrogen (Appendix VII D, method 2), beginning at the words "Transfer the content of the Kjeldahl flask into the distillator C...". Each ml of sulfuric acid (0.005 mol/L) VS is equivalent to 0.4834 mg of $C_{10}H_{15}N_5 \cdot HCl$.

Category As described under Phenformin Hydrochloride.

Strength 25 mg

Storage Preserve in tightly closed containers.

Phenobarbital



$C_{12}H_{12}N_2O_3$ 232.24

[50-06-6]

Phenobarbital is 5-ethyl-5-phenyl-2,4,6 (1H, 3H, 5H)-pyrimidinetrione. It contains not less than 98.5% of $C_{12}H_{12}N_2O_3$, calculated on the dried basis.

Description A white lustrous crystalline powder; odourless; taste, slight bitter. The saturated aqueous solution yields acid reaction.

Soluble in ethanol or ether; sparingly soluble in chloroform; very slightly soluble in water; soluble in solutions of sodium hydroxide or sodium carbonate.

Melting range 174.5-178°C (Appendix VI C).

Identification (1) Mix about 10 mg with 2 drops of sulfuric

acid and about 5 mg of sodium nitrite, an orange-yellow colour is produced and then changes to orange-red.

(2) Boil about 50 mg with 1 ml of formaldehyde TS in a test tube and cool. Add slowly 0.5 ml of sulfuric acid along the wall to form a subjacent layer and heat in a water bath, a rose-red ring is formed at the junction of the liquids.

(3) The infrared absorption spectrum (Appendix IV C) is concordant with the reference spectrum of phenobarbital (Appendix XVI).

(4) Yields the reactions characteristic of malonylureas (Appendix III).

Acidity Boil 0.20 g with 10 ml of water for 1 minute with stirring, cool and filter. To 5 ml of the filtrate add 1 drop of methyl orange IS, no red colour is produced.

Clarity of ethanolic solution Heat 1.0 g with 5 ml of ethanol for 3 minutes under reflux, the resulting solution is clear.

Neutral or basic substances Dissolve 1.0 g in 10 ml of sodium hydroxide TS in a separator, add 5 ml of water and 25 ml of ether, shake for 1 minute, allow to separate. Wash the ether layer with three portions, each of 5 ml of water, filter the ether solution through dry filter paper to an evaporating dish dried to constant weight at 105°C previously and evaporate to dryness. The residue, dried at 105°C for 1 hour, weights not more than 3 mg.

Loss on drying When dried at 105°C to constant weight, loses not more than 1.0% of its weight (Appendix VIII L).

Residue on ignition Not more than 0.1% (Appendix VIII N).

Assay Dissolve about 0.2 g, accurately weighed, in 40 ml of methanol, add 15 ml of freshly prepared 3% anhydrous sodium carbonate solution. Carry out the method for potentiometric titration (Appendix VII A), titrate with silver nitrate (0.1 mol/L) VS. Each ml of silver nitrate (0.1 mol/L) VS is equivalent to 23.22 mg of $C_{12}H_{12}N_2O_3$.

Category Sedative, hypnotic and anticonvulsant.

Storage Preserve in tightly closed containers.

Preparation Phenobarbital Tablets

Phenobarbital Tablets

Phenobarbital Tablets contain not less than 93.0% and not more than 107.0% of the labelled amount of phenobarbital ($C_{12}H_{12}N_2O_3$).

Description White tablets.

Identification Shake thoroughly a quantity of the powdered tablet equivalent to about 0.1 g of phenobarbital with 10 ml of dehydrated ethanol, filter, evaporate the filtrate on a water bath to dryness. The residue complies with the tests (1), (2) and (4) for Identification described under Phenobarbital.

Content uniformity Comply with the requirements (Appendix X E). Transfer 1 tablet (for strength 15 mg and 30 mg) to a 100 ml volumetric flask, add a quantity of ethanol-borate potassium chloride BS (Dissolve 12.37 g of boric acid and 14.91 g of potassium chloride in 1000 ml of water with shaking. To 50 ml of the resulting solution, add 36.9 ml of potassium hydroxide TS and dilute to 200 ml with water, adjust pH to 9.6 using 1 mol/L hydrochloric acid solution or potassium hydroxide TS when necessary) (1 : 20), shake thoroughly, dilute to volume and mix well, filter. Measure accurately a quantity of the successive filtrate, dilute with above described buffer solution to produce a solution of 10 µg per ml as the test solution. Dissolve an accurately weighed quantity of

solution of 10 µg per ml as the reference solution. Carry out the method for the spectrophotometry (Appendix IV A). Measure the absorbances of two solutions at 240 nm. Calculate the content of phenobarbital.

Dissolution Carry out the dissolution test (Appendix X C, method 2), using 900 ml of water as the dissolution medium, adjust the rotational speed of the paddle to 50 rpm. Withdraw a quantity of the solution after exact 45 minutes and filter. Dilute 3 ml (for strength 100 mg), 10 ml (for strength 30 mg) or 20 ml (for strength 15 mg) of the successive filtrate, accurately measured, with borate-potassium chloride BS (pH 9.6) to 50 ml and mix well. Dissolve an accurately weighed quantity of phenobarbital CRS in above described buffer solution to produce a solution of 5 µg per ml. Measure absorbances of the two solutions at 240 nm (Appendix IV A). Calculate the dissolution of $C_{12}H_{12}N_2O_3$ from each tablet. Not less than 75% of the labelled amount is dissolved.

Other requirements Comply with the general requirements for tablets (Appendix I A).

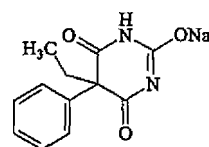
Assay Carry out the method for high performance liquid chromatography (Appendix V D), using a column packed with octadecylsilane bonded silica gel and a mixture of methanol-phosphate BS (mix 6.8 g of potassium dihydrogen phosphate with 4 ml of triethylamine, dilute with water to 1000 ml) (40 : 60) as the mobile phase. Detection wavelength is at 215 nm, and the number of theoretical plates of the column is not less than 2000, calculated with reference to the peak of phenobarbital. Weigh accurately 20 tablets of the powdered tablets equivalent to 30 mg of phenobarbital, to a 100 ml volumetric flask and add a quantity of 40% methanol solution, ultrasonicate for 10 minutes to dissolve phenobarbital, dilute with 40% methanol solution to the volume, mix well and filter. Measure accurately 5 ml of the successive filtrate in 50 ml volumetric flask, dilute with 40% methanol solution to the volume, mix well. Inject 20 µl into the column and record the chromatogram. Dissolve a quantity of phenobarbital CRS, accurately weighed, in 40% methanol solution to produce a solution containing 30 µg per ml. Repeat the operation. Calculate the content of $C_{12}H_{12}N_2O_3$ with respect to the peak area obtained in the chromatogram by the external standard method.

Category As described under Phenobarbital.

Strength (1) 15 mg (2) 30 mg (3) 100 mg

Storage Preserve in tightly closed containers.

Phenobarbital Sodium



$C_{12}H_{11}N_2NaO_3$ 254.22

[57-30-7]

Phenobarbital Sodium is 5-ethyl-5-phenyl-2,4,6 (1*H*,3*H*,5*H*)-pyrimidinetrione, monosodium salt. It contains not less than 98.5% of $C_{12}H_{11}N_2NaO_3$, calculated on the dried basis.

Description A white crystalline granule or powder; odourless; taste, bitter; hygroscopic. Very soluble in water; soluble in ethanol; practically insoluble in chloroform or ether.

... (1) Dissolve about 0.5 g in 5 ml of water.

add dilute hydrochloric acid in slight excess, a white crystalline precipitate is produced. Filter, wash the residue with water and dry at 105°C, it has a melting point of 174-178°C (Appendix VI C) and complies with the tests for Identification described under Phenobarbital.

(2) The infrared absorption spectrum (Appendix IV C) is concordant with the reference spectrum of phenobarbital sodium (Appendix XVI).

(3) Yields the reactions characteristic of sodium salts (Appendix III).

Alkalinity Dissolve 1.0 g in 10 ml of water, pH 9.5-10.5 (Appendix VI H).

Clarity of solution Dissolve 1.0 g in 10 ml of freshly boiled and cooled water, the resulting solution is clear (for injection).

Loss on drying When dried to constant weight at 150°C, loses not more than 6.0% of its weight (Appendix VIII L).

Heavy metals Dissolve 2.0 g in 32 ml of water, add slowly 8 ml of 1 mol/L hydrochloric acid solution, shake thoroughly, allow to stand for a few minutes, filter. To 20 ml of the filtrate add 1 drop of phenolphthalein IS and a quantity of ammonia TS until the solution becomes pink, then add 2 ml of acetate BS (pH 3.5) and sufficient water to produce 25 ml. Carry out the limit test for heavy metals (Appendix VIII H, method 1); not more than 0.001%.

Sterility Dissolve 0.2 g in 4 ml of sterile water, the resulting solution complies with the test for sterility (for injection) (Appendix XI H).

Assay Carry out the Assay described under Phenobarbital, using about 0.2 g, weighed accurately. Each ml of silver nitrate (0.1 mol/L) VS is equivalent to 25.42 mg of $C_{12}H_{11}N_2NaO_3$.

Category Sedative, hypnotic and Anticonvulsant.

Storage Preserve in tightly sealed containers, protected from light.

Preparation Phenobarbital Sodium for Injection

Phenobarbital Sodium for Injection

Phenobarbital Sodium for Injection is a sterile crystals or powder of Phenobarbital Sodium preparation. It contains not less than 98.5% of $C_{12}H_{11}N_2NaO_3$, calculated on the dried basis. It contains not less than 93.0% and not more than 107.0% of the labelled amount of phenobarbital sodium ($C_{12}H_{11}N_2NaO_3$), calculated on the basis of average weight of content.

Description White crystalline granules or powder.

Identification Complies with the tests for Identification described under Phenobarbital Sodium.

Alkalinity Complies with the test for alkalinity as described under Phenobarbital Sodium.

Loss on drying When dried at 150°C to constant weight, loses not more than 7.0% of its weight (Appendix VIII L).

Sterility Complies with the test for sterility (Appendix XI H), using a solution of 50 mg per ml in sterile water.

Other requirements Complies with the general requirements for injections (Appendix I B).

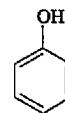
Assay Carry out the Assay described under Phenobarbital, using the mixed contents obtained in the tests for weight variation. Each ml of silver nitrate (0.1 mol/L) VS is equivalent to 25.42 mg of $C_{12}H_{11}N_2NaO_3$.

Category As described under Phenobarbital Sodium.

Strength (1) 50 mg (2) 100 mg (3) 200 mg

Storage Preserve in well closed containers, protected from light.

Phenol



C_6H_6O 94.11

[108-95-2]

Phenol contains not less than 99.0% of C_6H_6O .

Description Colourless to faint pink needle crystals or a crystalline mass; odour, characteristic; hygroscopic; the colour gradually darkens on exposure to light and air. The aqueous solution exhibits weak acid reaction.

Freely soluble in ethanol, chloroform, ether, glycerin or fixed and volatile oils; soluble in water; sparingly soluble in liquid paraffin.

Congeeing point Not lower than 40°C (Appendix VI D).

Identification Dissolve 0.1 g in 10 ml of water, the solution complies the following tests:

(1) To 5 ml add 1 drop of ferric chloride TS, a violet colour is produced.

(2) To 5 ml add bromine TS, a transient white precipitate is formed, but the precipitate is stable in an excess of the reagent.

(3) The infrared absorption spectrum (Appendix IV C) is concordant with the reference spectrum of phenol (Appendix XVI).

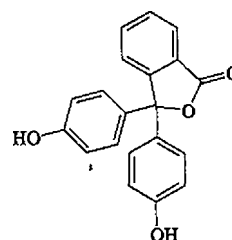
Nonvolatile matter When 5.0 g is volatilized on a water bath and dried to constant weight at 105°C, not more than 2.5 mg of residue is obtained.

Assay Dissolve about 0.75 g, accurately weighed, in sufficient water to produce 500 ml. Transfer 25 ml, accurately measured to an iodine flask, add 30.0 ml of bromine (0.05 mol/L) VS, 5 ml of hydrochloric acid, immediately stopper the flask. Shake occasionally for 30 minutes and allow to stand for 15 minutes. Add quickly 6 ml of potassium iodide TS, and immediately stopper the flask, shake thoroughly, then add 1 ml of chloroform and mix well. Titrate with sodium thiosulfate (0.1 mol/L) VS, adding starch IS towards the end-point. Continue the titration until the blue colour disappeared. Perform a blank determination and make any necessary correction. Each ml of bromine (0.05 mol/L) VS is equivalent to 1.569 mg of C_6H_6O .

Category Antiseptic Disinfectant.

Storage Preserve in tightly closed containers, protected from light.

Phenolphthalein



$C_{20}H_{14}O_5$ 318.33

[77-09-8]

Phenolphthalein is 3,3-bis (4-hydroxyphenyl)-1 (3H)-isobenzofuranone. It contains not less than 98.0% and not more than 102.0% of the labelled amount of phenolphthalein ($C_{20}H_{14}O_4$), calculated on the dried basis.

Description White to pale yellow crystals or powder; odourless; tasteless. Soluble in ethanol; sparingly soluble in ether; practically insoluble in water.

Melting range 260-263°C (Appendix VI C).

Identification To a few mg add 2 ml of sodium hydroxide TS or hot sodium carbonate TS. It dissolves to produce a red solution. The colour is disappeared on addition of excess acids.

Colour of ethanol solution Dissolve 0.50 g in 30 ml of ethanol. The solution is colourless or almost colourless.

Fluoran Carry out the method for thin-layer chromatography (Appendix V B), using silica gel G as the coating substance and dehydrated ethanol-cyclohexane-xylene (1 : 1 : 4) as the mobile phase, using (1) a solution of 20 mg per ml of the substance being examined in dehydrated ethanol as the test solution, (2) a solution of 0.10 mg per ml of fluoran CRS in dehydrated ethanol as the reference solution. Apply separately to the plate 25 μ l of (1) and 5 μ l of (2). After developing and removal of the plate, dry in air and spray with sulfuric acid-dehydrated ethanol (1 : 1). Heat the plate at 105°C for 5-10 minutes and examine under ultra-violet light (365 nm). The fluorescence produced by any spot, other than the principal spot in the chromatogram obtained with solution (1) is not more intense than the principal spot obtained with solution (2) (0.10%).

Sensitivity Dissolve 0.10 g in 10 ml of ethanol. To 0.50 ml of the solution add 50 ml of freshly boiled and cooled water, mix well and add 0.25 ml of sodium hydroxide (0.02 mol/L) VS. Pink colour is produced.

Loss on drying When dried to constant weight at 105°C, loses not more than 1.0% of its weight (Appendix VIII L).

Residue on ignition Not more than 0.1% (Appendix VIII N).

Heavy metals Add 10 ml of dilute hydrochloric acid to 1.0 g, heat on a water bath for 5 minutes, cool and filter. Evaporate the filtrate to dryness, add 2 ml of acetate BS (pH 3.5) and a quantity of water to produce 25 ml. Carry out the limit test for heavy metals (Appendix VIII H, method 1); not more than 0.001%.

Assay Dissolve 38 mg, accurately weighed in a 100 ml volumetric flask with 60 ml of ethanol with shaking. Add 10 ml of 0.01 mol/L hydrochloric acid solution and mix well, dilute with ethanol to volume and mix well. Measure accurately 10 ml to another 100 ml volumetric flask, add 10 ml of ethanol and mix well, dilute with 0.01 mol/L hydrochloric acid solution to volume and mix well. Measure the absorbance at 275 nm (Appendix IV A), using 0.01 mol/L hydrochloric acid solution as blank, calculate the content of $C_{20}H_{14}O_4$, taking 134 as the value of A (1%, 1 cm).

Category Laxatives.

Storage Preserve in tightly closed containers.

Preparation Phenolphthalein Tablets

Phenolphthalein Tablets

Phenolphthalein Tablets contain not less than

amount of phenolphthalein ($C_{20}H_{14}O_4$).

Description White to slight yellow tablets.

Identification The powdered tablets comply with the test for Identification described under Phenolphthalein.

Other requirements Comply with the general requirements for tablets (Appendix I A).

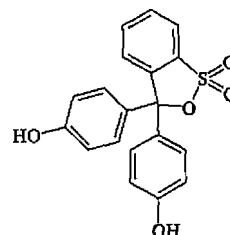
Assay Weigh accurately and powder 10 tablets. Transfer an accurately weighed quantity equivalent to about 0.19 g of phenolphthalein to a 100 ml volumetric flask, add ethanol to volume and shake. Filter with a dry filter paper and discard the initial filtrate. Measure accurately 20 ml of the successive filtrate to another 100 ml volumetric flask, add about 40 ml of ethanol and 10 ml of 0.01 mol/L hydrochloric acid solution and mix well, dilute with ethanol to volume and mix well. Transfer accurately 10 ml to a 100 ml volumetric flask, add 10 ml of ethanol and mix well, dilute with 0.01 mol/L hydrochloric acid solution to volume and mix well. Measure the absorbance at 275 nm (Appendix IV A), using 0.01 mol/L the hydrochloric acid solution as blank. Calculate the content of $C_{20}H_{14}O_4$, taking 134 as the value of A (1%, 1 cm).

Category As described under Phenolphthalein.

Strength (1) 50 mg (2) 100 mg

Storage Preserve in tightly closed containers.

Phenolsulfonphthalein



$C_{19}H_{14}O_5S$ 354.37

[143-74-8]

Phenolsulfonphthalein is 4,4'-(3H-2, 1-benzoxathiol-3-ylidene) bis-phenol, (s, s-dioxide). It contains not less than 98.0% and not more than 102.0% of $C_{19}H_{14}O_5S$, calculated on the dried basis.

Description A red or dark red crystalline powder; odourless. Slightly soluble in ethanol; very slightly soluble in water; practically insoluble in chloroform or ether; freely soluble in alkaline solution.

Identification (1) Dissolve about 10 mg in 1 ml of ethanol, add 100 ml of freshly boiled and cooled water and 0.5 ml of 0.02 mol/L sodium hydroxide solution; a dark red colour develops which changes to orange-yellow or yellow on addition of 1 drop of dilute hydrochloric acid.

(2) Dissolve about 5 mg in a few drops of sodium hydroxide TS, add 2 ml of 0.1 mol/L bromine solution and 1 ml of dilute hydrochloric acid, mix well. Allow to stand for 5 minutes and make alkaline with sodium hydroxide TS; a dark bluish-violet colour is produced.

Alkali insoluble matter To 1 g add 20 ml of 2.5% sodium bicarbonate solution, swirl frequently for 1 hour. Dilute with water to 100 ml and allow to stand for 12 hours. Filter

weight at 105°C and wash the residue with 25 ml of 1% sodium bicarbonate solution, then with 25 ml of water, dry at 1-5°C for 1 hour, the residue is no more than 2 mg (0.2%).

Loss on drying When dried to constant weight over sulfuric acid, loses not more than 1.0% of its weight (Appendix VIII L).

Residue on ignition Not more than 0.2% (Appendix VIII N).

Arsenic Mix thoroughly 0.2 g with 0.5 g of calcium hydroxide in a crucible, add a small quantity of water and evaporate to dryness, ignite gently until it is thoroughly charred, then ignite at 500-600°C until free from carbon. Cool, add 23 ml of water and 5 ml of hydrochloric acid, carry out the limit test for arsenic (Appendix VIII J, method 1); not more than 0.001%.

Assay Dissolve about 0.1 g, accurately weighed, in 20 ml of 0.4% sodium hydroxide solution in an iodine flask and dilute with water to 200 ml. Add accurately 40 ml of bromine (0.05 mol/L) VS, and 10 ml of hydrochloric acid, stopper the flask immediately, shake well and allow to stand for 5 minutes. Remove the stopper cautiously, add 6 ml of potassium iodide TS, stopper again and shake for 1 minute. Titrate with sodium thiosulfate (0.1 mol/L) VS until the end point is nearly approached, add starch IS, titrate until the blue colour just disappears. Perform a blank determination and make any necessary correction. Each ml of bromine (0.05 mol/L) VS is equivalent to 4.430 mg of $C_{18}H_{22}ClNO$.

Category Diagnostic agent.

Storage Preserve in tightly closed containers.

Preparation Phenolsulfonphthalein Injection

Phenolsulfonphthalein Injection

Phenolsulfonphthalein Injection is a sterile solution of phenolsulfonphthalein in Water for Injection made isotonic by the addition of Sodium Chloride. It contains not less than 95.0% and not more than 105.0% of the labelled amount of phenolsulfonphthalein ($C_{19}H_{14}O_5S$).

Description A clear, red liquid.

Identification To a quantity of injection equivalent to about 5 mg of phenolsulfonphthalein add 2 ml of 0.1 mol/L bromine solution and 1 ml of dilute hydrochloric acid and shake well. Allow to stand for 5 minutes, make alkaline with sodium hydroxide TS; a dark bluish-violet colour is produced.

pH value 6.5-8.5 (Appendix VI H).

Other requirements Complies with the general requirements for injections (Appendix I B).

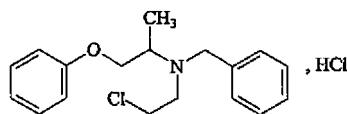
Assay Accurately measure 10 ml, to an iodine flask, add 40 ml of water, 20 ml of bromine (0.05 mol/L) VS and 3 ml of hydrochloric acid. Carry out the Assay described under Phenolsulfonphthalein beginning at the words "stopper the flask immediately...". Each ml of bromine (0.05 mol/L) VS is equivalent to 4.430 mg of $C_{19}H_{14}O_5S$.

Category As described under Phenolsulfonphthalein.

Strength 1 ml : 6 mg

Storage Preserve in well closed containers.

Phenoxybenzamine Hydrochloride



$C_{18}H_{22}ClNO \cdot HCl$ 340.29

[63-92-3]

Phenoxybenzamine Hydrochloride is *N*-(2-chloroethyl)-*N*-(1-methyl-2-phenoxy-ethyl) benzyl-amine hydrochloride. It contains not less than 98.5% of $C_{18}H_{22}ClNO \cdot HCl$, calculated on the dried basis.

Description A white or almost white crystalline powder; odourless; almost tasteless. Freely soluble in ethanol or chloroform; slightly soluble in water.

Melting range 137-140°C (Appendix VI C).

Identification (1) Dissolve 50 mg in 50 ml of chloroform in a separator, wash with 0.01 mol/L hydrochloric acid solution for three times, each of 20 ml. Discard the acid washings, filter the chloroform layer through absorbant cotton. Dilute 5 ml of the successive filtrate to 50 ml with chloroform treated with acid [chloroform washed with 0.01 mol/L hydrochloric acid solution, dehydrated with anhydrous sodium sulfate and distilled]. The light absorption of the resulting solution exhibits maxima at 272 nm and 279 nm; the absorbance is about 0.55 and 0.45, respectively (Appendix IV A).

(2) The infrared absorption spectrum (Appendix IV C) is concordant with the reference spectrum of phenoxybenzamine hydrochloride (Appendix XVI).

(3) The aqueous solution yields the reactions characteristic of chlorides (Appendix III).

Loss on drying When dried in vacuum over phosphorus pentoxide to constant weight, loses not more than 0.5% of its weight (Appendix VIII L).

Residue on ignition Not more than 0.1%; use 1.0 g (Appendix VIII N).

Heavy metals Carry out the limit test for heavy metals (Appendix VIII H, method-2), using the residue obtained in the test for Residue on ignition; not more than 0.002%.

Assay Dissolve about 0.2 g, accurately weighed in 15 ml of glacial acetic acid and 5 ml of mercuric acetate TS, add 1 drop of crystal violet IS and titrate with perchloric acid (0.1 mol/L) VS until the colour changes to bluish-green. Perform a blank determination and make any necessary correction. Each ml of perchloric acid (0.1 mol/L) VS is equivalent to 34.03 mg of $C_{18}H_{22}ClNO \cdot HCl$.

Category α -Adrenergic receptor inhibitor.

Storage Preserve in tightly closed containers, protected from light.

Preparation (1) Phenoxybenzamine Hydrochloride Injection

(2) Phenoxybenzamine Hydrochloride Tablets

Phenoxybenzamine Hydrochloride Injection

Phenoxybenzamine Hydrochloride Injection is a sterile solution of Phenoxybenzamine Hydrochloride in Water for Injection. It contains not less than 90.0% and not more than 110.0% of the labelled amount of phenoxybenzamine hydrochloride ($C_{18}H_{22}ClNO \cdot HCl$).

Description A clear, colourless liquid.

Identification To 1 ml add 20 ml of 0.01 mol/L hydrochloric acid solution and extract with chloroform. The chloroform extract is diluted with chloroform treated with acid [chloroform washed with 0.01 mol/L hydrochloric acid solution, dehydrated with anhydrous sodium sulfate and distilled] to produce a solution of 0.1 mg per ml. The light absorption of this solution exhibits maxima at 272 nm and ... 9 nm.

pH value 1.3-3.0 (Appendix VI H).

Other requirements Complies with the general requirements for injections (Appendix I B).

Assay Evaporate 10 ml, accurately measured to dryness on a water bath and dry at 105°C for 30 minutes. Allow to cool, dissolve the residue in 10 ml of glacial acetic acid and 5 ml of mercuric acetate TS, add 1 drop of crystal violet IS and then titrate with perchloric acid (0.05 mol/L) VS until the colour changes to bluish green. Perform a blank determination and make any necessary correction. Each ml of perchloric acid (0.05 mol/L) VS is equivalent to 17.02 mg of $C_{18}H_{22}ClNO \cdot HCl$.

Category As described under Phenoxybenzamine Hydrochloride.

Strength 1 ml : 10 mg

Storage Preserve in well closed containers, protected from light.

Phenoxybenzamine Hydrochloride Tablets

Phenoxybenzamine Hydrochloride Tablets contain not less than 90.0% and not more than 110.0% of the labelled amount of phenoxybenzamine hydrochloride ($C_{18}H_{22}ClNO \cdot HCl$).

Description White tablets.

Identification (1) The light absorption of the solution obtained in Assay exhibits maxima at 262 nm, 267 nm and 274 nm (Appendix IV A).

(2) The aqueous solution yields the reactions characteristic of chlorides (Appendix III).

Content uniformity Comply with the requirements (Appendix X E). Transfer 1 tablet to a 100 ml (10 mg strength) or 50 ml (5 mg strength) volumetric flask, add a quantity of 0.1 mol/L hydrochloric acid solution, shake thoroughly, dilute to volume and mix well, filter. Carry out the procedure described under Assay using the filtrate. Calculate the content of $C_{18}H_{22}ClNO \cdot HCl$.

Other requirements Comply with the general requirements

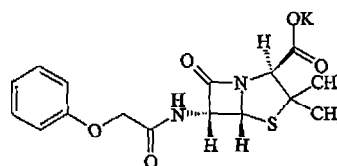
Assay Weigh accurately and powder 20 tablets. To an accurately weighed quantity of the powder equivalent to about 10 mg of phenoxybenzamine hydrochloride in a 100 ml volumetric flask add 0.1 mol/L hydrochloric acid solution, dilute to volume and mix well, filter, use the successive filtrate as the test solution. To 10 mg of phenoxybenzamine hydrochloride CRS, accurately weighed, in a 100 ml volumetric flask, add 0.1 mol/L hydrochloric acid solution dilute to volume and mix well, use the solution as the reference solution. Measure the absorbances of two solutions at 267 nm (Appendix IV A), calculate the content of $C_{18}H_{22}ClNO \cdot HCl$.

Category As described under Phenoxybenzamine Hydrochloride.

Strength (1) 5 mg (2) 10 mg

Storage Preserve in tightly closed containers, protected from light.

Phenoxymethylpenicillin Potassium



$C_{16}H_{17}KN_2O_5S$ 388.49

[132-98-9]

Phenoxymethylpenicillin Potassium is monopotassium (2S,5R,6R)-3,3-dimethyl-7-oxo-6-(2-phenoxyacetamido)-4-thia-1-azabicyclo [3.2.0] heptane-2-carboxylate. It contains not less than 85.7% of phenoxymethylpenicillin potassium ($C_{16}H_{17}KN_2O_5S$), calculated on the anhydrous basis.

Description White crystals or a crystalline powder; odourless or slight odour; taste, bitter.

Freely soluble in water; practically insoluble in chloroform, ether or liquid paraffin.

Specific optical rotation +215° to +230°, in a solution of 10 mg per ml in freshly boiled and cooled water (Appendix VI E).

Identification (1) The retention time of principal peaks of the solution being examined in the chromatogram obtained in the Assay are identical with that the principal peaks of the reference solution correspondingly.

(2) The infrared absorption spectrum (Appendix VI C) is concordant with the reference spectrum of phenoxymethylpenicillin potassium (Appendix XVI).

(3) Yields the flame reaction of potassium salts (Appendix III).

Light Absorbance Measure the absorbance of a solution of 1 mg per ml in 0.1 mol/L sodium hydroxide solution at 306 nm (Appendix IV A), the value of A is not more than 0.33; and measure the absorbance of a solution of 0.2 mg per ml in 0.1 mol/L sodium hydroxide solution at 274 nm (Appendix IV A), the value of A is not less than 0.50.

Crystallinity Comply with the requirements for crystallinity test (Appendix IX D).

Acidity or alkalinity An aqueous solution of 5 mg per ml, pH 5.0-7.5 (Appendix VI H).

Related substances Dissolve a quantity of the substance

being examined, accurately weighed, in the phosphate buffer solution (pH 6.5) described under the Assay, to produce a solution of 2.5 mg per ml as the test solution. Transfer accurately 1 ml to a 100 ml volumetric flask, add phosphate buffer solution (pH 6.5) to volume and mix well, as the reference solution. Carry out the method as described under Assay. Inject 20 μ l of the reference solution into the column. Adjust the attenuation so that the principal peak height in the chromatogram is 20% of full scale of the chart. Inject separately 20 μ l each of the test solution and the reference solution into the column, and record the chromatogram for three times the retention time of the principal peak. If peaks other than the principal peak in the chromatogram obtained with test solution, the sum of the areas of all secondary peaks are not greater than three times the area of the principal peak in the chromatogram obtained with reference solution. Disregard any peak with an area less than 0.05 time the area of the principal peak in the chromatogram obtained with reference solution.

Phenoxymethylpenicillin polymer Carry out the method for size-exclusion chromatography (Appendix V H). Using a column with 1.3-1.6 cm in internal diameter and 30-40 cm height packed with sephadex G-10. (40-120 μ m). A phosphate buffer solution [0.1 mol/L disodium hydrogen phosphate-0.1 mol/L sodium dihydrogen phosphate (61 : 39)] as mobile phase A, and water as mobile phase B. The flow rate is 1.5 ml per minute; the detection wavelength is 254 nm. Inject 200 μ l of a solution of 0.1 mg per ml of dextran blue 2000 into the column, elute separately using mobile A and mobile B. The number of the theoretical plates of the column is not less than 700 and the tailing factor is not more than 2.0, calculated with reference to the peak of dextran blue 2000. The ratio of retention time of dextran blue 2000 peak in the two mobile phase is between 0.93-1.07, the ratio of retention time of the polymer peak of the test solution and the dextran blue 2000 peak in mobile phase A is between 0.93-1.07, the ratio of retention time of the principal peak of the reference solution and the dextran blue 2000 peak in mobile phase B is between 0.93-1.07. The relative standard deviation (RSD) of the areas of the principal peak in chromatogram obtained with 200 μ l of the reference solution for several replicate injection is not more than 5.0%, using mobile phase B as the eluent.

Reference solution Dissolve an accurately weighed quantity of phenoxymethylpenicillin RS in water to produce a solution of 0.2 mg per ml.

Procedure Dissolve 0.4 g of the substance being examined, accurately weighed, in a 10 ml volumetric flask, dilute to volume with water, mix well. Inject immediately 200 μ l into the column and record the chromatogram using mobile phase A as the eluent. Inject 200 μ l the reference solution into the column and record the chromatogram using mobile phase B as the eluent. The content of phenoxymethylpenicillin polymer is not more than 0.6%, calculated as phenoxymethylpenicillin with respect to the peak area obtained in the chromatogram by the external standard method.

Water Not more than 1.5% (Appendix VIII M, method 1 A).

Assay Carry out the method for high performance liquid chromatography (Appendix V D), using a column packed with octadecylsilane bonded silica gel and water-acetonitrile-glacial acetic acid (65 : 35 : 1) as mobile phase. Detection wavelength is 268 nm. Dissolve an accurately weighed 10 mg each of benzylpenicillin RS and penicillin V RS to a 10 ml volumetric flask, add phosphate buffer solution (pH 6.5) to volume and mix well, inject 20 μ l into the column and record the chromatogram. The resolution factor between

peaks of penicillin V and benzylpenicillin is not less than 3.0.

Procedure Dissolve about 50 mg, accurately weighed, to a 50 ml volumetric flask, add phosphate buffer solution (pH 6.5) (measure 125 ml of 0.2 mol/L potassium dihydrogen phosphate solution, add 250 ml of water, mix well, adjust to pH 6.5 with sodium hydroxide, dilute with water to 500 ml) to volume and mix well. Inject accurately 20 μ l into the volume and record the chromatogram. Repeat the operation, using penicillin V RS instead of the substance being examined, calculate the content of $C_{16}H_{18}N_2O_5S$ with respect to the peak area obtained in the chromatogram by the external standard method. Each mg of $C_{16}H_{18}N_2O_5S$ is equivalent to 1695 penicillin V Units.

Category β -Lactam antibiotic.

Storage Preserve in tightly closed containers, stored in a cool and dark place and protected from light.

Preparation (1) Phenoxymethylpenicillin Potassium Capsules
(2) Phenoxymethylpenicillin Potassium Tablets

Phenoxymethylpenicillin Potassium Capsules

Phenoxymethylpenicillin Potassium Capsules contain not less than 90.0% and not more than 110.0% of the labelled amount of phenoxymethylpenicillin ($C_{16}H_{18}N_2O_5S$).

Description White or almost white crystalline granules or powder.

Identification (1) The retention time of principal peaks of the solution being examined in the chromatogram obtained in the Assay are identical with that the principal peaks of the reference solution correspondingly.

(2) Weigh about 1 g of mixed contents and ignite. To the cooled residue add 5 ml of 2 mol/L hydrochloric acid solution and heat to boiling, then cool and filter. The filtrate yields the reaction characteristic of potassium salts (Appendix III).

Related substances Dissolve an accurately weighed quantity of the mixed contents obtained in the test for weight variation of contents, to produce a solution of 2.5 mg per ml in the pH 6.5 phosphate buffer solution obtained in the Assay. Calculate as labelled amount. Filter and use the successive filtrate as the test solution. Carry out the test of related substances under Phenoxymethylpenicillin Potassium, the sum of the area of all impurity peaks is not greater than of area of the principal peak in the chromatogram obtained with reference solution (5.0%) Disregard any peak with an area less than 0.05 times area of the principal peak in the chromatogram obtained with reference solution.

Dissolution Carry out the dissolution test (Appendix X C, method 2), using phosphate BS (pH 6.8) 900 ml as the dissolution medium, adjust the rotational speed of the paddle to 100 rpm. Withdraw 5 ml of the solution after exact 30 minutes and filter. Dilute an accurately measured quantity of the successive filtrate with the above phosphate BS to produce a solution of 0.15 mg per ml. Measure the absorbance of the resulting solutions at 268 nm (Appendix IV A). Dissolve an accurately weighed quantity of phenoxymethylpenicillin RS in the above phosphate BS to produce a solution of 0.15 mg per ml. Calculate the dissolution of $C_{16}H_{18}N_2O_5S$ from each capsule. Not less than 75% of the labelled amount is dissolved.

Phenoxymethylpenicillin polymer Dissolve an accurately weighed quantity of the mixed contents in the mobile phase A

to produce a solution of 40 mg per ml. Filter and use the successive filtrate as the test solution. Complies with the test under phenoxymethylpenicillin Potassium. The content of Phenoxymethylpenicillin polymer is not more than 0.6%, calculate as phenoxymethylpenicillin.

Loss on drying When dried to constant weight at 105°C, loses not more than 2.0% of its weight (Appendix VIII L).

Other requirements Comply with the general requirements for capsules (Appendix I E).

Assay Weigh accurately and powder finely the mixed contents obtained in the test for weight variation of contents. Weigh accurately a quantity of powder equivalent to about 50 mg of phenoxymethylpenicillin to a 50 ml volumetric flask, add phosphate buffer solution (pH 6.5) to volume and mix well, filter and use the successive filtrate as the test solution. Carry out the assay described under Phenoxymethylpenicillin Potassium. Each mg of $C_{16}H_{18}N_2O_5S$ is equivalent to 1695 penicillin V Units.

Category As described under Phenoxymethylpenicillin Potassium.

Strength 0.236 g (400000 Units) calculated as $C_{16}H_{18}N_2O_5S$

Storage Preserve in tightly closed containers, stored in a cool and dark place and protected from light.

Phenoxymethylpenicillin Potassium Tablets

Phenoxymethylpenicillin Potassium Tablets contain not less than 90.0% and not more than 110.0% of the labeled amount of phenoxymethylpenicillin ($C_{16}H_{18}N_2O_5S$).

Description White tablets or film coated tablets or sugar coated tablets with white core.

Identification (1) The retention time of principal peaks of the solution being examined in the chromatogram obtained in the Assay are identical with that the principal peaks of the reference solution correspondingly.

(2) Weight about 1 g of powdered tablets and ignite. To the cooled residue add 5 ml of 2 mol/L hydrochloric acid solution and heat to boiling, then cool and filter. The filtrate yields the reaction characteristic of potassium salts (Appendix III).

Related substances Weigh accurately and powder finely 10 tablets. Dissolve accurately a quantity of powdered tablets in the phosphate buffer solution (pH 6.5) obtained in the Assay, to produce a solution of 2.5 mg per ml, calculate as labelled amount. Filter and use the successive filtrate as the test solution. Carry out the test for related substances under Phenoxymethylpenicillin Potassium, the sum of the area of all impurity peaks are not greater than of area of the principal peak in the chromatogram obtained with reference solution (5.0%). Disregard any peak with an area less than 0.05 time of area of the principal peak in the chromatogram obtained with reference solution.

Dissolution Carry out the dissolution test (Appendix X C method 2), using 900 ml phosphate BS (pH 6.8) as the dissolution medium, adjust the rotational speed of the paddle to 100 rpm. Withdraw 5 ml of the solution after exactly 30 minutes and filter. Dilute an accurately measured quantity of the successive filtrate with the above phosphate BS to produce a solution of 0.15 mg per ml. Measure the absorbance of the resulting solution at 268 nm (Appendix IV).

phenoxymethylpenicillin RS in the above phosphate BS to produce a solution of 0.15 mg per ml, repeat the operation. Calculate the dissolution of $C_{16}H_{18}N_2O_5S$ from each tablet. Not less than 75% of the labelled amount is dissolved.

Other requirements Comply with the general requirements for tablets (Appendix I A).

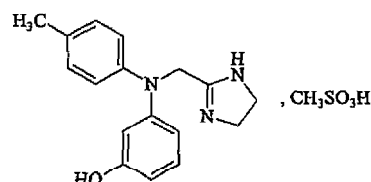
Assay Weigh accurately and powder finely 10 tablets. Weigh accurately a quantity of powdered tablets equivalent to about 50 mg of phenoxymethylpenicillin to a 50 ml volumetric flask, add phosphate buffer solution (pH 6.5) (measure 0.2 mol/L potassium dihydrogen phosphate 125 ml, add water 250 ml, mix well, adjust to pH 6.5 with sodium hydroxide, dilute with water to 500 ml) to volume and mix well, filter and use the successive filtrate as the test solution. Carry out the Assay described under Phenoxymethylpenicillin Potassium. Each mg of $C_{16}H_{18}N_2O_5S$ is equivalent to 1695 penicillin V Units.

Category As described under Phenoxymethylpenicillin Potassium.

Strength Calculated as $C_{16}H_{18}N_2O_5S$
0.236 g (400000 Units)

Storage Preserve in tightly closed containers, stored in a cool and dark place and protected from light.

Phentolamine Mesylate



$C_{17}H_{19}N_3O \cdot CH_4O_3S$ 377.46

[65-28-1]

Phentolamine Mesylate is 3-[(4,5-dihydro-1H-imidazol-2-yl) methyl] (4-methylphenyl) amino phenol monomethane sulfonate. It contains not less than 99.0% of $C_{17}H_{19}N_3O \cdot CH_4O_3S$, calculated on the dried basis.

Description A white or almost white crystalline powder; odourless; taste, bitter.

Freely soluble in water or ethanol; slightly soluble in chloroform.

Melting range 176-181°C, with decomposition (Appendix VI C).

Identification (1) Melting point of the trichloroacetate obtained in the Assay, 136-141°C with decomposition (Appendix VI C).

(2) Dissolve about 30 mg in 15 ml of water and divide into 3 portions. To one portion add iodine TS, to another portion add mercuric potassium iodide TS, to the last portion add trinitrophenol TS, precipitates are produced in all these portions.

(3) Dissolve a mixture of 50 mg with 0.2 g of sodium hydroxide in a few drops of water and evaporate to dryness. Heat gently to fusion and continue the heating for a few minutes. Cool, add 0.5 ml of water and a slight excess of dilute hydrochloric acid; sulfur dioxide is produced which is recognized by its odour.

Acidity or alkalinity Dissolve 0.10 g in 10 ml of water, add 1 drop of methyl red TS, a red colour is produced; add 0.05 ml of 0.1 mol/L sodium hydroxide VS, the colour

changes to yellow.

Chlorides To 0.10 g add 5 ml of water and 1 ml of dilute nitric acid, warm to 80°C, add 1 ml of silver nitrate TS; no white turbidity is produced.

Loss on drying When dried to constant weight at 105°C, loses not more than 0.5% of its weight (Appendix VIII L).

Residue on ignition Not more than 0.1% (Appendix VIII N).

Assay Dissolve about 0.2 g, accurately weighed, in 20 ml of water, add slowly 40 ml of 10% trichloroacetic acid solution with stirring. Allow to stand for 2 hours, filter with a tared sintered glass funnel. Wash the precipitate with a small quantity of 10% trichloroacetic acid solution and then with 20 ml of cold water in portions at a temperature below 10°C. Dry the trichloroacetate in vacuum over phosphorous pentoxide to constant weight. Each g of residue is equivalent to 0.8487 g of $C_{17}H_{19}N_3O \cdot CH_4O_3S$.

Category α -adrenergic receptor blocking agent.

Storage Preserve in tightly closed containers, protected from light.

Preparation Phentolamine Mesylate Injection

Phentolamine Mesylate Injection

Phentolamine Mesylate Injection is a sterile solution of Phentolamine Mesylate in Water for Injection containing 5% of Dextrose. It contains not less than 95.0% and not more than 105.0% of the labelled amount of phentolamine mesylate ($C_{17}H_{19}N_3O \cdot CH_4O_3S$).

Description A colourless or slight yellow clear liquid.

Identification (1) Melting point of trichloroacetate obtained in the Assay, 136–141°C, with decomposition (Appendix VI C).

(2) To about 3 ml add 12 ml of water, the solution complies with test (2) for Identification described under Phentolamine Mesylate.

pH value 2.5–5.0 (Appendix VI H).

Other requirements Complies with the general requirements for injections (Appendix I B).

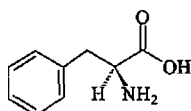
Assay To a quantity equivalent to about 0.1 g of phentolamine mesylate, accurately measured, add 20 ml of water, carry out the Assay described under Phentolamine Mesylate, beginning at the words "add slowly 40 ml of 10% trichloroacetic acid solution with stirring...".

Category As described under Phentolamine Mesylate.

Strength (1) 1 ml : 5 mg (2) 1 ml : 10 mg

Storage Preserve in tightly closed containers, protected from light.

Phenylalanine



Phenylalanine is *L*-2-amino-3-phenylpropanoic acid. It contains not less than 98.5% of $C_9H_{11}NO_2$, calculated on the dried basis.

Description White crystals or crystalline powder; odourless; taste, slight bitter.

Freely soluble in hot water, sparingly soluble in water, insoluble in ethanol, freely soluble in dilute acid or sodium hydroxide solutions.

Specific optical rotation -33.0° to -35.0° , in a solution of 20 mg per ml in water (Appendix VI E).

Identification The infrared absorption spectrum (Appendix IV C) is concordant with the reference spectrum of Phenylalanine (Appendix XVI).

Acidity Dissolve 0.20 g in 20 ml of water, pH 5.4–6.0 (Appendix VI H).

Transmittance of solution Dissolve 0.50 g in 25 ml of water, the transmittance at 430 nm is not less than 98.0% (Appendix IV A).

Chlorides Carry out the limit test for chlorides (Appendix VII A), using 0.30 g. Any opalescence produced is not more pronounced than that of a reference solution using 6.0 ml of sodium chloride standard solution (0.02%).

Sulfates Carry out the limit test for sulfates (Appendix VII B), using 0.70 g. Any opalescence produced is not more pronounced than that of a reference solution using 1.4 ml of potassium sulfate standard solution (0.02%).

Ammonium Carry out the limit test for ammonium (Appendix VII K), using 0.10 g. Any colour produced is not more intense than that of a reference solution using 2.0 ml of ammonium chloride standard solution (0.02%).

Other amino acids Carry out the method for thin-layer chromatography (Appendix V B), using silica gel G as the coating substance and *n*-butanol-glacial acetic acid-water (5 : 1 : 2) as the mobile phase. Apply to the plate 5 μ l of a solution containing 6 mg per ml of substance being examined in water. After developing and removal of the plate, dry in air, spray with ninhydrin acetone solution (1→50), heat at 90°C until the colour reveal and examine immediately. Only one purple spot is obtained in the chromatogram.

Loss on drying When dried at 105°C for 3 hours, loses not more than 0.2% of its weight (Appendix VIII L).

Residue on ignition Not more than 0.1% (Appendix VIII N), using 1.0 g.

Iron Carry out the limit test for iron (Appendix VIII G), using 1.0 g. Any colour produced is not more intense than that of a reference solution using 1.0 ml of iron standard solution (0.001%).

Heavy metals Carry out the limit test for heavy metals (Appendix VIII H, method 2), using the residue obtained in the test for Residue on ignition; not more than 0.001%.

Arsenic Dissolve 2.0 g in 23 ml of water, add 5 ml of hydrochloric acid, carry out the limit test for arsenic (Appendix VIII J, method 1); not more than 0.0001%.

Bacterial endotoxin Carry out the test for bacterial endotoxin (Appendix XI E); less than 25 EU per g of phenylalanine (for injection).

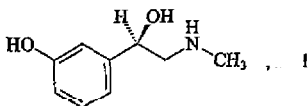
Assay Dissolve about 0.13 g, accurately weighed, in 3 ml of anhydrous formic acid, add 50 ml of glacial acetic acid. Carry out the method for potentiometric titration (Appendix VII A), titrate with perchloric acid (0.1 mol/L) VS. Perform a blank determination and make any necessary correction. Each ml of perchloric acid (0.1 mol/L) VS is

equivalent to 16.52 mg of $C_9H_{11}NO_2$.

Category Amino acid.

Storage Preserve in tightly closed containers.

Phenylephrine Hydrochloride



$C_9H_{13}NO_2 \cdot HCl$ 203.67

[61-76-7]

Phenylephrine Hydrochloride is 3-Hydroxy- α -[(methylamino) methyl]-(*R*) benzenemethanol hydrochloride. It contains not less than 98.5% and not more than 102.0% of $C_9H_{13}NO_2 \cdot HCl$.

Description A white or almost white, crystalline powder; odourless; taste, bitter. Freely soluble in water or ethanol; insoluble in chloroform or ether.

Melting range 140-145°C (Appendix VI C).

Specific optical rotation -42° to -47° , in a solution of 20 mg per ml in water (Appendix VI E).

Identification (1) Dissolve 10 mg in 1 ml of water, add 1 drop of cupric sulfate TS and 1 ml of sodium hydroxide TS, mix well, a purple colour is produced; add 1 ml of ether and shake, no colour is produced in the ether layer.

(2) Dissolve 10 mg in 1 ml of water, add 1 drop of ferric chloride TS, a purple colour is produced.

(3) The infrared absorption spectrum (Appendix IV C) is concordant with the reference spectrum of phenylephrine hydrochloride (Appendix XVI)

(4) The aqueous solution yields the reactions characteristic of chlorides (Appendix III).

Acidity Dissolve 0.50 g in 50 ml of water, pH 4.5-5.5 (Appendix VI H).

Ketones The absorbance of an aqueous solution of 2.0 mg per ml at 310 nm is not greater than 0.2 (Appendix IV A).

Related substances Protect from light throughout the procedure. Carry out the method for thin-layer chromatography (Appendix V B), using silica gel G as the coating substance and isopropanol-chloroform-concentrated ammonia solution (80 : 5 : 15) as the mobile phase. Apply separately to the plate 10 μ l each of two solutions in methanol containing (1) 20 mg per ml, (2) 0.10 mg per ml of the substance being examined. After developing and removal of the plate, dry in air and spray with diazotized sulfanilic acid TS. Any spot other than the principal spot in the chromatogram obtained with solution (1) is not more intense than the principal spot obtained with solution (2).

Loss on drying When dried to constant weight at 105°C, loses not more than 1.0% of its weight (Appendix VIII L).

Residue on ignition Not more than 0.2% (Appendix VIII N).

Assay Dissolve about 0.1 g, accurately weighed, in a conical flask with glass stopper in 20 ml of water. Add accurately 50 ml of bromine (0.05 mol/L) VS and 5 ml of hydrochloric acid. Insert the stopper immediately and allow to stand for 15 minutes with frequent shaking. Cautiously remove the stopper and add quickly 10 ml of potassium iodide

VS, add starch IS towards the end of the titration and continue the titration until the blue colour is discharged. Perform a blank determination and make any necessary correction. Each ml of bromine (0.05 mol/L) VS is equivalent to 3.395 mg of $C_9H_{13}NO_2 \cdot HCl$.

Category Adrenergic receptor stimulant.

Storage Preserve in tightly closed containers, protected from light.

Preparation Phenylephrine Hydrochloride Injection

Phenylephrine Hydrochloride Injection

Phenylephrine Hydrochloride Injection is a sterile solution of Phenylephrine Hydrochloride in Water for Injections. It contains not less than 95.0% and not more than 105.0% of the labelled amount of phenylephrine hydrochloride ($C_9H_{13}NO_2 \cdot HCl$).

Description A clear, colourless liquid.

Identification (1) Complies with the test (1) for Identification described under Phenylephrine Hydrochloride.

(2) Dissolve a quantity of phenylephrine hydrochloride CRS in methanol to produce a solution of 20 mg per ml as the reference solution. The solution (1) obtained in the test for Related substances is used as the test solution. Carry out the test for Related substances, beginning at the words "Carry out the method for thin-layer chromatography...". The colour and position of the principal spot in the chromatogram obtained with the test solution corresponds to the principal spot obtained with the reference solution.

(3) The aqueous solution yields the reactions characteristic of chlorides (Appendix III).

pH value 3.0-5.0 (Appendix VI H).

Related Substances Protect from light throughout the procedure. Evaporate a quantity of the injection on a water bath to dryness, add methanol to produce a solution of (1) 20 mg per ml; (2) 0.2 mg of phenylephrine hydrochloride per ml. Carry out the method for thin-layer chromatography (Appendix V B), using silica gel G as the coating substance and a mixture of isopropanol-chloroform-concentrated ammonia solution (80 : 5 : 15) as the mobile phase. Apply separately to the same plate 10 μ l each of above two solutions. After developing and removal of the plate, dry it in air, spray with diazotized sulfanilic acid TS. Any spot, other than the principal spot in the chromatogram, obtained with solution (1) is not more intense than the principal spot obtained with solution (2).

Other requirements Complies with the general requirements for injections (Appendix I B).

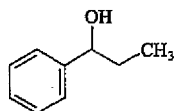
Assay Accurately measure 5 ml to conical flask with glass stopper, add 1 ml of dilute hydrochloric acid, boil gently to almost dryness and cool. Add 20 ml of water, 25 ml, of bromine (0.05 mol/L) VS accurately measured and 2 ml of hydrochloric acid. Insert the stopper immediately, mix well and allow to stand for 15 minutes with frequent shaking. Cautiously remove the stopper and add quickly 7 ml of potassium iodide TS, insert the stopper immediately and shake thoroughly. Titrate with sodium thiosulfate (0.1 mol/L) VS, add starch IS towards the end of the titration, and continue the titration until the blue colour is discharged. Perform a blank determination and make any necessary correction. Each ml of bromine (0.05 mol/L) VS is

Category As described under Phenylephrine Hydrochloride.

Strength 1 ml : 10 mg

Storage Preserve in tightly closed containers, protected from light.

Phenylpropanol



$C_9H_{12}O$ 136.19

[90-43-7]

Phenylpropanol is α -ethylbenzenemethanol. It contains not less than 98.5% of $C_9H_{12}O$.

Description A colourless or pale yellow oily liquid; odour, aromatic; taste, sweet and acid. Very soluble in methanol, ethanol or chloroform; slightly soluble in water.

Relative density 0.992-0.996 (Appendix VI A).

Refractive index 1.517-1.522 (Appendix VI F).

Identification (1) Mix 10 ml of nitric acid solution (1→2) with 5 drops of 5% potassium dichromate solution. To the mixture add 2 drops of the substance being examined and shake, a pale blue colour is produced.

(2) The light absorption of a solution containing 0.5 mg per ml in ethanol exhibits maxima at 247, 252, 258 and 264 nm (Appendix IV A).

(3) The infrared absorption spectrum (Appendix IV C) is concordant with the reference spectrum of phenylpropanol (Appendix XVI).

Propiophenone The ratio of the absorbance at 247 nm to that at 258 nm obtained under the test for Identification (2) is not greater than 0.79.

Assay To about 0.8 g, accurately weighed, add accurately 5 ml of a freshly prepared mixture of acetic anhydride-pyridine (1 : 4), heat on a water bath under reflux for 1 hour, add 10 ml of water and continue heating for 10 minutes. Allow to cool, rinse the condenser and the neck of the flask with *n*-butanol (previously neutralized to phenolphthalein IS), add 2 drops of phenolphthalein IS. Titrate with sodium hydroxide (0.5 mol/L) VS. Perform a blank determination and make any necessary correction. Each ml of sodium hydroxide (0.5 mol/L) VS is equivalent to 68.1 mg of $C_9H_{12}O$.

Category Chologagic.

Storage Preserve in tightly closed containers.

Preparation Phenylpropanol soft Capsules

Phenylpropanol Soft Capsules

Phenylpropanol Soft Capsules contain not less than 90.0% and not more than 110.0% of the labelled amount of phenylpropanol ($C_9H_{12}O$).

Description Capsules containing colourless or pale yellow oily liquid; odour, aromatic; taste, sweet and acid.

tests (1) and (2) for Identification described under Phenylpropanol.

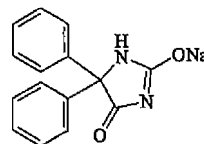
Other requirements Comply with the general requirements for Capsules (Appendix I E).

Assay Mix the contents obtained in the test for weight variation. Carry out the Assay described under Phenylpropanol. Each ml of sodium hydroxide (0.5 mol/L) VS is equivalent to 68.1 mg of $C_9H_{12}O$.

Category, Storage As described under Phenylpropanol.

Strength (1) 0.1 g (2) 0. g

Phenytoin Sodium



$C_{15}H_{11}N_2NaO_2$ 274.25

[630-93-3]

Phenytoin Sodium is 5,5-diphenylhydantoin sodium salt. It contains not less than 98.5% of $C_{15}H_{11}N_2NaO_2$, calculated on the dried basis.

Description A white powder; odourless; taste, bitter; slightly hygroscopic. It gradually absorbs carbon dioxide on exposure to air and decompose to phenytoin. The aqueous solution yields an alkaline reaction and often becomes turbid due to partial hydrolysis.

Freely soluble in water; soluble in ethanol; practically insoluble in chloroform or ether.

Identification (1) Dissolve about 0.1 g in 2 ml of water, add a few drops of mercuric chloride TS, a white precipitate is produced, which is insoluble in ammonia TS.

(2) To about 10 mg add 10 mg of potassium permanganate, 0.25 g of sodium hydroxide and 10 ml of water, heat gently for 5 minutes, cool. Extract 5 ml of the supernatant liquid with 20 ml of *n*-heptane, allow to separate into two layers. The light absorption of *n*-heptane extract exhibits a maximum at 248 nm (Appendix IV A).

(3) Dissolve about 150 mg of phenytoin sodium in 20 ml of water, add 5 ml of 3 mol/L hydrochloric acid and extract with 20 ml chloroform. Separate the chloroform layer and wash with 20 ml of water. Evaporate the chloroform to dryness on a water bath, dry the residue at 105°C for 1 hour. The infrared absorption spectrum (Appendix IV C) is concordant with the reference spectrum of phenytoin (Appendix XVI).

(4) Yields the characteristic flame reaction of sodium salts (Appendix III).

Clarity and colour of solution Dissolve 0.5 g in 20 ml of freshly boiled and cooled water, add 2 ml of 0.4% sodium hydroxide solution, the solution is clear and colourless.

Loss on drying When dried at 105°C to constant weight, loses not more than 2.0% (for injection) or 2.5% (for oral administration) of its weight (Appendix VIII L).

Heavy metals Dissolve 2.0 g in 37 ml of water by boiling, allow it to cool, add 2.5 ml of dilute hydrochloric acid, mix well and filter. To 20 ml of the filtrate add 1 drop of phenolphthalein IS and a quantity of ammonia TS until the solution becomes pale red, then add 2 ml of acetate BS (pH 3.5) and sufficient water to produce 25 ml. Carry out the limit test for heavy metals (Appendix VIII H, method 1); not more than 0.001%.

Sterility Dissolve 0.25 g (for injection) in 10 ml of sterile water, the solution complies with the test for sterility (Appendix XI H).

Assay Weigh accurately about 0.3 g and dissolve it in 50 ml of water, add 10 ml of dilute hydrochloric acid, mix well. Extract with ether, 100 ml at first, followed by four 25 ml portions. Wash the combined ether extracts with two portions of water, each of 5 ml. Extract the combined washings with 10 ml of ether and evaporate the combined ether solution in an evaporating dish, previously dried to constant weight at 105°C, dry the residue at 105°C to constant weight. Each g of residue is equivalent to 1.087 g of $C_{15}H_{11}N_2NaO_2$.

Category Anti-epileptic and anti-arrhythmic.

Storage Preserve in tightly closed containers (for oral administration) or in hermetically sealed containers (for injection), protected from light.

Preparation (1) Phenytoin Sodium for Injection
(2) Phenytoin Sodium Tablets

Phenytoin Sodium for Injection

Phenytoin Sodium for Injection is a sterile mixture of ten parts of phenytoin sodium and four parts of anhydrous sodium carbonate. It contains not less than 93.0% and not more than 107.0% of the labelled amount of phenytoin sodium ($C_{15}H_{11}N_2NaO_2$), calculated with reference to the average weight of content.

Description A white powder.

Identification (1) Dissolve a quantity equivalent to about 50 mg of phenytoin sodium in 5 ml of water and add drop-wise dilute sulfuric acid to precipitate phenytoin, filter. Dissolve the precipitate in a mixture of 1 ml of water and 8-10 drops of 0.4% sodium hydroxide solution, add a few drops of mercuric chloride TS, a white precipitate is produced, which is insoluble in ammonia TS.
(2) Complies with tests (2) and (4) for Identification described under Phenytoin Sodium.

Alkalinity Dissolve 0.35 g in 10 ml of water, pH 9.5-11.5 (Appendix VI H).

Loss on drying When dried at 105°C to constant weight, loses not more than 2.5% of its weight (Appendix VIII L).

Sterility Comply with the test for sterility (Appendix XI H), using a solution of 25 mg per ml in sterile water.

Other requirements Complies with the general requirements for injections (Appendix I B).

Assay Weigh accurately about 0.3 g of the mixed contents obtained in the test for weight variation. Carry out the Assay under Phenytoin Sodium, beginning at the words "dissolve it in 50 ml of water, ...". Calculate on the average weight of content.

Category As described under Phenytoin Sodium.

Strength (1) 0.1 g (2) 0.25 g

Storage Preserve in tightly closed containers, protected from light.

Phenytoin Sodium Tablets

Phenytoin Sodium Tablets contain not less than 93.0% and not more than 107.0% of the labelled amount of phenytoin sodium ($C_{15}H_{11}N_2NaO_2$).

Description White tablets and film coated tablets.

Identification To a quantity of the powdered tablets equivalent to about 1 g of phenytoin sodium add 20 ml of water to dissolve phenytoin sodium and filter. The filtrate complies with tests (1) and (2) for Identification described under Phenytoin Sodium. Evaporate a quantity of the filtrate to dryness, the residue complies with test (4) for Identification described under Phenytoin sodium.

Dissolution Carry out dissolution test (Appendix X C, method 2), using 500 ml of water as the dissolution medium, adjust the rotational speed of the paddle to 100 rpm. Withdraw a quantity of the solution after exactly 45 minutes and filter, the successive filtrate is used as the test solution. Dissolve phenytoin sodium CRS in water to produce a solution of 0.2 mg per ml as the reference solution. Measure the absorbances of two solutions at 258 nm (Appendix IV A). Calculate the dissolution of $C_{15}H_{11}N_2NaO_2$ from each tablet. Not less than 75% of the labelled amount is dissolved.

Other requirements Comply with the general requirements for tablets (Appendix I A).

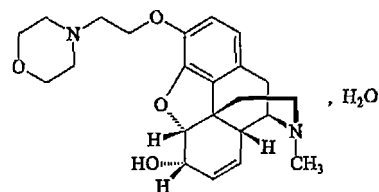
Assay Weigh and powder finely 10 (for strength 100 mg) or 20 (for strength 50 mg) tablets. Weigh accurately a quantity equivalent to 0.3 g of phenytoin sodium to a separator, add 25 ml of water, shake to dissolve phenytoin sodium. Add 50 ml of ether, shake and add 10 drops of bromophenol blue IS. Titrate with hydrochloric acid (0.1 mol/L) VS, shaking vigorously, until the aqueous layer becomes bluish-grey. Transfer the aqueous layer to a stoppered conical flask, wash the ether layer with 5 ml of water. Combine the washing with the aqueous layer in the conical flask, add 20 ml of ether, continue the titration with hydrochloric acid (0.1 mol/L) VS, shaking vigorously, until the aqueous layer becomes pale green. Each ml of hydrochloric acid (0.1 mol/L) VS is equivalent to 27.43 mg of $C_{15}H_{11}N_2NaO_2$.

Category As described under Phenytoin Sodium.

Strength (1) 50 mg (2) 100 mg

Storage Preserve in tightly closed containers, protected from light.

Pholcodine



$C_{23}H_{30}N_2O_4 \cdot H_2O$ 416.52

[509-67-1]

Pholcodine is (5R,6S)-4,5-epoxy-9a-methyl-3-

ohydrate. It contains not less than 98.0% of $C_{23}H_{30}N_2O_4$, calculated on the dried basis.

Description A white or almost white crystalline powder; odourless; taste, bitter. The aqueous solution exhibits an alkaline reaction.

Freely soluble in ethanol, acetone or chloroform; sparingly soluble in water; slightly soluble in ether; soluble in dilute hydrochloric acid.

Specific optical rotation -94° to -98° , in a solution of 20 mg per ml in ethanol (Appendix VI E).

Identification (1) Dissolve about 50 mg in 1 ml of sulfuric acid, add 1 drop of ammonium molybdate TS, a pale blue colour is produced which changes to deep blue on warming, then changes to brownish red on adding 1 drop of dilute nitric acid.

(2) The light absorption of a solution of 0.1 mg per ml in 0.4% sodium hydroxide solution in the range of 230–350 nm (Appendix IV A) exhibits a maximum at 284 nm and a minimum at 262 nm.

(3) The infrared absorption spectrum (Appendix IV C) is concordant with the reference spectrum of Pholcodine (Appendix XVI).

Morphine Dissolve 0.10 g in 5 ml of hydrochloric acid solution (9→1000), add 2 ml of sodium nitrite TS, mix well, allow to stand for 15 minutes, add 3 ml of ammonia TS, mix well. Any colour produced is not more intense than that of a reference solution using 5 ml of morphine solution [dissolve 2 mg of anhydrous morphine in hydrochloric acid solution (9→1000) to produce 100 ml] (0.1%).

Related substances Carry out the method for thin-layer chromatography (Appendix V B), using silica gel G as the coating substance and a mixture of ethanol-toluene-acetone-concentrated ammonia solution (70 : 70 : 65 : 5) as the mobile phase. Apply separately to the plate 10 μ l each of the following solutions in chloroform containing (1) 25 mg per ml, (2) 0.25 mg per ml, (3) 0.125 mg per ml of the substance being examined. After developing and removal of the plate, dry in air, visualize with iodine vapour. Any spot, other than the principal spot in the chromatogram, obtained with solution (1) is not more intense than the principal spot obtained with solution (2); not more than one secondary spot above the principal spot is more intense than the principal spot obtained with solution (3).

Loss on drying When dried to constant weight at 105°C , loses not more than 3.9% and not less than 4.5% of its weight (Appendix VIII L); use 0.50 g.

Residue on ignition Not more than 0.1% (Appendix VIII N).

Assay Dissolve about 0.15 g, accurately weighed, in 10 ml of glacial acetic acid, add 1 drop of crystal violet IS, titrate with perchloric acid (0.1 mol/L) VS until the colour changes to green. Perform a blank determination and make any necessary correction. Each ml of perchloric acid (0.1 mol/L) VS is equivalent to 19.93 mg of $C_{23}H_{30}N_2O_4$.

Category Antitussive.

Storage Preserve in tightly closed containers, protected from light.

Preparation Pholcodine Tablets

Pholcodine Tablets

and not more than 110.0% of the labelled amount of pholcodine ($C_{23}H_{30}N_2O_4 \cdot H_2O$).

Description White or almost white tablets.

Identification (1) To a quantity of the powdered tablets equivalent to about 0.2 g of pholcodine add 20 ml of dehydrated ethanol, shake for 5 minutes to dissolve pholcodine, filter and evaporate the filtrate to dryness on a water bath. The residue complies with test (1), (2) for Identification described under Pholcodine.

(2) Dissolve the residue obtained in test (1) for Identification in chloroform to produce a solution containing 25 mg of pholcodine per ml as test solution. Prepare reference solution of 25 mg per ml of pholcodine CRS in chloroform. Carry out the method for thin-layer chromatography (Appendix V B), using silica gel G as the coating substance and a mixture of ethanol-toluene-acetone-concentrated ammonia solution (70 : 70 : 65 : 5) as the mobile phase. Apply separately to the same plate 10 μ l each of above two solutions, after developing and removal of the plate, dry in air, visualize with iodine vapour. The colour and position of the principal spot in the chromatogram obtained with the test solution correspond to the principal spot obtained with the reference solution.

Content uniformity Comply with the requirements (Appendix X E). Triturate 1 tablet with 25 ml of hydrochloric acid solution (9→1000) and transfer to a 50 ml volumetric flask, add water to volume, shake thoroughly and filter, measure accurately a quantity of the successive filtrate to produce a solution of 30 μ g per ml in water as the test solution. Carry out the procedure described under Assay, calculate the content of $C_{23}H_{30}N_2O_4 \cdot H_2O$.

Other requirements Comply with the general requirements for tablets (Appendix I A).

Assay *Reference solution* Dissolve about 30 mg of pholcodine CRS, accurately weighed, in a 50 ml volumetric flask with 25 ml of hydrochloric acid solution (9→1000), dilute with water to volume, mix well. Measure accurately 5 ml to a 100 ml volumetric flask, dilute with water to volume, mix well.

Test solution Weigh and powder 20 tablets. Transfer an accurately weighed quantity of the powder, equivalent to about 30 mg of pholcodine, to a 50 ml volumetric flask, add 25 ml of hydrochloric acid solution (9→1000), shake thoroughly to dissolve pholcodine, dilute with water to volume. Filter, measure accurately 5 ml of the successive filtrate to a 100 ml volumetric flask, dilute with water to volume.

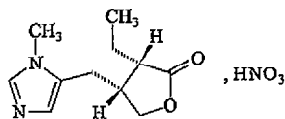
Procedure Measure accurately 2 ml each of the two solutions to two separators containing 10 ml of chloroform accurately measured, respectively. Add 6.0 ml of bromocresol green solution [dissolve 50 mg of bromocresol green and 1.021 g of potassium bipthalate in 1.6 ml of 0.2 mol/L hydrochloric acid solution, dilute with water to 100 ml, filter if necessary], extract for 2 minutes with shaking, allow to stand. Dry the chloroform extracts by shaking with 0.5 g of anhydrous sodium sulfate. Measure the absorbances of the resulting solutions at 420 nm (Appendix IV A). Calculate the content of $C_{23}H_{30}N_2O_4 \cdot H_2O$.

Category As described under Pholcodine.

Strength (1) 5 mg (2) 10 mg (3) 15 mg

Storage Preserve in tightly closed containers, protected from light.

Pilocarpine Nitrate



$C_{11}H_{16}N_2O_2 \cdot HNO_3$ 271.27 [148-72-1]

Pilocarpine Nitrate is 3-ethyl-4-[(1-methyl-1H-imidazol-5-yl)methyl]-2-(3H)-furanone nitrate. It contains not less than 99.0% of $C_{11}H_{16}N_2O_2 \cdot HNO_3$, calculated on the dried basis.

Description A colourless crystal or white crystalline powder; odourless; deteriorates easily on exposure to light. Freely soluble in water; slightly soluble in ethanol; insoluble in chloroform or ether.

Melting range 174-178°C, with decomposition (Appendix VI C).

Specific optical rotation +80° to +83°, in a solution of 0.10 g per ml in water (Appendix VI E).

Identification (1) Dissolve about 10 mg in 2 ml of water, add 2 drops of potassium dichromate TS, 1 ml of hydrogen peroxide solution and 2 ml of chloroform in order, shake, the chloroform layer exhibits a violet colour.

(2) The infrared absorption spectrum (Appendix IV C) is concordant with the reference spectrum of pilocarpine nitrate (Appendix XVI).

(3) The aqueous solution yields the reactions characteristic of nitrates (Appendix III).

Acidity or alkalinity Dissolve 1.0 g in 20 ml of water, divide the solution into two equal portions; to one portion add 1 drop of methyl red IS, a red colour is produced; to the other portion add 2 drops of bromophenol blue IS, a blue colour is produced.

Chlorides Dissolve 0.10 g in 5 ml of water, acidify with dilute nitric acid and add a few drops of silver nitrate TS; no opalescence is produced immediately.

Other alkaloids Dissolve 0.2 g in 20 ml of water, divide the solution into two equal portions; to one portion add a few drops of ammonia TS; to the other portion add a few drops of potassium dichromate TS; no opalescence is produced in any one of the solutions.

Readily carbonizable substances Dissolve 10 mg in 1 ml of sulfuric acid and 0.5 ml of nitric acid; the solution is colourless.

Loss on drying When dried to constant weight at 105°C, loses not more than 0.5% of its weight (Appendix VIII L).

Residue on ignition Not more than 0.1% (Appendix VIII N).

Assay Dissolve about 0.2 g, accurately weighed, in 30 ml of glacial acetic acid by warming and allow to cool. Carry out the method for potentiometric titration (Appendix VII A), titrate with perchloric acid (0.1 mol/L) VS. Perform a blank determination and make any necessary correction. Each ml of perchloric acid (0.1 mol/L) VS is equivalent to 27.13 mg of $C_{11}H_{16}N_2O_2 \cdot HNO_3$.

Category Miotic.

Storage Preserve in tightly closed containers, protected

Preparation Pilocarpine Nitrate Eye Drops

Pilocarpine Nitrate Eye Drops

Pilocarpine Nitrate Eye Drops contain not less than 90.0% and not more than 110.0% of the labelled amount of pilocarpine nitrate ($C_{11}H_{16}N_2O_2 \cdot HNO_3$).

Description A clear, colourless liquid.

Identification Comply with tests (1) and (3) for Identification described under Pilocarpine Nitrate.

pH value 4.0-6.0 (Appendix VI H).

Other requirements Comply with the general requirements for eye preparations (Appendix I G).

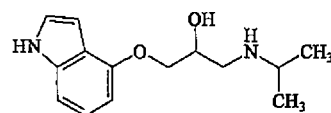
Assay Carry out the method for high performance liquid chromatography (Appendix V D), using a column packed with octadecylsilane bonded silica gel. The mobile phase is prepared as following: dissolve 2.94 g of sodium acetate in 38.4 ml of dilute acetic acid, 600 ml of water (pH 4.5), mix with 400 ml of methanol. The wavelength of the detection is 230 nm. The number of theoretical plates of the column is not less than 1000, calculated with reference to the peak of pilocarpine and the resolution factor between the peaks of pilocarpine and the internal standard complies with related requirements. Dissolve 50 mg of pilocarpine nitrate CRS previously dried at 105°C for 2 hours, accurately weighed, in a 50 ml volumetric flask in the mobile phase, dilute to volume with the same solvent and mix well (reference solution). Dissolve a quantity of benzoic acid in the mobile phase to produce a solution of 90 µg per ml (internal standard). Measure accurately 10 ml of the reference solution and 10 ml of the internal standard into a 50 ml volumetric flask, dilute to volume with the mobile phase and mix well. Inject about 20 µl of the solution into the column and record the chromatogram. To a quantity of the eye drops equivalent to 10 mg of pilocarpine nitrate in a 50 ml volumetric flask add 10 ml of the internal standard solution, measured accurately, and dilute to volume with the mobile phase, mix well. Inject about 20 µl into the column, record the chromatogram. Calculate the content of $C_{11}H_{16}N_2O_2 \cdot HNO_3$ with respect to the peak area in the chromatogram by internal standard method.

Category As described under Pilocarpine Nitrate.

Strength (1) 5 ml : 25 mg (2) 5 ml : 100 mg
(3) 10 ml : 50 mg (4) 10 ml : 100 mg
(5) 10 ml : 200 mg

Storage Preserve in tightly closed containers, protected from light and stored in a cool place.

Pindolol



$C_{14}H_{20}N_2O_2$ 248.32 [13523-86-9]

Pindolol is 1-(indol-4-yloxy)-3-(isopropylamino)-2-propanol. It contains not less than 99.0% of $C_{14}H_{20}N_2O_2$, calculated on the dried basis.

Description A white or almost white crystalline powder; odour, slight characteristic.

Freely soluble in glacial acetic acid; slightly soluble in methanol or ethanol; practically insoluble in water or benzene.

Melting range 167-171°C (Appendix VI C).

Identification (1) The light absorption of a solution of 10 µg per ml in dehydrated ethanol exhibits two maxima at 265 nm and 288 nm (Appendix IV A).

(2) The infrared absorption spectrum (Appendix IV C) is concordant with the reference spectrum of pindolol (Appendix XVI).

Loss on drying When dried to constant weight at 105°C, loses not more than 0.5% of its weight (Appendix VIII L).

Residue on ignition Not more than 0.1% (Appendix VIII N); use 1.0 g.

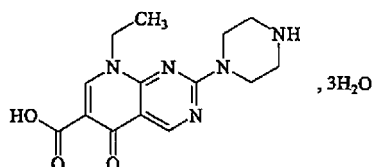
Heavy metals Carry out the limit test for heavy metals (Appendix VIII H, method 2), using the residue obtained in the test for Residue on ignition; not more than 0.001%.

Assay Dissolve about 0.1 g, accurately weighed, in 10 ml of glacial acetic acid, add 1 drop of crystal violet IS, titrate with perchloric acid (0.1 mol/L) VS, until the colour changes to blue. Perform a blank determination and make any necessary correction. Each ml of perchloric acid (0.1 mol/L) VS is equivalent to 24.83 mg of $C_{14}H_{20}N_2O_2$.

Category Adrenaline receptor blocking agent.

Storage Preserve in tightly closed containers, protected from light.

Pipemidic Acid



$C_{14}H_{17}N_5O_3 \cdot 3H_2O$ 357.37

[51940-44-4]

Pipemidic Acid is 8-ethyl-5-oxo-5,8-dihydro-2-(1-piperazinyl)-pyrido [2,3-d] pyrimidine-6-carboxylic acid. It contains not less than 98.5% of $C_{14}H_{17}N_5O_3$, calculated on the dried basis.

Description A slight yellow to yellowish crystalline powder; odourless; taste, bitter.

Slightly soluble in methanol or dimethylformamide; very slightly soluble in water or chloroform; insoluble in ethanol, ether or benzene; freely soluble in acid or alkaline solution.

Melting range 251-256°C, with decomposition (Appendix VI C).

Identification (1) To about 10 mg in a dry test tube add a small quantity of malonic acid and 3 drops of acetic anhydride, warm in a water bath for 5 minutes; a deep brown colour is produced.

(2) The light absorption of a solution of about 4 µg per ml in 0.04% sodium hydroxide solution exhibits maxima at 273 nm and 333 nm (Appendix IV A).

(3) The infrared absorption spectrum (Appendix IV C) is concordant with the reference spectrum of pipemidic acid (Appendix XVI).

Clarity of alkaline solution Dissolve 0.50 g in 10 ml of sodium hydroxide TS, the solution is clear.

Related substances Carry out the method for thin-layer chromatography (Appendix V B), using silica HF₂₅₄ as the coating substance and a mixture of methanol-chloroform-toluene-diethylamine-water (45 : 40 : 20 : 14 : 8) as the mobile phase. Apply separately to the plate 5 µl each of three solutions in the mixture of dichloromethane-methanol (1 : 1) containing (1) 10 mg per ml of the substance being examined, (2) 0.10 mg per ml, (3) 0.05 mg per ml of the solution. After developing and removal of the plate, dry it in air and examine under ultraviolet (254 nm). Not more than 2 secondary spots are observed in the chromatogram obtained with the substance. Any secondary spot is not more intense than the principal spot obtained with solution (2); if one spot is more intense, it is not more intense than the principal spot obtained with solution (1).

Loss on drying When dried to constant weight at 105°C, loses not less than 15.0%, and not more than 16.0% of its weight (Appendix VIII L).

Residue on ignition Not more than 0.2% (Appendix VIII N).

Assay Dissolve about 0.2 g, accurately weighed, in 20 ml of glacial acetic acid, add 1 drop of crystal violet IS. Titrate with perchloric acid (0.1 mol/L) VS until the solution becomes pure blue. Perform a blank determination and make any necessary correction. Each ml of perchloric acid (0.1 mol/L) VS is equivalent to 30.33 mg of $C_{14}H_{17}N_5O_3$.

Category Antibacterial agent.

Storage Preserve in tightly closed containers.

Preparation (1) Pipemidic Acid Capsules
(2) Pipemidic Acid Tablets

Pipemidic Acid Capsules

Pipemidic Acid Capsules contain not less than 95.0% and not more than 105.0% of the labelled amount of Pipemidic Acid ($C_{14}H_{17}N_5O_3 \cdot 3H_2O$).

Identification (1) The contents of pipemidic acid capsules equivalent to about 10 mg of pipemidic acid comply with test for Identification (1) described under Pipemidic Acid.

(2) The light absorption of the solution obtained in Assay exhibits maxima at 273 nm and 333 nm (Appendix IV A).

Dissolution Comply with the dissolution test (Appendix X C, method 1), using hydrochloric acid solution (dilute 24 ml of dilute hydrochloric acid TS with water to 1000 ml) as the dissolution medium, adjust the rotation speed of the basket to 100 rpm. Withdraw the solution at 30 minutes and filter. Dilute 2 ml of the successive filtrate with the hydrochloric acid solution to 100 ml and mix well. Dissolve pipemidic acid CRS in the hydrochloric acid solution to produce a solution of about 4 mg $C_{14}H_{17}N_5O_3 \cdot 3H_2O$ per ml (the calculation converting factor from $C_{14}H_{17}N_5O_3$ to $C_{14}H_{17}N_5O_3 \cdot 3H_2O$ is 1.178). Measure the absorbances of the resulting solutions at 275 nm (Appendix IV A). Calculate the dissolution of $C_{14}H_{17}N_5O_3 \cdot 3H_2O$ from each capsule. Not less than 75% of the labelled amount is dissolved.

Other requirements Comply with the general requirements for capsules (Appendix I E).

Assay Dissolve an accurately weighed quantity of mixed contents obtained from test for weight variation of contents

equivalent to about 50 mg of pipemidic acid in a 250 ml volumetric flask, add a quantity of 0.04% sodium hydroxide solution, shake thoroughly, then dilute to volume, shake well and filter. Dilute 2ml of the successive filtrate with 0.04% sodium hydroxide solution to 100 ml and mix well. Measure the absorbance of the solution at 273 nm (Appendix IV A), using the 0.04% sodium hydroxide solution as the blank, calculate the content of $C_{14}H_{17}N_5O_3 \cdot 3H_2O$, taking 1339 as the value of A (1%, 1 cm).

Category As described under pipemidic acid.

Strength 0.25 g

Storage Preserve in tightly closed containers.

Pipemidic Acid Tablets

Pipemidic Acid Tablets contain not less than 95.0% and more than 105.0% of the labelled amount of pipemidic acid ($C_{14}H_{17}N_5O_3 \cdot 3H_2O$).

Description Yellow or film-coated tablets with pale yellow core.

Identification (1) 10 mg of powdered tablets comply with test (1) for Identification described under pipemidic acid. (2) The light absorption of the solution obtained in Assay exhibits maxima at 273 nm and 333 nm (Appendix IV A).

Dissolution Carry out the dissolution test (Appendix X C, method 1), using 24 ml of dilute hydrochloric acid diluted with water to produce 1000 ml as the dissolution medium, adjust the rotational speed of the basket to 100 rpm. Withdraw the solution at 30 minutes and filter, measure accurately 2 ml of the successive filtrate, dilute with the same medium to 100 ml (for strength 0.25 g) or to 200 ml (for strength 0.5 g), mix well. Measure the absorbance at 273 nm (Appendix IV A), calculate the dissolution of $C_{14}H_{17}N_5O_3 \cdot 3H_2O$ from each tablet, taking 1339 as the value of A (1%, 1 cm): not less than 75% of the labelled amount is dissolved.

Other requirements Comply with the general requirements for tablets (Appendix I A).

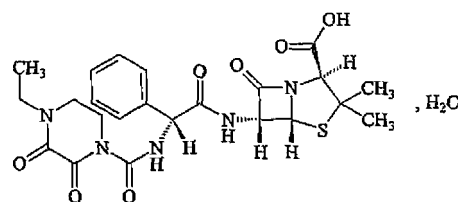
Assay Weigh accurately and powder 20 tablets. To an accurately weighed quantity of the powdered tablets, equivalent to about 0.1 g of pipemidic acid in a 500 ml volumetric flask add a quantity of 0.04% sodium hydroxide solution, shake thoroughly and dilute to volume, shake well and filter. Transfer accurately 2 ml of the successive filtrate, to a 100 ml volumetric flask, dilute to volume with 0.04% sodium hydroxide solution, shake well. Measure the absorbance of the solution at 273 nm, using the 0.04% sodium hydroxide solution as the blank (Appendix IV A), calculate the content of $C_{14}H_{17}N_5O_3 \cdot 3H_2O$, taking 1339 as the value of A (1%, 1 cm).

Category As described under Pipemidic acid.

Strength (1) 0.25 g (2) 0.5 g

Storage Preserve in tightly closed containers.

Piperacillin



$C_{23}H_{27}N_5O_7S \cdot H_2O$ 535.58

[61477-96-1]

Piperacillin is (2S,5R,6R)-3,3-dimethyl-6-[(4-ethyl-2,3-dioxo-1-piperazinecarboxamido)phenylacetamido]-7-oxo-4-thia-1-azabicyclo[3.2.0]heptane-2-carboxylic acid monohydrate. It contains not less than 92.0% of $C_{23}H_{27}N_5O_7S$, calculated on the anhydrous basis.

Description A white crystalline powder; odourless; slightly hygroscopic.

Freely soluble in methanol; soluble in dehydrated ethanol or acetone; very slightly soluble in water.

Specific optical rotation +160° to +178°, in a solution of 10 mg per ml in dehydrated ethanol (Appendix VI E).

Identification (1) To 10 mg add 2 ml of water and 3 ml of hydroxylamine hydrochloride solution [mix one volume of 34.8% hydroxylamine hydrochloride solution with one volume of sodium acetate-sodium hydroxide solution (to 10.3 g of sodium acetate and 86.5 g of sodium hydroxide add water to produce a solution of 1000 ml) and 4 volumes of ethanol], shake thoroughly. Allow to stand for 5 minutes, add 1 ml of acidic ferric ammonium sulfate TS, mix well; a reddish-brown colour is produced.

(2) The retention time of principal peak of the substance being examined is identical with that of piperacillin CRS.

(3) The infrared absorption spectrum (Appendix IV C) is concordant with the reference spectrum of piperacillin (Appendix XVI).

Acidity Mix well a quantity with water to produce a suspension of 10 mg per ml, pH 2.5-4.0 (Appendix VI H).

Clarity and colour of solution To each of 5 portions add methanol to produce solutions of 0.1 g per ml. The solutions are clear and colourless; any opalescence produced is not more pronounced than that of reference suspension I (Appendix IX B); any colour produced is not more intense than that of reference solution YG₂ or Y₂ (Appendix IX A, method 1).

Water Not more than 5.0% (Appendix VIII M, method 1 A).

Assay Carry out the method for high performance liquid chromatography (Appendix V D), using a column packed with octadecylsilane bonded silica gel and a mixture of methanol-0.2 mol/L sodium dihydrogen phosphate solution 10% tetraethyl ammonium hydroxide solution-water (400 : 50 : 3 : 547) as the mobile phase, adjust the pH with phosphoric acid to 5.5, wavelength of the detector is 254 nm. The number of theoretical plates of the column is not less than 1600, calculated with reference to the peak of piperacillin.

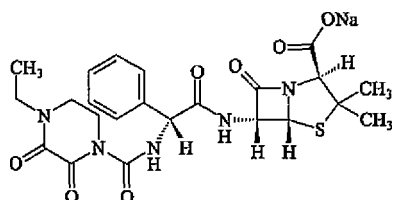
Procedure Dissolve about 40 mg of the substance being examined, accurately weighed, in a quantity of methanol in which it is freely soluble, add 10 ml of the mobile phase to

volume and mix well. Inject 10 μ l into the column. Repeat the operation using piperacillin CRS instead of the substance being examined, calculate the content of $C_{23}H_{27}N_5O_7S$.

Category β -lactam antibiotic, penicillins.

Storage Preserve in hermetically sealed containers, protected from light, stored in a cool and dry place.

Piperacillin Sodium



$C_{23}H_{26}N_5O_7S$ 539.54

[59703-84-3]

Piperacillin Sodium is sodium (2S,5R,6R)-3,3-dimethyl-6-[(4-ethyl-2,3-dioxo-1-piperazinecarboxamido) phenylacetamido]-7-oxo-4-thia-1-azabicyclo[3.2.0]heptane-2-carboxylate. It contains not less 87.0% of piperacillin ($C_{23}H_{27}N_5O_7S$), calculated on the anhydrous basis.

Description A White or almost white powder; odourless; very hygroscopic.

Freely soluble in water or methanol, soluble in dehydrated ethanol, insoluble in acetone.

Specific optical rotation $+175^\circ$ to $+190^\circ$, in an aqueous solution of 10 mg per ml (Appendix VI E).

Identification (1) Complies with tests (1) and (2) for Identification described under Piperacillin.

(2) Yields the characteristic flame reaction of sodium salts (Appendix III).

Acidity An aqueous solution of 100 mg per ml, pH 5.0-7.0 (Appendix VI H).

Clarity and colour of solution To each of 5 portions add water to produce solutions of 0.1 g per ml, the solutions are clear and colourless; any opalescence produced is not more pronounced than that of reference suspension I (Appendix IX B); any colour produced is not more intense than that of reference solution YG₂ or Y₂ (Appendix IX A).

Water Not more than 2.0% (Appendix VIII M, method 1 A).

Pyrogens Complies with the test for pyrogens (Appendix XI D), using 1 ml of a solution of 0.1 g per ml in sterile Water for Injections per kg of the rabbit's weight.

Sterility Complies with the test for sterility (Appendix XI H, membrane filtration method), dissolve each container in a feasible solvent and dilute with all of 500 ml of 0.9% steril sodium chloride solution respectively.

Assay Dissolve an accurately weighed quantity in water, carry out the assay described under Piperacillin.

Category β -lactam antibiotic, penicillins.

Storage Preserve in hermetically sealed containers, stored in a cool, dark and dry place.

Preparation Piperacillin Sodium for Injection

Piperacillin Sodium for Injection

Piperacillin Sodium for Injection is a sterile powder of Piperacillin sodium or sterile lyophilized preparation of sodium salt of Piperacillin. It contains not less than 87.0% of piperacillin ($C_{23}H_{27}N_5O_7S$), calculated on the anhydrous basis. Each container contains not less than 95.0% of piperacillin ($C_{23}H_{27}N_5O_7S$), calculated with reference to the average weight of contents.

Description A white or almost white powder or friable solid; odourless; highly hygroscopic. Very soluble in water or methanol, soluble in dehydrated ethanol, insoluble in acetone.

Specific optical rotation $+175^\circ$ to $+190^\circ$ in a solution of 10 mg per ml in water (Appendix VI E).

Identification Complies with the tests for Identification described under Piperacillin Sodium.

Acidity Dissolve a quantity in water produce a solution of 100 mg per ml, pH 5.0-7.0 (Appendix VI H).

Clarity and colour of solution To each of 5 containers add water to produce a solution of 0.1 g per ml, the solutions are clear and colourless; any opalescence produced is not more pronounced than that of reference suspension I (Appendix IX B); any colour produced is not more intense than that of reference solution YG₂ of Y₂ (Appendix IX A, method 1).

Water, Pyrogens, Sterility Complies with the corresponding requirements described under Piperacillin Sodium.

Other requirements Complies with the general requirements for injections (Appendix I B).

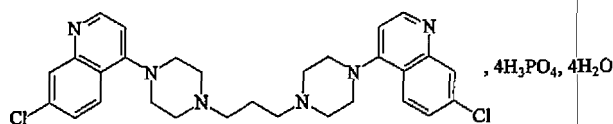
Assay Carry out the assay described under Piperacillin, using an accurately weighed quantity of mixed contents obtained from the test for weight variation of contents.

Category β -lactam antibiotic, penicillins.

Strength Calculated as $C_{23}H_{27}N_5O_7S$
(1) 0.5 g (2) 1.0 g (3) 2.0 g

Storage Preserve in well closed containers, stored in a cool, dark and dry place.

Piperaquine Phosphate



$C_{29}H_{32}Cl_2N_6 \cdot 4H_3PO_4 \cdot 4H_2O$ 999.56

Piperaquine Phosphate is 1,3-bis[4-(7-chloroquinolinyl)-4]-piperazinyl-1] propane tetraphosphate tetrahydrate. It contains not less than 98.0% of $C_{29}H_{32}Cl_2N_6 \cdot 4H_3PO_4$, calculated on the anhydrous basis.

Description An almost white to pale yellow crystalline powder; odourless; taste, slightly bitter; deepened easily

Slightly soluble in water; practically insoluble in dehydrated ethanol or chloroform.

Melting range 246-252°C, with decomposition (Appendix VI C).

Identification (1) Dissolve 50 mg in 3 ml of water by warming. Cool, divide the solution into two portions. To one portion, add a few drops of ammonium thiocyanate TS; a white precipitate is produced. To the other portion, add a few drops of potassium dichromate TS; a yellow precipitate is produced.

(2) The light absorption of a solution of 10 µg per ml in hydrochloric acid solution (9→1000) exhibits maxima at 226 nm, 240 nm and 347 nm (Appendix IV A).

(3) The infrared absorption spectrum (Appendix IV C) is concordant with the reference spectrum of piperaquine phosphate (Appendix XVI).

(4) Dissolve a quantity in hot water, add ammonia TS and filter. The filtrate yields the reactions characteristic of phosphates (Appendix III).

Acidity Dissolve 0.10 g in 40 ml of water, pH 3.0-4.0 (Appendix VI H).

Water 6.0%-8.0% (Appendix VIII M, method 1 A).

Assay Dissolve about 0.2 g, accurately weighed, in a small beaker with 0.5 ml of hydrochloric acid, add 10 ml of water and stir thoroughly. Transfer the solution to a separator, wash the beaker successively with small quantities of water, add the washings to the separator. Add 10 ml of 20% sodium hydroxide solution, mix and extract with four 20 ml portions of chloroform. Wash each chloroform extract with the same 10 ml portion of water. Combine the chloroform extracts and filter, wash the filter paper with chloroform. Combine the filtrate and washings, evaporate on a water bath to about 5 ml, then add 20 ml of acetic anhydride. Shake to dissolve. Add 1 drop of crystal violet IS, titrate with perchloric acid (0.1 mol/L) VS to a bright green colour. Perform a blank determination and make any necessary correction. Each ml of perchloric acid (0.1 mol/L) VS is equivalent to 23.19 mg of $C_{29}H_{32}Cl_2N_6 \cdot 4H_3PO_4$.

Category Antimalarial.

Storage Preserve in tightly closed containers, protected from light.

Preparation Piperaquine Phosphate Tablets

Piperaquine Phosphate Tablets

Piperaquine Phosphate Tablets contain not less than 93.0% and not more than 107.0% of the labelled amount of piperaquine phosphate ($C_{29}H_{32}Cl_2N_6 \cdot 4H_3PO_4$).

Description Sugar coated tablets with white or light yellow core.

Identification (1) To a quantity of powdered tablets, equivalent to about 0.1 g of piperaquine phosphate, add 5 ml of water, dissolve the piperaquine phosphate by heating and filter. The filtrate complies with test (1) for Identification described under Piperaquine Phosphate.

(2) To the remaining filtrate obtained in the test described above, add 0.5 ml of ammonia TS, stir and filter. To the filtrate add 4 drops of nitric acid solution (1→2), 1 ml of ammonium molybdate TS and heat; a yellow precipitate is produced, which is soluble in ammonia TS.

Assay exhibits maxima at 226 nm and 240 nm (Appendix IV A).

Other requirements Comply with the general requirements for tablets (Appendix I A).

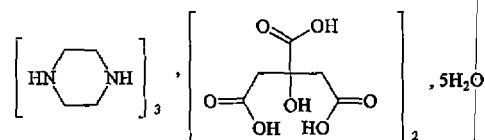
Assay Weigh and powder 10 tablets with coating removed. To a quantity of the powder equivalent to about 20 mg of piperaquine phosphate, accurately weighed, in a 100 ml volumetric flask add a quantity of hydrochloric acid solution (9→1000), heat on a water bath with shaking. Cool to room temperature, dilute with hydrochloric acid solution (9→1000) to volume and mix. Filter, transfer accurately 5 ml of the successive filtrate to another 100 ml volumetric flask, dilute with hydrochloric acid solution (9→1000) to volume and mix well. Measure the absorbance of the resulting solution at 240 nm (Appendix IV A). Calculate the content of $C_{29}H_{32}Cl_2N_6 \cdot 4H_3PO_4$, taking 566 as the value of A (1%, 1 cm).

Category As described under Piperaquine Phosphate.

Strength Calculated on $C_{29}H_{32}Cl_2N_6 \cdot 4H_3PO_4$
0.25 g

Storage Preserve in tightly closed containers, protected from light.

Piperazine Citrate



$(C_4H_{10}N_2)_3 \cdot 2C_6H_8O_7 \cdot 5H_2O$ 732.74 [110-85-0]

Piperazine Citrate contains not less than 98.5% of $(C_4H_{10}N_2)_3 \cdot 2C_6H_8O_7$, calculated on anhydrous basis.

Description A white crystalline powder or translucent crystalline granule; odourless; taste, sour; slightly hygroscopic.

Very soluble in water; slightly soluble in methanol; insoluble in ethanol, chloroform, ether, benzene or petroleum ether.

Identification (1) Dissolve about 0.1 g in 5 ml of water, add 0.5 g of sodium bicarbonate, 0.5 ml of potassium ferricyanide TS and 1 drop of mercury, shake vigorously for 1 minute and allow to stand for about 20 minutes at a temperature above 20°C, a red colour is slowly produced.

(2) The aqueous solution yields the reactions characteristic of citrates (Appendix III).

Primary amines and ammonia Dissolve 0.50 g in 10 ml of water and 1.0 ml of 10% sodium hydroxide solution. Add 1.0 ml each of acetone and sodium nitroprusside TS, mix well and allow to stand for exact 10 minutes. Measure the absorbance of the resulting solution at 520 nm and 600 nm (Appendix IV B), using a blank consisting of the same quantities of the reagents, but substituting water for the sodium hydroxide solution, the ratio of the absorbance at 600 nm to that at 520 nm is not greater than 0.50 (equivalent to about 0.7% of primary amines and ammonia).

Water 10.0%-14.0% (Appendix VIII M, method 1 A).

Residue on ignition Not more than 0.1% (Appendix VII

Iron Dissolve 2.0 g in a mixture of 35 ml of water and 3 ml of hydrochloric acid, add 50 mg of ammonium persulfate, 3 ml of ammonium thiocyanate solution (30 → 100) and sufficient water to produce 50 ml, mix well. Extract with 20 ml of *n*-butanol. Any colour produced in the *n*-butanol layer is not more intense than that of a reference using 1.0 ml of iron standard solution prepared in a similar manner (0.0005%).

Heavy metals Dissolve 2.0 g in 20 ml of water, add 4.0 ml of dilute hydrochloric acid, carry out the limit test for heavy metals (Appendix VIII H, method 1); not more than 0.001%.

Assay Dissolve about 0.1 g, accurately weighed, in 30 ml of glacial acetic acid, add 1 drop of crystal violet IS, titrate with perchloric acid (0.1 mol/L) VS until the solution changes to greenish-blue. Perform a blank determination and make any necessary correction. Each ml of perchloric acid (0.1 mol/L) VS is equivalent to 10.71 mg of $(C_4H_{10}N_2)_3 \cdot 2C_6H_8O_7 \cdot 5H_2O$.

Category Anthelmintic.

Storage Preserve in tightly closed containers, protected from light.

Preparation (1) Piperazine Citrate Syrup
(2) Piperazine Citrate Tablets

Piperazine Citrate Syrup

Piperazine Citrate Syrup contains not less than 14.4% and not more than 17.6% (g/ml) of the labelled amount of piperazine citrate $[C_4H_{10}N_2]_3 \cdot 2C_6H_8O_7 \cdot 5H_2O$.

Formula	Piperazine Citrate	160 g
	Sucrose	650 g
	Preservative	a sufficient quantity
	Flavouring agent	a sufficient quantity
	Water	a sufficient quantity
	Total	1000 ml

Description A clear, viscous liquid with an aromatic odour.

Identification Dilute 3 ml with 2 ml of Water. Complies with the test (1) for Identification described under Piperazine Citrate.

Relative density 1.270–1.305 (Appendix VI A).

Other requirements Complies with the general requirements for syrups (Appendix I K).

Assay Transfer accurately 5 ml with a “to contain” pipet to a 50 ml volumetric flask. Wash the inner wall of the pipet with a small amount of water, add the washings into the flask, dilute to volume with water and mix well. Transfer accurately 10 ml into a 150 ml beaker, add 70 ml of trinitrophenol TS, stir and heat until the supernatant liquid is clear. Cool to room temperature and allow it to stand for one hour. Filter through a tared sintered glass crucible previously dried to constant weight at 105°C. Wash the precipitate with successive quantities of a saturated solution of piperazine trinitrophenol derivative $(C_4H_{10}N_2 \cdot 2C_6H_3N_3O_7)$. Dry to constant weight at 105°C and weigh accurately. Each g of precipitate is equivalent to 0.4487 g of $(C_4H_{10}N_2)_3 \cdot 2C_6H_8O_7 \cdot 5H_2O$.

Category As described under Piperazine Citrate.

Storage Preserve in tightly closed containers, protected

from light.

Piperazine Citrate Tablets

Piperazine Citrate Tablets contain not less than 93.0% and not more than 107.0% of the labelled amount of piperazine citrate $[(C_4H_{10}N_2)_3 \cdot 2C_6H_8O_7 \cdot 5H_2O]$.

Description White tablets.

Identification To a quantity of the finely powdered tablets, equivalent to about 0.5 g of piperazine citrate, add 20 ml of water, shake to dissolve piperazine citrate and filter. The filtrate complies with the tests for Identification described under Piperazine Citrate.

Other requirements Comply with the general requirements for tablets (Appendix I A).

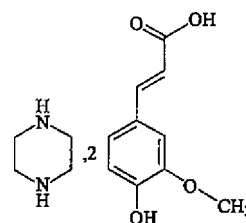
Assay Weigh and powder 20 tablets. Weigh accurately a quantity of the powder equivalent to about 0.1 g of piperazine citrate and carry out the Assay described under Piperazine Citrate. Each ml of perchloric acid (0.1 mol/L) VS is equivalent to 12.21 mg of $(C_4H_{10}N_2)_3 \cdot 2C_6H_8O_7 \cdot 5H_2O$.

Category As described under Piperazine Citrate.

Strength (1) 0.25 g (2) 0.5 g

Storage Preserve in tightly closed containers, protected from light.

Piperazine Ferulate



$C_4H_{10}N_2 \cdot 2C_{10}H_{10}O_4$ 474.51

Piperazine Ferulate is 3-methoxy-4-hydroxy cinnamate piperazine. It contains not less than 99.0% of $C_4H_{10}N_2 \cdot 2C_{10}H_{10}O_4$, calculated on the dried basis.

Description White or almost white crystalline flakes or crystalline powder; odourless; taste, slightly astringency. Slightly soluble in water; very slightly soluble in ethanol; practically insoluble in trichloromethane.

Specific absorbance Protected from light throughout the procedure. Measure the absorbance of a solution of 6 µg per ml in water at 310 nm (Appendix IV A), the value of A (1%, 1 cm) is 637–669.

Identification (1) The light absorption of a solution of 6 µg per ml in water exhibits two maxima at 287 nm and 310 nm, and a minimum at 254 nm (Appendix IV A).

(2) The infrared absorption spectrum (Appendix IV C) is concordant with the reference spectrum of piperazine ferulate (Appendix XVI).

Acidity An aqueous solution of 0.1 mg per ml, pH 4.5–6.0 (Appendix VI H).

Related substances Protected from light throughout the

procedure. Carry out the method for thin-layer chromatography (Appendix V B), using silica gel G as the coating substance and a mixture of ethyl acetate-methanol-concentrated ammonia solution (10 : 6 : 3) as mobile phase. Apply separately to the plate 20 μ l each of three solutions in methanol containing (1) 80 μ g per ml of ferulic acid CRS, (2) 50 μ g per ml of piperazine CRS and (3) 5 mg per ml of the substance being examined. After developing and removal of the plate, dry it in air, visualize in iodine vapour and observe immediately. Not more than 2 secondary spots, other than the spots correspond to the principal spots obtained with solutions (1), (2) are observed with solution (3); and any secondary spot is not more intense than the principle spot obtained with solution (1).

Loss on drying When dried in vacuum to constant weight at 80°C, loses not more than 0.5% of its weight (Appendix VIII L).

Residue on ignition Not more than 0.1% (Appendix VIII N), using 1.0 g.

Heavy metals Carry out the limit test for heavy metals (Appendix VIII H, method 2), using the residue obtained in the test for Residue on ignition: not more than 0.001%.

Assay Dissolve about 0.2 g, accurately weighed, in 20 ml glacial acetic acid, add 1 drop of crystal violet IS, titrate with perchloric acid (0.1 mol/L) VS until the colour changes to bluish green. Perform a blank determination and make any necessary correction. Each ml of perchloric acid (0.1 mol/L) VS is equivalent to 23.73 mg of $C_4H_{10}N_2 \cdot 2C_{10}H_{10}O_4$.

Category Anticoagulant.

Storage Preserve in tightly closed containers, protected from light.

Preparation Piperazine Ferulate Tablets

Piperazine Ferulate Tablets

Piperazine Ferulate Tablets contain not less than 90.0% and not more than 110.0% of the labelled amount of piperazine ferulate ($C_4H_{10}N_2 \cdot 2C_{10}H_{10}O_4$).

Description White or almost white tablets.

Identification The light absorption of the solution obtained under the Assay exhibits maxima at 287 nm and 310 nm, and minimum at 254 nm (Appendix IV A).

Dissolution Protected from light throughout the procedure. Carry out the dissolution test (Appendix X C, method 1), using 1000 ml of water as the dissolution medium, adjust the rotational speed of the basket to 50 rpm. Withdraw 10 ml of the solution at 30 minutes and filter. Dilute 3 ml of the successive filtrate, accurately measured, with water to 25 ml (for strength 50 mg) or 50 ml (for strength 100 mg), shake thoroughly, carry out the method as described under the Assay. Calculate the dissolution of $C_4H_{10}N_2 \cdot 2C_{10}H_{10}O_4$ from each tablet. Not less than 75% of the labelled amount is dissolved.

Other requirements Comply with the general requirements for tablets (Appendix I A).

Assay Protected from light throughout the procedure. Weigh accurately and powder 10 tablets. Weigh accurately a

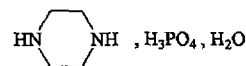
piperazine ferulate into a 250 ml volumetric flask, dissolve and dilute with water to volume, mix well and filter. Transfer accurately 5 ml of the successive filtrate to a 100 ml volumetric flask, dilute to volume with water and mix well. Measure the absorbance of the resulting solution at 310 nm (Appendix IV A). Dissolve a quantity of piperazine ferulate CRS, weigh accurately in water to produce a reference solution of 6 μ g per ml. Measure the absorbance of the reference solution in the same manner. Calculate the content of $C_4H_{10}N_2 \cdot 2C_{10}H_{10}O_4$.

Category As described under Piperazine Ferulate.

Strength (1) 50 mg (2) 100 mg

Storage Preserve in tightly closed containers, protected from light.

Piperazine Phosphate



$C_4H_{10}N_2 \cdot H_3PO_4 \cdot H_2O$ 202.15 [18534-18-4]

Piperazine Phosphate contains not less than 98.5% of $C_4H_{10}N_2 \cdot H_3PO_4$, calculated on the anhydrous basis.

Description White crystalline scales of a crystalline powder; odourless; taste, slightly acerbic. Sparingly soluble in water; soluble in boiling water; insoluble in ethanol, chloroform or ether.

Identification (1) Dissolve 0.1 g in 5 ml of water, add 0.5 g of sodium bicarbonate, 0.5 ml of potassium ferricyanide TS and 1 drop of mercury. Shake vigorously for 1 minute and allow to stand for 20 minutes at a temperature above 20°C; a reddish colour develops slowly.

(2) The infrared absorption spectrum (Appendix IV C) is concordant with the reference spectrum of piperazine phosphate (Appendix XVI).

(3) The aqueous solution yields the reactions characteristic of phosphates (Appendix III).

Primary amines and ammonia Dissolve 0.50 g in 10 ml of water and 1.0 ml of 10% sodium hydroxide solution. Add 1.0 ml of acetone and 1.0 ml of sodium nitroprusside TS, mix and allow to stand for exactly 10 minutes. Measure the absorbance of the resulting solution at 520 nm and 600 nm (Appendix IV A), using a blank consisting of the same quantities of the reagents, but using water in place of sodium hydroxide solution. The ratio A_{600}/A_{520} is not greater than 0.50 (equivalent to about 0.7% of primary amines and ammonia).

Water 8.0%-9.5% (Appendix VIII M, method 1 A).

Iron Dissolve 2.0 g in 35 ml of water and 5 ml of hydrochloric acid. Add 50 mg of ammonium persulfate, 3 ml of ammonium thiocyanate solution (30→100) and dilute with water to 50 ml, mix well. Extract the solution with 20 ml of *n*-butanol. Any colour produced in the *n*-butanol layer is not more intense than that of a reference using 1.0 ml of iron standard solution (0.0005%).

Heavy metals Dissolve 2.0 g in 20 ml of water and 4 ml of dilute hydrochloric acid, carry out the limit test for heavy metals (Appendix VIII H, method 1): not more than

Assay Dissolve about 80 mg, accurately weighed, in 4 ml of dehydrated formic acid by warming. Add 50 ml of glacial acetic acid and 1 drop of crystal violet IS, titrate with perchloric acid (0.1 mol/L) VS until the colour changes to green. Perform a blank determination and make any necessary correction. Each ml of perchloric acid (0.1 mol/L) VS is equivalent to 9.207 mg of $C_4H_{10}N_2 \cdot H_3PO_4$.

Category Anthelmintic.

Storage Preserve in tightly closed containers.

Preparation Piperazine Phosphate Tablets

Piperazine Phosphate Tablets

Piperazine Phosphate Tablets contain not less than 93.0% and not more than 107.0% of the labelled amount of piperazine phosphate ($C_4H_{10}N_2 \cdot H_3PO_4 \cdot H_2O$).

Description White tablets.

Identification To a quantity of powdered tablets equivalent to about 0.5 g of piperazine phosphate add 20 ml of water, heat and shake well and filter. The filtrate complies with the tests (1) and (3) for Identification described under Piperazine Phosphate.

Other requirements Comply with the general requirements for tablets (Appendix I A).

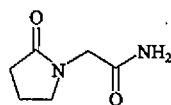
Assay Weigh accurately and powder 10 tablets. To a quantity of the powder equivalent to about 1 g of piperazine phosphate, accurately weighed, in a 100 ml volumetric flask add 90 ml of water, shake thoroughly, dilute with water to volume and mix. Filter, measure accurately 10 ml of the successive filtrate, add 70 ml of trinitrophenol TS, stir and warm until the supernatant liquid is clear. Cool to room temperature, allow to stand for 1 hour, filter through a sintered glass crucible previously dried to constant weight at 105°C, and wash the residue with successive quantities of saturated solution of piperazine trinitrophenol derivative ($C_4H_{10}N_2 \cdot 2C_6H_3N_3O_7$). Dry the residue to constant weight at 105°C and weigh. Each g of residue is equivalent to 0.3714 g of $C_4H_{10}N_2 \cdot H_3PO_4 \cdot H_2O$.

Category As described under Piperazine Phosphate.

Strength (1) 0.2 g (2) 0.5 g

Storage Preserve in tightly closed containers.

Piracetam



Piracetam is 2-oxyl-1-pyrrolidinoacetamide. It contains not less than 98.0% and not more than 102.0% of $C_6H_{10}N_2O_2$, calculated on the dried basis.

Description White or almost white crystalline powder; odourless, taste, slightly bitter. Freely soluble in water; sparingly soluble in ethanol; practically insoluble in ether.

Melting range 151-154°C (Appendix III C)

Identification (1) To 0.1 g add several drops of water to dissolve, and add a drop of potassium permanganate TS and sodium hydroxide TS respectively, mix well, a violet colour is produced, turning to blue gradually, and green at last.

(2) The retention time of principal peak of piracetam in the substance being examined in the chromatogram obtained in the Assay is identical with that of the principal peak of piracetam CRS in the chromatogram of the reference solution correspondingly.

(3) The infrared absorption spectrum (Appendix IV C) is concordant with the reference spectrum of piracetam (Appendix XIII 185).

Clarity and colour of solution Dissolve 2.0 g in 10 ml of water, the solution is clear and colourless; any opalescence produced is not more pronounced than that of reference suspension 1 (Appendix IX B).

Acidity Dissolve 1.0 g in 20 ml of water, pH 5.0-7.0 (Appendix VI H).

Related substances Prepare test solution of 0.5 mg of piracetam per ml and reference solution of 5 µg of piracetam CRS per ml with the mobile phase. Carry out the chromatography conditions as described under Assay. Inject 10 µl of the reference solution into column. Adjust the sensitivity of the detector so that the principal peak height in the chromatogram is about 10% of the full scale of the recorder. Inject separately 10 µl of above two solutions into column, and record the chromatogram for three times of the retention time of the principal peak. The sum of the areas of all impurity peaks in the chromatogram obtained with test solution is not greater than the principal peak in the chromatogram obtained with reference solution.

Loss on drying When dried to constant weight at 105°C, losses not more than 0.5% of its weight (Appendix VIII L).

Residue on ignition Not more than 0.1% (Appendix VIII N).

Heavy metals Dissolve 1.0 g in 25 ml of water. Carry out the limit test for heavy metals (Appendix VIII H, method 1): not more than 0.002%.

Assay Carry out the method for high performance liquid chromatography (Appendix V D), using a column packed with octadecylsilane bonded silica gel and a mixture of methanol-water (10 : 90) as the mobile phase. Detection wavelength is 210 nm, the number of theoretical plates of the column is not less than 2000, calculated with reference to the peak of piracetam.

Procedure Dissolve a sufficient quantity, accurately weighed, and dilute with the mobile phase to produce a solution of 0.1 mg of piracetam per ml, inject 10 µl of the solution into the column. Record the peak areas correspondingly obtained in the chromatogram. Repeat the operation, using piracetam CRS instead of the substance being examined, calculate the content of $C_6H_{10}N_2O_2$, with respect to the peak area obtained in the chromatogram by external standard method.

Category Nootropic.

Storage Preserve in tightly closed containers and protected from light.

Preparation (1) Piracetam and Sodium Chloride Injection
(2) Piracetam Capsules
(3) Piracetam Injection
(4) Piracetam Oral Solution
(5) Piracetam Tablets

Piracetam and Sodium Chloride Injection

Piracetam and Sodium Chloride Injection is a sterile solution of Piracetam and Sodium Chloride in Water for Injection. It contains not less than 95.0% and not more than 105.0% of the labelled amount of piracetam ($C_6H_{10}N_2O_2$) and sodium chloride (NaCl) respectively.

Description A clear, colourless liquid.

Identification (1) To a quantity equivalent to about 0.1 g of piracetam add a drop of potassium permanganate TS and sodium hydroxide TS respectively, mix well, a violet colour is produced, turning to blue gradually, and green at last.

(2) The retention time of principal peak of piracetam in the substance being examined in the chromatogram obtained in the Assay is identical with that of the principal peak of piracetam CRS in the chromatogram of the reference solution correspondingly.

(3) Yields the reactions characteristic of sodium salts and chlorides (Appendix III).

pH value 4.0-7.0 (Appendix VI H).

Related substances Prepare test solution of 0.5 mg of piracetam per ml and reference solution of 5 μ g of piracetam per ml with mobile phase. Inject 10 μ l of the reference solution into column. Carry out the chromatography conditions as described under Assay. Adjust the sensitivity of the detector so that the principal peak height in the chromatogram is about 10% of the full scale of the recorder. Inject separately 10 μ l of above two solutions into column, and record the chromatogram for three times of the retention time of the principal peak. The sum of the areas of all impurity peaks in the chromatogram obtained with the test solution is not greater than 1.5 times the area of the principal peak in the chromatogram obtained with reference solution.

Heavy metals To 20 ml add 2 ml of acetate BS pH 3.5 and sufficient water to produce 25 ml. Carry out the limit test for heavy metals (Appendix VIII H, method 1): not more than 0.00001%.

Bacterial endotoxin Carry out the test for bacterial endotoxin (Appendix XI C): less than 0.5 EU per ml.

Other requirements Complies with the general requirements for injection (Appendix I B).

Assay Piracetam Dilute a quantity, accurately measured, with mobile phase to produce a solution of 0.1 mg of piracetam per ml. Carry out the method as described under Assay of Piracetam, beginning at the words "inject 10 μ l of the solution into the column".

Sodium chloride To 10 ml of injection, accurately measured, add 30 ml of water, 5 ml of dextrin solution (1 \rightarrow 50), 2 ml of borax solution (2.5 \rightarrow 100) and 5-8 drops of fluorescein IS, titrate with silver nitrate (0.1 mol/ml) VS. Each ml of silver nitrate (0.1 mol/ml) VS is equivalent to 5.844 mg of NaCl.

Category As described under Piracetam.

Strength 250 ml : 8 g of Piracetam and 2.25 g of Sodium Chloride

Storage Preserve in well closed containers and protected from light.

Piracetam Capsules

Piracetam Capsules contain not less than 93.0% and not more than 107.0% of the labelled amount of piracetam ($C_6H_{10}N_2O_2$).

Description Capsules containing a white or almost white granular powder or powder.

Identification (1) To a quantity equivalent to about 0.5 g of piracetam, add 10 ml of water, shake to dissolve and filter, to 2 ml of the filtrate add a drop of potassium permanganate TS and sodium hydroxide TS respectively, mix well, a violet colour is produced, turning to blue gradually, and green finally.

(2) The retention time of principal peak of piracetam in the substance being examined in the chromatogram obtained in the Assay is identical with that of the principal peak of piracetam CRS in the chromatogram of the reference solution correspondingly.

Other requirements Comply with the general requirements for capsules (Appendix I E).

Assay Weigh accurately and dissolve a quantity of the mixed contents of capsules obtained in the test for weight variation of content equivalent to 0.1 g of piracetam with mobile phase in a 100 ml volumetric flask, and dilute to volume, mix well and filter, transfer 5 ml of the successive filtrate accurately to a 50 ml volumetric flask and dilute with mobile phase to volume, mix well. Carry out the method as described under Assay of Piracetam, beginning at the words "inject 10 μ l of the solution into the column".

Category As described under Piracetam.

Strength (1) 0.2 g (2) 0.4 g

Storage Preserve in tightly closed containers and protected from light.

Piracetam Injection

Piracetam Injection is a sterile solution of Piracetam in Water for Injection. It contains not less than 95.0% and not more than 105.0% of the labelled amount of piracetam ($C_6H_{10}N_2O_2$).

Description A clear, colourless liquid.

Identification (1) To a quantity equivalent to about 0.1 g of piracetam add a drop of potassium permanganate TS and sodium hydroxide TS respectively, mix well, a violet colour is produced, turning to blue gradually, and green at last.

(2) The retention time of principal peak of piracetam in the substance being examined in the chromatogram obtained in the Assay is identical with that of the principal peak of piracetam CRS in the chromatogram of the reference solution correspondingly.

pH value 4.0-7.0 (Appendix VI H).

Related substances Prepare test solution of 0.5 mg of piracetam per ml and reference solution of 5 μ g of piracetam per ml with mobile phase. Carry out the chromatography conditions as described under Assay. Inject 10 μ l of the reference solution into column. Adjust the sensitivity of the detector so that the principal peak height in the chromatogram is about 10% of the full scale of the recorder. Inject separately 10 μ l of above two solutions into column,

and record the chromatogram for three times of the retention time of the principal peak. The sum of the area of all impurity peaks in the chromatogram obtained with test solution is not greater than 1.5 times of the area of the principal peak in the chromatogram obtained with reference solution.

Bacterial endotoxin Carry out the test for bacterial endotoxin (Appendix XI C): less than 0.0375 EU per 1 mg of piracetam.

Other requirements Complies with the general requirements for injection (Appendix I B).

Assay Dilute an accurately measured quantity with mobile phase to produce a solution of 0.1 mg of piracetam per ml. Carry out the method as described under Assay of Piracetam, beginning at the words "inject 10 μ l of the solution into the column".

Category As described under Piracetam.

Strength (1) 20 ml : 4 g (2) 5 ml : 1 g

Storage Preserve in well closed containers and protected from light.

Piracetam Oral Solution

Piracetam Oral Solution contains not less than 93.0% and not more than 107.0% of the labelled amount of piracetam ($C_6H_{10}N_2O_2$).

Description A clear, orange yellow to brown yellow liquid; sweet; taste, slightly bitter.

Identification (1) To a quantity equivalent to about 0.5 g of piracetam, add 10 ml of chloroform, shake and allow to separate into two layers; to 3 ml of chloroform solution add 5 drops of potassium permanganate TS and sodium hydroxide TS respectively, shake, a green colour is produced in the upper layer.

(2) The retention time of principal peak of piracetam in the substance being examined in the chromatogram obtained in the Assay is identical with that of the principal peak of piracetam CRS in the chromatogram of the reference solution correspondingly.

Relative density Not less than 1.10 (Appendix VI A).

pH value 4.0-6.5 (Appendix VI H).

Related substances Prepare test solution of 0.5 mg of piracetam per ml and reference solution of 5 μ g of piracetam per ml with mobile phase. Carry out the chromatography conditions as described under Assay. Inject 10 μ l of the reference solution into column. Adjust the sensitivity of the detector so that the principal peak height in the chromatogram is about 10% of the full scale of the recorder. Inject separately 10 μ l of above two solutions into column, and record the chromatogram for three times of the retention time of the principal peak. The sum of the areas of all impurity peaks in the chromatogram obtained with test solution is not greater than 1.5 times of the area of the principal peak in the chromatogram obtained with reference solution.

Other requirements Complies with the general requirements for oral solution (Appendix I O).

Assay Dilute a quantity, accurately measured, with mobile phase to produce a solution of 0.1 mg of piracetam per ml. Carry out the method as described under Assay of Piracetam, beginning at the words "inject 10 μ l of the solution into the column".

column".

Category As described under Piracetam.

Strength 10 ml : 0.8 g

Storage Preserve in tightly closed containers and protected from light.

Piracetam Tablets

Piracetam Tablets contain not less than 95.0% and not more than 105.0% of the labelled amount of piracetam ($C_6H_{10}N_2O_2$).

Description White or almost white tablets.

Identification (1) To a quantity of powdered tablets equivalent to about 0.5 g of piracetam, add 10 ml of water, shake to dissolve and filter, to 2 ml of the filtrate add a drop of potassium permanganate TS and sodium hydroxide TS respectively, mix well, a violet colour is produced, turning to blue gradually, and green at last.

(2) The retention time of principal peak of piracetam in the substance being examined in the chromatogram obtained in the Assay is identical with that of the principal peak of piracetam CRS in the chromatogram of the reference solution.

Other requirements Comply with the general requirements for tablets (Appendix I A).

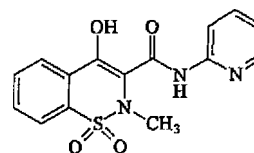
Assay Weigh accurately and powder 20 tablets. Dissolve an accurately weighed quantity of the powder equivalent to 0.1 g of piracetam with mobile phase in a 100 ml volumetric flask, and dilute to volume, mix well and filter, transfer accurately 5 ml of the successive filtrate to a 50 ml volumetric flask and dilute with mobile phase to volume, mix well. Carry out the method as described under Assay of Piracetam, beginning at the words "inject 10 μ l of the solution into the column".

Category As described under Piracetam.

Strength 0.4 g

Storage Preserve in tightly closed containers and protected from light.

Piroxicam



$C_{15}H_{13}N_3O_4S$ 331.35

[36322-90-4]

Piroxicam is 2-methyl-4-hydroxy-N-(2-pyridyl)-2H-1,2-benzothiazine-3-carboxamide 1,1-dioxide. It contains not less than 98.5% of $C_{15}H_{13}N_3O_4S$, calculated on the dried basis.

Description Almost white or pale yellowish-green crystalline powder; odourless, tasteless. Freely soluble in chloroform; sparingly soluble in acetone; slightly soluble in ethanol or ether; practically insoluble in water; soluble in acid; sparingly soluble in alkali.

decomposition.

Identification (1) Dissolve about 30 mg in 1 ml of chloroform, add 1 drop of ferric trichloride TS; a rose-colour is produced.

(2) The light absorption of a solution of 5 µg per ml in 0.1 mol/L methanolic hydrochloric acid solution exhibits two maxima at 243 nm and 334 nm respectively. (Appendix IV A).

(3) The infrared absorption spectrum (Appendix IV C) is concordant with the reference spectrum of piroxicam (Appendix XVI).

Related substances Carry out the method for thin-layer chromatography (Appendix V B), using silica gel GF₂₅₄ [a mixture of 0.5% sodium carboxy methyl cellulose solution with 1 mol/L sodium hydroxide solution (1 : 1) as the binder] as the coating substance and a mixture of chloroform-acetone-methanol (25 : 25 : 5) as the mobile phase. Apply separately to the plate 10 µl of each of two solutions in chloroform containing (1) 20 mg per ml, (2) 0.2 mg per ml of the substance being examined. After developing and removed of the plate, dry it in air, examine under an ultraviolet light (254 nm); any spot, other than the principal spot, obtained in chromatogram of solution (1) is not more intense than the principal spot obtained in chromatogram of solution (2).

Chlorides Spread 2 g of anhydrous sodium carbonate on the bottom and around of a crucible, place 1.0 g on the anhydrous sodium carbonate, moisten with water, after drying, heat gently until it is completely incinerated, cool. Add a quantity of water to dissolve, filter, wash the crucible and filter with water. Combine the filtrate and washings, add water to produce 20 ml, mix well. Measure 1 ml of the filtrate, neutralize by adding nitric acid dropwise, then add 1 drop of nitric acid, mix well. Heat in a 75-85°C water bath to expel hydrogen sulfide thoroughly. Allow to cool, neutralize by adding 1% sodium carbonate solution dropwise, add water to produce 25 ml, carry out the limit test for chlorides (Appendix VIII A). Any opalescence produced is not more pronounced than that of a reference using 5.0 ml of sodium chloride standard solution (0.1%).

Loss on drying When dried to constant weight at 105°C, loses not more than 0.5% of its weight (Appendix VIII L).

Residue on ignition Not more than 0.1% (Appendix VIII N), use 1.0 g.

Heavy metals Carry out the limit test for heavy metals (Appendix VIII H, method 2), using the residue obtained in the test for Residue on ignition; not more than 0.001%.

Arsenic To 10 ml of the remained solution obtained in the test for chloride add 5 ml of hydrochloric acid and 13 ml of water, carry out the limit test for arsenic (Appendix VIII J, method 1); not more than 0.0004%.

Assay Dissolve about 0.2 g, accurately weighed, in 20 ml of glacial acetic acid, add 1 drop of crystal violet IS, titrate with perchloric acid (0.1 mol/L) VS until the colour changes to bluish-green. Perform a blank determination and make any necessary correction. Each ml of perchloric acid (0.1 mol/L) VS is equivalent to 33.14 mg of C₁₅H₁₃N₃O₄S.

Category Antipyretic and analgesic non-steroids anti-inflammatory agent.

Storage Preserve in tightly closed containers, protected from light.

Preparation (1) Piroxicam Capsules

(4) Piroxicam Ointment

(5) Piroxicam Tablets

Piroxicam Capsules

Piroxicam Capsules contain not less than 90.0% and not more than 110.0% of the labelled amount of piroxicam (C₁₅H₁₃N₃O₄S).

Identification A quantity of the contents of capsules complies with the tests for Identification (1), (2) as described under Piroxicam tablets.

Other requirements Comply with the general requirements for capsules (Appendix I E).

Assay Mix the contents obtained in the test for weight variation of contents, carry out the Assay as described under piroxicam tablets, beginning at the words "Weigh accurately a quantity, equivalent to about 10 mg of piroxicam..."

Category, Storage As described under piroxicam.

Strength (1) 10 mg (2) 20 mg

Piroxicam Gel

Piroxicam Gel contains not less than 90.0% and not more than 110.0% of the labelled amount of Piroxicam (C₁₅H₁₃N₃O₄S).

Description A yellow-green gel.

Identification (1) To a little of the gel add 1 drop of ferric chloride TS, stir well, a rose red colour is produced.

(2) The light absorption of the test solution obtained from assay exhibits maxima at 252 nm, 286 nm and 353 nm.

Acidity or alkalinity Dissolve a quantity of the gel in freshly boiled and cooled water to produce an 1% emulsion of piroxicam, pH 7.0-8.5 (Appendix VI H).

Other requirements Complies with the general requirements for gel (Appendix I U).

Assay Transfer about 2 g, rapidly accurately weighed, to a beaker. Add a quantity of borate-potassium chloride BS (pH 9.0), stir well to disperse the gel, add borate-potassium chloride BS with stirring to dissolve piroxicam, transfer it to a 100 ml volumetric flask, wash the container with borate-potassium chloride BS. Transfer the washings to the same volumetric flask, dilute with the same solvent to volume, shake thoroughly and filter. Transfer 5 ml of the successive filtrate, accurately measured, in a 50 ml volumetric flask, dilute to volume with borate-potassium chloride BS, mix well. Dissolve a quantity of Piroxicam CRS, accurately weighed, in borate acid-potassium chloride BS (pH 9.0) to produce a solution of 10 µg per ml. Filter the two resulting solutions through a membrane with pores of 0.8 µm in diameter, and measure the absorbances of the two filtrates at 353 nm respectively, calculate the content of C₁₅H₁₃N₃O₄S.

Category As described under Piroxicam.

Strength 10 g : 50 mg

Storage Preserve in tightly closed containers, stored in a cool place, protected from light.

Piroxicam Injection

Piroxicam Injection is a sterile solution of Piroxicam and suitable auxiliary solvent in water for Injection. It contains not less than 93.0% and not more than 107.0% of the labelled amount of Piroxicam ($C_{15}H_{13}N_3O_4S$).

Description A clear, light yellowish-green liquid.

Identification (1) To a quantity of the injection add 1 mol/L hydrochloric acid solution to acidify. Extract with chloroform by shaking, to the chloroform layer, add 1 drop of ferric trichloride TS; a rose-red colour is produced gradually.

(2) To a few drops of chloroform extract obtained in test for Identification (1) add bromine TS until the yellow colour keeps lasting, then add saturated solution of sulfosalicylic acid, until the yellow colour fades, add a quantity of 5% potassium iodide solution and several drops of starch IS, a blue colour is produced.

pH value 8.5-9.5 (Appendix VI H).

Other requirements Complies with the general requirements for injections (Appendix I B).

Assay Transfer accurately a quantity of the injection equivalent to about 0.2 g of Piroxicam to a separator, acidify with 2 ml of 1 mol/L hydrochloric acid solution. Extract with chloroform for 4 times, using 75 ml initially, then with 25 ml each. Combine the chloroform extracts, wash with water twice, 2 ml each. Discard the washing solution and evaporate the chloroform extract on a water bath to dryness, then dry the residue at 105°C for 3 hours. Dissolve the residue with 30 ml of glacial acetic acid, add 1 drop of crystal violet IS, titrate with perchloric acid (0.1 mol/L) VS until the colour changes to blue. Perform a blank determination to make any necessary correction. Each ml of perchloric acid (0.1 mol/L) VS is equivalent to 33.13 mg of $C_{15}H_{13}N_3O_4S$.

Category As described under piroxicam.

Strength 2 ml : 20 mg

Storage Preserve in well closed containers, protected from light.

Piroxicam Ointment

Piroxicam Ointment contains not less than 90.0% and not more than 110.0% of the labelled amount of piroxicam ($C_{15}H_{13}N_3O_4S$).

Description A pale-yellow ointment.

Identification (1) To a quantity of the ointment equivalent to about 40 mg of piroxicam, add 10 ml of chloroform, heat to melt on a water bath at 70°C. Allow to cool in ice bath, filter, add 1 drop of ferric chloride TS to the filtrate; a rose red colour is produced.

(2) The light of absorption of the solution obtained in Assay exhibits two maxima at 243 nm and 334 nm (Appendix IV A).

Other requirements Complies with the general requirements for ointment (Appendix I F).

ointment equivalent to about 10 mg of piroxicam to a 100 ml beaker, add 30 ml of 0.01 mol/L methanolic hydrochloric acid solution, stir on a water bath at 70°C, extract for 10 min, allow to cool in an ice bath to freeze the ointment base and filter. Transfer the filtrate to a 100 ml volumetric flask, extract the residue as described above twice more. Combine the extracts, dilute with 0.01 mol/L methanolic hydrochloric acid solution to volume, mix well. Measure the absorbance of the resulting solution at 334 nm (Appendix IV A). Calculate the content of $C_{15}H_{13}N_3O_4S$, taking 856 as the value of A (1%, 1 cm).

Category As described under piroxicam.

Strength (1) 10 g : 0.1 g (2) 20 g : 0.2 g

Storage Preserve in tightly closed containers, stored in a cool place.

Piroxicam Tablets

Piroxicam Tablets contain not less than 90.0% and not more than 110.0% of the labelled amount of Piroxicam ($C_{15}H_{13}N_3O_4S$).

Description Almost white pale yellowish-green tablets or sugar coated tablets, with an almost white or pale yellowish-green core.

Identification (1) Shake a quantity of the powdered tablets, with the sugar coat removed, equivalent to about 40 mg of piroxicam with 10 ml of chloroform to dissolve piroxicam and filter. The filtrate complies with the tests for Identification (1) described under Piroxicam.

(2) The light absorption of a solution obtained in the Assay exhibits maxima at 243 nm and 334 nm (Appendix IV A).

Dissolution Carry out the method for dissolution test (Appendix X C, method 2), using 900 ml hydrochloric acid solution (9→1000) as the dissolution medium, adjust the rotational speed of the paddle to 75 rpm. Withdraw a quantity of the solution at 40 minutes and filter. Measure accurately 3 ml of the successive filtrate to a 10 ml (for strength 20 mg) or 5 ml (for strength 10 mg) volumetric flask, dilute with dissolution medium to volume, mix well. Weigh accurately a quantity of piroxicam CRS, dilute with dissolution medium to produce a solution of 6 µg per ml. Measure the absorbances of two solutions at 335 nm (Appendix IV A) and calculate the dissolution of piroxicam from each tablet. The dissolution of piroxicam is not less than 70% of the labelled amount.

Other requirements Comply with the general requirements for tablets (Appendix I A).

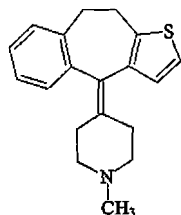
Assay Weigh and powder 20 tablets, with sugar coat removed. Weigh accurately a quantity of the powder equivalent to about 10 mg of piroxicam in 100 ml volumetric flask, dilute with 0.1 mol/L methanolic hydrochloric acid solution to volume, mix well and filter. Discard the initial filtrate, measure accurately 5 ml of the successive filtrate to a 100 ml volumetric flask, dilute with 0.1 mol/L methanolic hydrochloric acid solution to volume, mix well. Measure the absorbance of the resulting solution at 334 nm (Appendix IV A), calculate the content of $C_{15}H_{13}N_3O_4S$, taking 856 as the value of A (1%, 1 cm).

Category As described under Piroxicam.

Strength (1) 10 mg (2) 20 mg

Storage Preserve in tightly closed containers, protected

Pizotifen



$C_{19}H_{21}NS$ 295.45

[15574-96-6]

Pizotifen is 1-methyl-4-(9,10-dihydro-4*H*-benzo [4,5]-cyclohepta [1,2-*b*]-thiophen-4-ylidene)-piperidine. It contains not less than 98.5% of $C_{19}H_{21}NS$, calculated on the dried basis.

Description An almost white crystalline powder; odourless; taste, bitter. Freely soluble in chloroform; sparingly soluble in ethanol; insoluble in water.

Melting range 147-152°C (Appendix VI C).

Specific absorbance Dissolve an accurately weighed quantity in hydrochloric acid solution (0.9 → 1000) to produce a solution of 10 µg per ml. Measure the absorbance at 230 nm, the value of *A* (1%, 1 cm) is 582-618 (Appendix IV A).

Identification (1) To about 5 mg add 1 drop of sulfuric acid, a reddish-brown colour is produced, which disappears on adding 1 ml of water.

(2) The infrared absorption spectrum (Appendix IV C) is concordant with the reference spectrum of pizotifen (Appendix XVI).

(3) Carry out the method for oxygen flask combustion (Appendix VII C), using 5 ml of 5% sodium hydroxide solution and 1 ml of concentrated hydrogen peroxide solution as the absorbing liquid. When the combustion is complete, acidify with dilute hydrochloric acid, the solution yields the reactions characteristic of sulfates (Appendix III).

Related substances Carry out the method for thin-layer chromatography (Appendix V B), using silica gel G as the coating substance, a mixture of butanol-acetic acid-water (4 : 1 : 5) as the mobile phase. Apply separately to the plate 10 µl each of two solutions in ethanol containing (1) 10 mg per ml (2) 0.10 mg per ml of the substance being examined. After developing and removal of the plate, dry it in air, visualize in iodine vapour. Any spot other than the principal spot in the chromatogram obtained with solution (1) is not more intense than the principal spot obtained with solution (2).

Loss on drying When dried to constant weight at 105°C, loses not more than 0.5% of its weight (Appendix VIII L).

Residue on ignition Not more than 0.1% (Appendix VIII N).

Assay Dissolve about 0.2 g, accurately weighed, in 10 ml of glacial acetic acid, add 1 drop of crystal violet IS. Titrate with perchloric acid (0.1 mol/L) VS until the colour changes to blue. Perform a blank determination and make any necessary correction. Each ml of perchloric acid (0.1 mol/L) VS is equivalent to 29.54 mg of $C_{19}H_{21}NS$.

Category Used in treatment of migraine.

Storage Preserve in tightly closed containers, protected

Preparation Pizotifen Tablets

Pizotifen Tablets

Pizotifen Tablets contain not less than 90.0% and not more than 110.0% of the labelled amount of pizotifen ($C_{19}H_{21}NS$).

Description Sugar coated tablets with white core.

Identification To a quantity of the powdered tablets with the coating removed equivalent to about 20 mg of pizotifen, add 20 ml of chloroform, shake well, separate the chloroform layer and filter. Evaporate the filtrate to dryness. The residue complies with tests (1) and (3) for Identification described under pizotifen.

Content uniformity Comply with the requirements (Appendix X E). Triturate 1 tablet with the coating removed with about 40 ml of 0.01 mol/L hydrochloric acid solution in portions and transfer to a 50 ml volumetric flask. Shake thoroughly, dilute with the same solvent to volume, mix well and filter. Proceed as described under Assay.

Dissolution Comply with the requirements for dissolution test (Appendix X C, method 3), using 100 ml of hydrochloric acid solution (9 → 1000) as the dissolution medium, adjust the rotational speed of the paddle to 75 rpm. Withdraw 10 ml of the solution at 45 minutes and filter, the successive filtrate as test solution. Dissolve pizotifen CRS in the dissolution medium to produce a solution of about 5 µg per ml. Measure the absorbance of the resulting solutions at 230 nm (Appendix IV A). Calculate the dissolution of $C_{19}H_{21}NS$ from each tablet. Not less than 70% of the labelled amount is dissolved.

Other requirements Comply with the general requirements for tablets (Appendix I A).

Assay Weigh accurately and powder 20 tablets with coating removed. To an accurately weighed quantity of the powdered tablets equivalent to 5 mg of pizotifen, accurately weighed, in a 100 ml volumetric flask. Add 70 ml of 0.01 mol/L hydrochloric acid solution, shake well, dilute to volume with 0.01 mol/L hydrochloric acid solution, mix well and filter. Transfer 10 ml of the successive filtrate, accurately measured, to a 50 ml volumetric flask, dilute to volume with 0.01 mol/L hydrochloric acid solution, mix well. Measure the absorbance at 230 nm (Appendix IV A). Calculate the content of $C_{19}H_{21}NS$, taking 600 as the value of *A* (1%, 1 cm).

Category As described under Pizotifen.

Strength 0.5 mg

Storage Preserve in tightly closed containers, protected from light.

Polymyxin B Sulfate

Polymyxin B Sulfate is the sulfate salt of a kind of polymyxin has a potency of not less than 6500 Polymyxin B Unit per mg, calculated on the dried basis.

Description White or almost white powder; practically odourless; hygroscopic.

Specific optical rotation -78° to -90° , in a solution of 20 mg per ml in water (Appendix VI E).

Identification (1) Dissolve 2 mg in 5 ml of water and add 5 ml of 10% sodium hydroxide solution. Shake and add dropwise 0.25 ml of 1% copper sulfate solution, shaking after each addition. A reddish-violet colour develops.

(2) **Test solution** Dissolve 5 mg of the substance to be examined in 1 ml of a mixture of equal volumes of hydrochloric acid and water. Heat at 135°C in a sealed tube for 5 hours. Evaporate to dryness on a water-bath and continue the heating until the hydrochloric acid has evaporated. Dissolve the residue in 0.5 ml of water.

Reference solution (a) Dissolve leucine in water to produce a solution of about 2 mg per ml.

Reference solution (b) Dissolve threonine in water to produce a solution of about 2 mg per ml.

Reference solution (c) Dissolve phenylalanine in water to produce a solution of about 2 mg per ml.

Reference solution (d) Dissolve serine in water to produce a solution of about 2 mg per ml.

Carry out the method for thin-layer chromatography (Appendix V B), using silica gel G as the coating substance and a mixture of phenol-water (75 : 25) as the mobile phase (leave the plate to become impregnated with the vapour of the solvent for at least 12 hours). Apply separately to the plate 5 μl each of five solutions above. Dry it at $100-105^{\circ}\text{C}$ and spray with ninhydrin solution. Heat at 110°C . The chromatogram obtained with the test solution shows bands corresponding to those in the chromatograms obtained with reference solutions (a), (b) and (c), but shows no band corresponding to that in the chromatograms obtained with reference solution (d). The chromatogram obtained with the test solution also shows a band with a very low R_f value.

(3) It gives reaction of sulfate (Appendix III).

Acidity An aqueous solution of 20 mg per ml, pH 5.0-7.0 (Appendix VI H).

Clarity and colour of solution Dissolve 5 portions each in water to produce solutions of about 50000 Units per ml, the solutions are clear and colourless (Appendix IX B, IX A).

Phenylalanine Dissolve a quantity, accurately weighed, in 0.1 mol/L hydrochloric acid solution and dilute to 0.4 g per ml with the same solvent. Measure the absorbances (Appendix IV A) at the maxima at 264 nm (A_{264}), 258 nm (A_{258}) and 252 nm (A_{252}) and the absorbances at 300 nm (A_{300}) and 280 nm (A_{280}), calculate the percentage content of phenylalanine from the expression:

$$\frac{9.4787/[W(A_{258} - 0.5 A_{252} + 0.5 A_{264} - 1.8 A_{280} + 0.8 A_{300})]}{100}$$

W: test weight (g)

A: absorbance

Phenylalanine is 9%-12%, calculated on the dried basis.

Loss on drying Not more than 6.0%, when dried at 60°C over diphosphorus pentoxide for 3 hours (Appendix VIII L).

Residue on ignition Not more than 0.75% (Appendix VIII N), using 1.0 g.

Pyrogens Complies with the test for pyrogens (Appendix XI D), using 1 ml of a solution of 20000 Units per ml in sterile water for injection per kg of rabbit's weight.

Sterility Complies with the test for sterility (Appendix XI H, membrane filtration method), using no less than 500 ml of 0.9% sterile sodium chloride solution.

Assay Dissolve an accurately weighed quantity in sterile water to produce a solution of about 10000 Units per ml, carry out the Microbiological Assay of Antibiotics

to 1 mg of Polymyxine B.

Category Polypeptide antibiotic.

Storage Preserve in tightly closed containers, stored in a dry place.

Preparation Polymyxine B sulfate for injection.

Polymyxine B Sulfate for Injection

Polymyxine B Sulfate for Injection is a sterile powder of polymyxine B sulfate. It has a potency of no less than 6500 Polymyxine B Units per mg, calculated on the dried basis. Each container contains not less than 90.0% and not more than 110.0% of the labelled amount of polymyxine B, calculated on the basis of the average weight of contents.

Description A white or almost white powder.

Identification Complies with the tests for Identification described under Polymyxine B Sulfate.

Clarity and colour of solution Dissolve 5 portions each in water to produce solutions of about 50000 Polymyxine B Sulfate Units per ml, the solutions are clear and colourless (Appendix IX B, IX A).

Loss on drying Not more than 7.0%, by decompressed-drying at 60°C over diphosphorus pentoxide for 3 hours (Appendix VIII L).

Acidity, Pyrogens, Sterility Complies with the corresponding requirement described under Polymyxine B Sulfate.

Other requirements Complies with the general requirements for injection (Appendix I B).

Assay Carry out the Assay description under Polymyxine B Sulfate, using an accurately weighed quantity of the mixed contents obtained from the test for weight variation of the contents.

Category As described under Polymyxine B Sulfate.

Strength 500000 Units

Storage Preserve in well closed containers, stored in a dry place.

Poppy Capsule Extractive

Poppy Capsule Extractive is extracted from the capsule of *Papaver somniferum* L., dried and prepared by addition of dried powder of the poppy capsule. It contains not less than 11.0% of morphine, calculated with reference to anhydrous morphine ($\text{C}_{17}\text{H}_{19}\text{NO}_3$).

Description A pale brown powder; odour, characteristic; taste, bitter.

Identification (1) Shake about 0.1 g with 5 ml of 5% acetic acid solution for 2 minutes, add a quantity of ammonia concentrated TS to adjust pH to about 9. Extract with 10 ml a mixture of chloroform-ethanol (9 : 1), transfer the organic layer and evaporate to dryness on a water bath. Add potassium ferricyanide dilute TS to the residue, a blue-green

(2) Shake about 0.1 g with 2 ml water and a few drops of ammonia TS and 10 ml chloroform for 10 minutes. Transfer the chloroform layer and evaporate to dryness on a water bath. Add 2 drops of formaldehyde-sulfuric acid TS to the residue, a deep red colour is produced immediately.

(3) Transfer about 25 mg into a conical flask, add 5 ml of 5% acetic acid solution, in ultrasonic bath for 5 minutes to dissolve morphine and filter. Adjust the filtrate to pH about 10 with ammonia concentrated TS, extract with 10 ml a mixture of chloroform-ethanol (9 : 1). Transfer the organic layer and evaporate in vacuum to dryness. Dissolve the residue in 1 ml of methanol as the test solution. Dissolve a quantity of morphine CRS in methanol to produce a solution of 1.0 mg morphine per ml as the reference solution. Carry out the method for thin-layer chromatography (Appendix V B), using silica gel G as the coating substance and a mixture of ethyl acetate-methanol-concentrated ammonia solution (85 : 10 : 5) as the mobile phase. Apply separately to the plate 10 μ l each of the above two solutions, after developing and removal of the plate, dry it in air and spray with dilute potassium iodobismuthate TS. The principal spot in the chromatogram obtained with the test solution corresponds in colour and position to the principal spot obtained with the reference solution.

Assay Carry out the method for high performance liquid chromatography (Appendix V D), using a column packed with octadecylsilane bonded silica gel and a mixture of 0.05 mol/L potassium dihydrogen phosphate solution-0.0025 mol/L sodium heptanesulfonate solution-acetonitrile (5 : 5 : 2) as the mobile phase. Detection wavelength is 220 nm and the number of the theoretical plates of the column is not less than 1000, calculated with reference to the peak of morphine.

System suitability test of solid phase extraction column

Using a solid phase extraction column packed with octadecylsilane bonded silica gel. Carry out the test as described under the Procedure. Transfer 0.5 ml of a solution in 5% acetic acid solution containing 0.5 mg of morphine CRS per ml, accurately measured, to the column pretreated, collect the eluate into a 5 ml volumetric flask to volume and mix well. Respectively inject 10 μ l of the eluate and the reference solution as described under the Procedure into the column, record the peak areas correspondingly obtained in the chromatogram. The ratio of the peak area of morphine obtained in the chromatogram of the eluate to that of the reference solution is not less than 0.97 and not more than 1.03.

Procedure Wash a solid phase extraction column with 15 ml of a mixture of methanol-water (3 : 1) and 5 ml of water in sequence, then wash the column with the ammonia solution of pH about 9 (add drops of ammonia TS to a quantity of water until the pH value is about 9) until the pH value of the eluate is about 9. Triturate about 10 g of the substance being examined (let it through No. 5 sieve). Transfer about 1 g, accurately weighed, into a 200 ml volumetric flask, add a quantity of 5% acetic acid solution, in ultrasonic bath for 30 minutes to dissolve morphine, cool and dilute to volume with 5% acetic acid solution, mix well and filter. Measure accurately 0.5 ml of the successive filtrate to the above washed column, drop a quantity of ammonia TS to adjust pH of the solution in the column to about 9 (defined the quantity of ammonia TS by using another same volume of the successive filtrate previously), mix well, rinse with 20 ml of water after no solvent drips. Elute with 5% acetic acid solution containing 10% of methanol, collect the eluate into a 5 ml of volumetric flask to volume and mix well. Inject 10 μ l of the eluate into the column, record the chromatogram. Repeat the operation, using a solution of 0.05 mg of

of $C_{17}H_{19}NO_3$ with respect to the peak areas obtained in the chromatogram by the external standard method.

Storage Preserve in tightly closed containers.

Powdered Poppy Capsule Extractive

Powdered Poppy Capsule Extractive is Poppy Capsule Extractive dried at a temperature below 70°C, reduced to fine powder and prepared by the addition of codeine phosphate or other diluents after determining the content of morphine. It contains not less than 9.5% and not more than 10.5% of morphine, calculated with reference to anhydrous morphine ($C_{17}H_{19}NO_3$), it contains not less than 4.5% of codeine phosphate ($C_{18}H_{21}NO_3 \cdot H_3PO_4 \cdot \frac{1}{2}H_2O$).

Description A light brown powder; odour, characteristic; taste, bitter.

Identification (1) Complies with the tests (1) and (2) for Identification described under Poppy Capsule Extractive.

(2) Transfer about 25 mg into a conical flask, add 5 ml of 5% acetic acid solution, in ultrasonic bath for 5 minutes to dissolve morphine and filter. Adjust the filtrate to pH about 10 with concentrated ammonia TS, extract with 10 ml a mixture of chloroform-ethanol (9 : 1). Transfer the organic layer and evaporate in vacuum to dryness. Dissolve the residue in 1 ml of methanol as the test solution. Dissolve each a quantity of morphine CRS and codeine phosphate CRS in methanol to produce a solution of 1.0 mg morphine and 1.0 mg codeine phosphate per ml as the reference solution. Carry out the method for thin-layer chromatography (Appendix V B), using silica gel G as the coating substance and a mixture of ethyl acetate-methanol-concentrated ammonia solution (85 : 10 : 5) as the mobile phase. Apply separately to the plate 10 μ l each of the above two solutions, after developing and removal of the plate, dry it in air and spray with dilute potassium iodobismuthate TS. The principal spot in the chromatogram obtained with the test solution corresponds in colour and position to the principal spot obtained with the reference solution.

Assay Carry out the method for high performance liquid chromatography (Appendix V D), using a column packed with octadecylsilane bonded silica gel and a mixture of 0.05 mol/L potassium dihydrogen phosphate solution-0.0025 mol/L sodium heptanesulfonate solution-acetonitrile (5 : 5 : 2) as the mobile phase. Detection wavelength is 220 nm and the number of the theoretical plates of the column is more than 1000, calculated with reference to the peak of morphine. The resolution factor between peak areas of morphine and codeine complies with related requirements.

System suitability test of solid phase extraction column

Using a solid phase extraction column packed with octadecylsilane bonded silica gel. Carry out the test as described under the Procedure. Transfer 0.5 ml of a solution in 5% acetic acid solution containing 0.5 mg of morphine CRS per ml, accurately measured, to the column pretreated, collect the eluate into a 5 ml volumetric flask to volume and mix well. Respectively inject 10 μ l of the eluate and the reference solution as described under the Procedure into the column, record the peak areas correspondingly obtained in the chromatogram. The ratio of the peak area of morphine obtained in the chromatogram of the eluate to that of the reference solution is

Procedure Wash a solid phase extraction column with 15 ml of a mixture of methanol-water (3 : 1) and 5 ml of water in sequence, then wash the column with the ammonia solution of pH about 9 (add drops of ammonia TS to a quantity of water until the pH value is about 9) until the pH value of the eluate is about 9. Triturate about 10 g of the substance being examined (let it through No. 5 sieve). Transfer about 1 g, accurately weighed, into a 200 ml volumetric flask, add a quantity of 5% acetic acid solution, in ultrasonic bath for 30 minutes to dissolve morphine, cool and dilute to volume with 5% acetic acid solution, mix well and filter. Measure accurately 0.5 ml of the successive filtrate to the above washed column, drop a quantity of ammonia TS to adjust pH of the solution in the column to about 9 (defined the quantity of ammonia TS by using another same volume of the successive filtrate previously), mix well, rinse with 20 ml of water after no solvent drips. Elute with 5% acetic acid solution containing 10% of methanol, collect the eluate into a 5 ml of volumetric flask to volume and mix well. Inject 10 μ l of the eluate into the column, record the chromatogram. Repeat the operation, using a solution of 0.05 mg of morphine CRS and 0.025 mg of codeine phosphate per ml in 5% acetic acid solution containing 10% of methanol instead of the eluate. Calculate the content of $C_{17}H_{19}NO_3$ with respect to the peak areas obtained in the chromatogram by the external standard method.

Storage Preserve in tightly closed containers.

Posterior Pituitary Injection

Posterior Pituitary Injection is a sterile solution of powdered posterior pituitary in dilute acetic acid solution. It contains not less than 87% and not more than 115% of the labelled potency of vasopressin, calculated on vasopressin.

Description A colourless, clear or almost clear liquid.

pH Value 3.0-4.0 (Appendix VI H).

Oxytocin Carry out the biological assay of oxytocin (Appendix XII F), the ratio of potency of oxytocin to that of vasopressin is not more than 1 : 0.6.

Other requirements Complies with the general requirements for injections (Appendix I B).

Assay vasopressin Carry out the biological assay of vasopressin (Appendix XII A), complies with the requirement of Posterior Pituitary Injection.

Strength Calculated on vasopressin
(1) 0.5 ml : 3 units (2) 1 ml : 6 units

Storage Preserve in well closed containers, stored in a cool place, protected from light.

Powdered Posterior Pituitary

Powdered Posterior Pituitary is prepared by dehydrating, drying and powdering of the posterior lobe of the pituitary body of healthy porcine, sheep and bovine animals. It contains not less than 0.6 unit of vasopressin per mg, calculated on the dried basis. The ratio of potency of vasopressin to that of oxytocin

Description A white to pale yellow powder. Odour characteristic. Practically insoluble in water.

Oxytocin Carry out the biological assay of oxytocin (Appendix XII F). The ratio of potency of oxytocin to that of vasopressin is not more than 1 : 0.6.

Assay Carry out the biological assay of vasopressin (Appendix XII O). It contains not less than 85% and not more than 120% of the labelled potency.

Category Vasoconstrictor and antidiuretic.

Storage Preserve in tightly closed containers stored in a cold place.

Preparation Posterior Pituitary Injection

Potassium Chloride

KCl 74.55 [7447-40-7]

Potassium Chloride contains not less than 99.5% of KCl, calculated on the dried basis.

Description Colourless, elongated prismatic or cubic crystals or a white crystalline powder; odourless; taste, saline and astringent. Freely soluble in water; insoluble in ethanol or ether.

Identification Yields the reactions characteristic of potassium salts and chlorides (Appendix III).

Acidity or alkalinity Dissolve 5.0 g in 50 ml of water, add 3 drops of phenolphthalein IS. No colour is produced. Add 0.30 ml of sodium hydroxide (0.02 mol/L) VS, a pink colour is produced.

Clarity of solution Dissolve 2.5 g in 25 ml of water, the solution is clear.

Sulfates Carry out the limit test for sulfates (Appendix VIII B), using 2.0 g. Any opalescence produced is not more pronounced than that of a reference using 2.0 ml of potassium sulfate standard solution (0.010%).

Sodium Introduce a solution (1→5) held on a platinum wire into a nonluminous flame, the flame is not imparted with a pronounced and persistent yellow colour.

Manganese Dissolve 2.0 g in 8 ml of water, add 2 ml of sodium hydroxide TS, mix well and allow to stand for 10 minutes, no colour is produced.

Iodide, Bromide, Barium, Calcium, Magnesium and Iron Carry out the respective tests described under Sodium Chloride, it complies with the requirements.

Loss on drying When dried at 130°C to constant weight, loses not more than 1.0% of its weight (Appendix VIII L).

Heavy metals Dissolve 4.0 g in 20 ml of water, add 2 ml of acetate BS (pH 3.5) and sufficient water to produce 25 ml, carry out the limit test for heavy metals (Appendix VIII H, method 1); not more than 0.0005%.

Arsenic Dissolve 2.0 g in 23 ml of water, add 5 ml of hydrochloric acid, carry out the limit test for arsenic (Appendix VIII J, method 1); not more than 0.0001%.

Assay Dissolve about 0.15 g, accurately weighed, in 50 ml of water, add 5 ml of dextrin solution (1→50) and 5-8 drops of fluorescein IS, titrate with silver nitrate (0.1 mol/L) VS. Each ml of silver nitrate (0.1 mol/L) VS is equivalent to 7.455 mg of KCl.

Storage Preserve in tightly closed containers.

Preparation (1) Potassium Chloride Injection
(2) Potassium Chloride Sustained-release Tablets
(3) Potassium Chloride Tablets

Potassium Chloride Injection

Potassium Chloride Injection is a sterile solution of Potassium Chloride in Water for Injection. It contains not less than 95.0% and not more than 105.0% of the labelled amount of potassium chloride (KCl).

Description A clear, colourless liquid.

Identification Yields the reactions characteristic of potassium salts and chlorides (Appendix III).

pH value 5.0-7.0 (Appendix VI H).

Bacterial endotoxin Carry out the test for bacterial endotoxin (Appendix XI E); less than 0.118 EU per mg of Potassium Chloride.

Other requirements Complies with the general requirements for injections (Appendix I B).

Assay Dilute 10 ml, accurately measured, with water to produce 100 ml, mix well. Measure accurately 10 ml of the diluted solution, add 40 ml of water, 5 ml of dextrin solution (1→5) and 5-8 drops of fluorescein IS, titrate with silver nitrate (0.1 mol/L) VS. Each ml of silver nitrate (0.1 mol/L) VS is equivalent to 7.455 mg of KCl.

Category As described under Potassium Chloride.

Strength (1) 10 ml : 1 g (2) 10 ml : 1.5 g

Storage Preserve in well closed containers.

Potassium Chloride Sustained-release Tablets

Potassium Chloride contain not less than 93.0% and not more than 107.0%.

Description Sugar-coated with white core.

Identification Powder the tablets with the sugar coating removed. Dissolve a quantity of the powder with water, filter, the filtrate yields the reactions characteristic of potassium salts and chlorides (Appendix III).

Drug release Carry out the drug release test (Appendix X D, method 1), using the apparatus described under dissolution test method 2 and 900 ml of water as the dissolution medium, adjust the rotational speed to 50 rpm. Withdraw each 25 ml of the solution after exactly 2, 4 and 8 hours, respectively, add 25 ml of water to the vessel to compensate the volume. Measure accurately 20 ml of the successive filtrate, dilute with 4 drops of Potassium Cyanide TS and titrate with silver nitrate (0.01 mol/L) VS until the solution becomes orange. Each ml of silver nitrate (0.01 mol/L) VS is equivalent to 0.7455 mg of KCl. The amount of KCl dissolved in 2, 4 and 8 hours is 10%-35%, 30%-70% and not less than 80% of the labelled amount respectively.

Assay Reference preparation When dried to the constant weight at 105°C for 2 hours, dissolve about 0.25 g of Potassium Chloride, accurately weighed, in a 250 ml volumetric flask with water and dilute to volume, mix well.

Measure accurately 5 ml to a 100 ml volumetric flask, dilute to volume with 1% hydrochloric acid solution (g/g) and mix well.

Test preparation Weigh accurately and powder 10 tablets with sugar coating removed, dried to the constant weight in Silica gel drying chamber for 24 hours, accurately weighed, transfer a quantity equivalent to about 0.5 g of Potassium Chloride to a 500 ml volumetric flask, dissolve and dilute to volume with water.

Procedure Transfer accurately 2.0 ml, 3.0 ml, 4.0 ml, 5.0 ml and 6.0 ml of reference preparation into a 100 ml volumetric flask, respectively. Add 2.0 ml of 20% sodium chloride solution in each flask and dilute with 1% hydrochloric acid (g/g) solution to volume, mix well. Transfer accurately 2 ml of the test preparation in a 50 ml of volumetric flask, add 2.0 ml of 20% sodium chloride solution, and dilute with 1% hydrochloric acid (g/g) solution to volume, mix well. Carry out the method for atomic absorption spectrophotometry (Appendix IV D), measure the absorption of above solutions at 766.5nm, with 20% sodium chloride solution; 1% hydrochloric acid (g/g) (2 : 98) as the blank solution and calculate the content of potassium chloride.

Category As described under Potassium Chloride.

Strength 5 g

Storage Preserve in tightly closed container, protected from light.

Potassium Chloride Tablets

Potassium Chloride Tablets contain not less than 95.0% and not more than 105.0% of the labelled amount of Potassium Chloride (KCl).

Description White tablets or sugar coated tablets or film tablets with white core.

Identification Dissolve a quantity of the powdered tablets with water, filter, the filtrate yields the reactions characteristic of potassium salts and chlorides (Appendix III).

Other requirements Comply with the general requirements for tablets (Appendix I A).

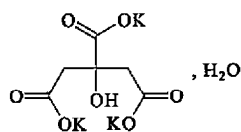
Assay Weigh and powder 10 tablets. Dissolve a quantity equivalent, to about 0.15 g of potassium chloride, accurately weighed, in 50 ml of water, add 5 ml of 2% dextrin solution and 5-8 drops of fluorescein IS, titrate with silver nitrate (0.1 mol/L) VS. Each ml of silver nitrate (0.1 mol/L) VS is equivalent to 7.455 mg of Potassium Chloride.

Category As described under potassium chloride.

Strength (1) 0.25 g (2) 0.5 g

Storage Preserve in tightly closed containers, stored in dry place.

Potassium Citrate



$C_6H_5K_3O_7 \cdot H_2O$ 324.41

[866-84-2]

Potassium Citrate is 2-hydroxy-1,2,3-propanetricarboxylic acid-tripotassium salt, monohydrate. It contains not less than 99.0% of $C_6H_5K_3O_7 \cdot H_2O$.

Description White, granular crystals or a crystalline powder; odourless; taste, salty and cool; slightly hygroscopic. Very soluble in water or glycerin; practically insoluble in ethanol.

Identification Yields the reaction characteristic of potassium salts and citrates (Appendix III).

Acidity or alkalinity Dissolve 2.0 g in 25 ml of water, add 1 drop of thymol blue IS. If the solution is blue, add 0.20 ml of hydrochloric acid (0.1 mol/L) VS, the solution becomes yellow; if the solution is yellow, add 0.20 ml of sodium hydroxide (0.1 mol/L) VS, the solution becomes blue.

Chlorides Carry out the limit test for chlorides (Appendix VII A), using 0.20 g. Any opalescence produced is not more intense than that of a reference using 7.0 ml of sodium chloride standard solution (0.035%).

Sulfates Carry out the limit test for sulfates (Appendix VII B), using 0.20 g. Any opalescence produced is not more intense than that of a reference using 3.0 ml of potassium sulfate standard solution (0.15%).

Readily carbonizable substances To 0.50 g add 5 ml of sulfuric acid [containing 94.5%-95.5% (g/g) of H_2SO_4], heat on a water bath for 1 hour and cool immediately. Carry out the limit test for readily carbonizable substances (Appendix VIII O). Any colour produced is not more intense than that of a reference (mix 0.5 ml of standard cobaltous chloride CS and 4.5 ml of standard potassium dichromate CS).

Oxalate Dissolve 1.0 g in a mixture of 1 ml of water and 3 ml of dilute hydrochloric acid, add 4 ml of 90% ethanol and 4 drops of calcium chloride TS, allow to stand for 1 hour; no opalescence is produced.

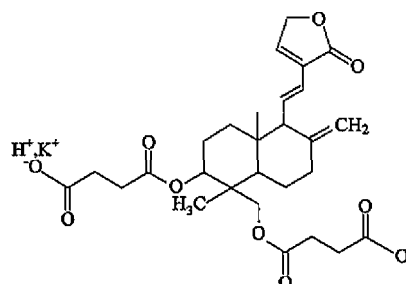
Heavy metals Dissolve 2.0 g in 10 ml of water, add 5 ml of dilute hydrochloric acid and sufficient water to produce 25 ml, carry out the limit test for heavy metals (Appendix VIII H, method 1); not more than 0.001%.

Arsenic Dissolve 1.0 g in 23 ml of water, add 5 ml of hydrochloric acid, carry out the limit test for arsenic (Appendix VIII J, method 1); not more than 0.0002%.

Assay To about 80 mg, accurately weighed, add 20 ml of glacial acetic acid and 2 ml of acetic anhydride, heat to dissolve and cool to room temperature. Add 1 drop of crystal violet IS and titrate with perchloric acid (0.1 mol/L) VS until the colour of the solution changes to blue. Perform a blank determination and make any necessary correction. Each ml of perchloric acid (0.1 mol/L) VS is equivalent to 10.81 mg of $C_6H_5K_3O_7 \cdot H_2O$.

Storage Preserve in tightly closed containers.

Potassium Dehydroandrographolide Succinate



$C_{28}H_{35}KO_{10}$ 570.68

Potassium Dehydroandrographolide Succinate is monopotassium 14-dehydro-11,12-didehydroandrographolide-3,19-disuccinate. It contains not less than 98.0% of $C_{28}H_{35}KO_{10}$, calculated on the dried basis.

Description An almost white or slightly yellow crystalline powder; odourless; taste, bitter; hygroscopic. Soluble in dilute ethanol; practically insoluble in chloroform or ethanol, soluble in 1% sodium bicarbonate solution.

Identification (1) Dissolve 2 mg in 1 ml of dilute ethanol, add two drops of 1.5% 3,5-dinitrobenzoic acid in ethanol and 2 drops of 2 mol/L sodium hydroxide solution, mix well, a violet-red colour is produced.

(2) The light absorption of a solution obtained in Assay exhibits a maximum at 251 nm (Appendix IV A).

(3) Yields the reaction for identification (1) characteristic of potassium salts (Appendix III).

Clarity and colour of solution in dilute ethanol Dissolve 0.1 g in 10 ml of dilute ethanol, the solution is clear and colourless; any colour produced is not more intense than that of reference solution Y_2 or YG_2 (Appendix IX A, method 1).

Loss on drying When dried over phosphorous pentoxide to constant weight at 60°C, loses not more than 3.0% of its weight (Appendix VII L).

Related substances Dissolve a quantity of the substance being examined in mobile phase to produce solutions of 0.4 mg per ml (solution 1) and 8 µg per ml (solution 2). Carry out the method described under Assay, inject 10 µl of the solution (2) into the column. Adjust the attenuation so that the principal peak height in the chromatogram is 10% of the full scale of the chart, then inject separately 10 µl of each of solution (1) and solution (2) into the column, and record the chromatogram for 3 times the retention time of the principal peak. The sum of the areas of all peaks other than the principal peak in the chromatogram obtained with solution (1) is not greater than the area of the principal peak in the chromatogram obtained with solution (2).

Insoluble matter in alkali Dissolve 1.0 g in 50 ml of 0.6% sodium bicarbonate solution by heating on a water bath at 70°C. Allow to cool, and filter through a tared sintered-glass filter (No. 3), previously dried to constant weight at 105°C. Wash the residue with 10 ml of 0.6% sodium bicarbonate solution in portions, then wash with 50 ml of water in portions, dry to constant at 105°C. The residue

Pyridine Dissolve 1 g, accurately weighed, in 5 ml of water and 0.3 ml of concentrated ammonia solution in a 10 ml volumetric flask, dilute with water to volume and mix well as the test solution. Prepare a reference solution by dissolving a quantity of pyridine CRS with the same solvents to produce a solution of 20 µg per ml. Carry out the method for residual solvents (Appendix VIII P, method 3), using a column packed with porous polymer beads with 0.25-0.18 mm in diameter containing diethylenebenzene-ethylenebenzene as the stationary phase, maintain the column temperature at 180°C and the FID temperature at 200°C. The number of theoretical plates of the column is not less than 1000, calculated with reference to pyridine. Inject separately 10 µl of each of the resulting solutions into the column, and record the chromatogram. The content of pyridine is not more than 0.02% calculated with respect to the peak area obtained in the chromatogram by the external standard method.

Pyrogens Complies with the test for pyrogens (Appendix XI D), using 1 ml of a solution of 20 mg per ml in sterile 1% sodium bicarbonate solution free from pyrogens per kg of rabbit's weight.

Assay Carry out the method for high performance liquid chromatography (Appendix V D), using a column packed with octadecylsilane bonded silica gel and a mixture of 0.05% potassium dihydrogen phosphate solution (adjust to pH 2.5 ± 0.05 with phosphoric acid)-methanol (3 : 7) as the mobile phase. Detection wavelength is 251 nm and the number of theoretical plates of the column is not less than 3000, calculated with reference to the peak of dehydroandrographolide succinate.

Procedure Dissolve about 10 mg, accurately weighed, in the mobile phase in a 100 ml volumetric flask, dilute to volume, and mix well. Inject 10 µl into the column, and record the chromatogram. Repeat the operation, using dehydroandrographolide succinate CRS instead of the substance being examined, calculate the content of $C_{28}H_{35}O_{10}$ with respect to the area obtained in the chromatogram by the external standard method, multiplied by 1.072.

Category Antivirus.

Storage Preserve in tightly closed containers, stored in a cool and dry place.

Preparation Potassium Dehydroandrographolide Succinate for Injection

Potassium Dehydroandrographolide Succinate for Injection

Potassium Dehydroandrographolide Succinate for Injection is the sterile lyophilized mass containing potassium dehydroandrographolide succinate with a quantity of sodium bicarbonate. It contains not less than 90.0% and not more than 110.0% of the labelled amount of $C_{28}H_{35}KO_{10}$, calculated with reference to the average amount.

Description A white or slightly yellow frozen mass or powder.

Identification (1) Dissolve 2 mg in dilute ethanol, add 2 drops of 1.5% 3,5-dinitrobenzoic acid in ethanol and 2 drops of 2 mol/L sodium hydroxide solution, mix well, a violet-red colour is produced.

(2) The light absorption of a solution of 25 µg per ml in

(3) Yields the reaction for identification (1) characteristic of potassium salts and for identification (1) characteristic of sodium salts (Appendix III).

Acidity or alkalinity An aqueous solution of 10 mg per ml, pH 6.5-8.0 (Appendix VI H).

Colour of solution A solution of 10 mg per ml in water is not more intense than that of reference solution Y₂ or YG₂ (Appendix IX A, method 1).

Related substances Carry out the method described under Assay. Dissolve a quantity of the mixed contents obtained in weight variation in mobile phase to produce solutions of 0.4 mg per ml (solution 1) and 8 µg per ml (solution 2). Inject 10 µl of the solution (2) into the column. Adjust the attenuation so that the principal peak height in the chromatogram is 10% of the full scale of the chart. Inject separately 10 µl of each of solution (1) and solution (2) into the column, and record the chromatogram for 3 times the retention time of the principal peak. The sum of the areas of all peaks other than the principal peak is not greater than 2.5 times the area of the principal peak in the chromatogram obtained with solution (2).

Loss on drying When dried over phosphorous pentoxide to constant weight at 60°C, loses not more than 5.0% of its weight (Appendix VIII L).

Pyrogens Complies with the test for pyrogens (Appendix XI D), using 1 ml of a solution of 20 mg per ml in sterile Water for Injections per kg of rabbit's weight.

Other requirements Complies with the general requirements for Injection (Appendix I B).

Assay Carry out the method described under Assay of potassium dehydroandrographolide succinate. Dissolve a quantity of the mixed contents obtained in weight variation equivalent to 10 mg of potassium dehydroandrographolide succinate, accurately weighed, in the mobile phase in a 100 ml volumetric flask, dilute to volume, and mix well. Inject 10 µl into the column, and record the chromatogram. Repeat the operation, using dehydroandrographolide succinate CRS instead of the substance being examined, calculate the content of $C_{28}H_{35}O_{10}$ with respect to the area obtained in the chromatogram by the external standard method, multiplied by 1.072.

Category As described under Potassium dehydroandrographolide succinate.

Strength (1) 20 mg (2) 40 mg (3) 100 mg
(4) 200 mg

Storage Preserve in tightly closed containers, stored in a cool and dry place.

Potassium Glutamate Injection

Potassium Glutamate Injection is a sterile solution of glutamic acid with a quantity of potassium hydroxide in Water for Injection. It contains not less than 95.0% and not more than 105.0% of the labelled amount of potassium glutamate ($C_5H_8KNO_4$).

Description A clear, colourless or almost colourless liquid.

Identification (1) Dilute 1 drop with 2 ml of water, add about 2 mg of ninhydrin and heat, the solution exhibits a blue to lavender blue colour.

(2) Yields the reactions characteristic of potassium salts

Colour Not more intense than that of reference solution Y₂ or YG₂ (Appendix IX A, method 1).

pH value 7.5-8.5 (Appendix VI H).

Bacterial endotoxin Carry out the test for bacterial endotoxin (Appendix XI E): less than 0.012 EU per mg of potassium glutamate.

Other requirements Complies with the general requirements for Injections (Appendix I B).

Assay Measure accurately 15 ml to a 50 ml volumetric flask, add 10 ml of hydrochloric acid, dilute with water to volume and mix well. Carry out the determination of the optical rotation (Appendix VI E) and multiply by 6.557 to obtain the amount (g) of C₅H₈KNO₄ per 100 ml.

Category As described under Glutamic acid.

Strength 20 ml : 6.3 g

Storage Preserve in well closed containers, protected from light.

Potassium Iodate

KIO₃ 214.00

Potassium Iodate contains not less than 99.0% of KIO₃, calculated on the dried basis.

Description Colourless or white crystals or powder; odourless; taste, slightly astringent. Soluble in water; practically insoluble in ethanol.

Identification (1) Dissolve about 20 mg in 5 ml of water, add 1 drop of saturated sulfur dioxide solution and mix well. Then add several drops of starch IS, a blue colour is produced.

(2) The aqueous solution yields the reactions characteristic of potassium salts (Appendix 3).

Acidity or alkalinity Dissolve 3.0 g in 40 ml of water, add 3 drops of Phenolphthalein IS, no colour is produced. Then add 0.2 ml of sodium hydroxide (0.02 mol/L) VS, a pink colour is produced.

Chlorate To 2.0 g of powder in a small beaker add 2 ml of sulfuric acid, the powder is still white, no colour is produced and no gas is evolved.

Iodide Dissolve 1.0 g in 10 ml of water, add 1 ml of dilute sulfuric acid and 1 drop of starch IS; no blue colour is produced.

Barium Dissolve 1.0 g in 20 ml of water, filter, divide the filtrate into two equal portions. To one portion of the filtrate add 1 ml of dilute sulfuric acid, and another portion add 1 ml of water, allow to stand for 15 minutes. The two solutions are clear similarly.

Loss on drying When dried to constant weight at 105°C, loses not more than 0.5% of its weight (Appendix VIII L).

Heavy metals To 5.0 g add 40 ml of hydrochloric acid solution (1→2), and evaporate to dryness on a water bath. Treat the residue again as described above with hydrochloric acid solution (1→2) twice of 15 ml each, then heat gently until the residue becomes white, allow to cool. Dissolve it in 20 ml of water, add ammonia TS dropwise until the solution is neutral to phenolphthalein IS, and dilute with water to 25 ml. Carry out the limit test for heavy metals (Appendix VIII H, method 1). Any colour produced is not more intense than that of a reference solution produced by mixing 2 ml of

than 0.001%.

Arsenic To 5 ml of the test solution obtained in Test for heavy metals, dilute with water to 30 ml. To 20 ml add sufficient water to produce 23 ml, add 5 ml of hydrochloric acid and carry out the limit test for arsenic (Appendix VIII J), it complies with the requirement (0.0003%).

Assay Dissolve about 0.8 g, accurately weighed, in a 250 ml volumetric flask with water, dilute to volume and mix well. Transfer accurately 25 ml to an iodine flask, add 2 g of potassium iodide and 10 ml of dilute hydrochloric acid, insert the stopper, mix well, allow to stand in the dark for 5 minutes. Add 100 ml of water, titrate with sodium thiosulfate (0.1 mol/L) VS towards the end of titration, add 2 ml of starch IS, continue the titration until the blue colour disappears. Perform a blank determination and make necessary correction. Each ml of sodium thiosulfate (0.1 mol/L) VS is equivalent to 3.567 mg of KIO₃.

Category Iodine replenisher.

Storage Preserve in tightly closed containers.

Preparation (1) Potassium Iodate Granules
(2) Potassium Iodate Tablets

Potassium Iodate Granules

Potassium Iodate Granules contain not less than 90.0% and not more than 110.0% of the labelled amount of potassium iodate (KIO₃).

Description White granules.

Identification (1) Triturate the content of 20 containers, add 6 ml of water, shake thoroughly to dissolve potassium iodate, filter, to the filtrate add 5 drops of silver nitrate TS, white precipitate is produced, which is soluble in ammonia TS and insoluble in dilute nitric acid.

(2) Dissolve the content of 1 container, in 10 ml of water, shake thoroughly to dissolve potassium iodate, Measure accurately 2 ml, add 2 ml of 1% potassium iodate solution, 5 ml of 0.2 mol/L sulfuric acid solution and 5.0 ml of starch IS, a blue colour is produced.

(3) Triturate the content of 10 containers, add 3 ml of water, shake thoroughly to dissolve potassium iodate, filter, to the filtrate add 5-10 drops of 0.1% sodium tetraphenylboron solution, white precipitate is produced.

Content uniformity Comply with the requirements for content uniformity except that the limit is ±20% (Appendix X E). Dissolve 1 container in water in a 50 ml volumetric flask and dilute with water to volume, mix well, filter. Measure accurately 10 ml of the successive filtrate to a 50 ml volumetric flask, add 2.0 ml of 1% potassium iodate solution, 5.0 ml of 0.2 mol/L sulfuric acid solution and 5.0 ml of starch IS, dilute with water to volume, mix well, measure the absorbance at 580 nm (Appendix IV B). Dissolve an accurately weighed quantity of potassium iodate CRS previously dried to constant weight at 105°C in water to produce a solution of about 15 µg per ml. Measure accurately 5 ml, repeat the procedure beginning at the words "to a 50 ml volumetric flask...", calculate the content of potassium iodate (KIO₃).

Loss on drying When dried to constant weight at 105°C, loses not more than 2.0% of its weight (Appendix VIII L).

Other requirements Comply with the general requirements for granules (Appendix I N).

dissolve an accurately weighed quantity in water to produce a solution of about 15 µg per ml, filter. Measure accurately 5 ml of the successive filtrate to a 50 ml volumetric flask, add 2.0 ml of 1% potassium iodate solution, 5.0 ml of 0.2 mol/L sulfuric acid solution and 5.0 ml of starch IS, dilute with water to volume, mix well, measure the absorbance at 580 nm (Appendix IV B). Repeat the operation, using an accurately weighed quantity of potassium iodate CRS previously dried to constant weight at 105°C instead of potassium iodate granules. Calculate the content of potassium iodate (KIO_3).

Category Iodine replenisher.

Strength 0.15 mg

Storage Preserve in tightly closed containers.

Potassium Iodate Tablets

Potassium Iodate Tablets contain not less than 90.0% and not more than 110.0% of the labelled amount of potassium iodate (KIO_3).

Description White tablets.

Identification (1) Triturate 10 tablets, add 3 ml of water, shake thoroughly to dissolve potassium iodate and filter, to the filtrate add 1-2 drops of silver Nitrate TS, white precipitate is produced, which is soluble in ammonia TS and insoluble in nitric acid.

(2) Dissolve 1 tablet in 25 ml of water, shake thoroughly to dissolve potassium iodate and filter, Measure accurately 2 ml, add 2 ml of 1% potassium iodate solution, 5 ml of 0.2 mol/L sulfuric acid solution and 5 ml of starch IS, a blue colour is produced.

(3) Triturate 30 tablets, add 10 ml of water, shake thoroughly to dissolve potassium iodate and filter, evaporate the filtrate to dryness on a water bath. Dissolve the residue in 1 ml of water, filter, add 10 drops of sodium tetraphenylenediamine solution, white precipitate is produced.

Content uniformity Comply with the requirements for content uniformity except that the limit is $\pm 20\%$ (Appendix X E). Dissolve 1 powdered tablet in water in a 50 ml volumetric flask and dilute with water to volume, mix well and filter. Measure accurately 10 ml of the successive filtrate to a 50 ml volumetric flask, add 2.0 ml of 1% potassium iodate solution 5.0 ml of 0.2 mol/L sulfuric acid solution and 5.0 ml of starch IS, dilute with water to volume, mix well. Measure the absorbance at 580 nm (Appendix IV B). Dissolve an accurately weighed quantity of potassium iodate CRS previously dried to constant weight at 105°C in water to produce a solution of about 10 µg per ml. Measure accurately 5 ml, repeat the procedure beginning at the words "to a 50 ml volumetric flask..." and calculate the content of KIO_3 .

Other requirement Comply with the general requirements for Tablets (Appendix I A).

Assay Weigh accurately and triturate 20 tablets. Dissolve an accurately weighed quantity in water to produce a solution of about 10 µg per ml, mix well and filter. Measure accurately 5 ml of the successive filtrate to a 50 ml volumetric flask, add 2.0 ml of 1% potassium iodate solution, 5.0 ml of 0.2 mol/L sulfuric acid solution and 5.0 ml of starch IS, dilute with water to volume, mix well, measure the absorbance at 580 nm (Appendix IV B). Repeat the operation, using an accurately weighed quantity of potassium iodate CRS previously dried to constant weight at 105°C

Category Iodine replenisher.

Strength (1) 0.3 mg (2) 0.4 mg

Storage Preserve in tightly closed containers.

Potassium Iodide

KI 166.00

[7681-11-0]

Potassium Iodide contains not less than 99.0% of KI, calculated on the dried basis.

Description Colourless crystals or a white crystalline powder; odourless; taste, saline and bitter; slightly hygroscopic.

Very soluble in water; soluble in ethanol.

Identification Yields the reactions characteristic of potassium and iodides (Appendix III).

Alkalinity Dissolve 1.0 g in 10 ml of water, add 0.10 ml of sulfuric acid (0.05 mol/L) VS and 1 drop of phenolphthalein IS, no red colour is produced.

Clarity and colour of solution A solution of 1.0 g in 10 ml of water is clear and not more intense coloured than reference solution Y_1 (Appendix IX A, method 1).

Chlorides Dissolve 0.25 g in 100 ml of water, add 1 ml of concentrated hydrogen peroxide solution and 1 ml of phosphoric acid, boil until the solution becomes colourless and cool. Add again 0.5 ml of concentrated hydrogen peroxide solution, boil and then cool. Transfer it to a 250 ml volumetric flask, dilute with water to volume and mix well. Carry out the limit test for chlorides (Appendix VIII A), using 5.0 ml of the solution. Any opalescence produced is not more intense than that of a reference, using 2.5 ml of standard sodium chloride solution (0.50%).

Sulfates Carry out the limit test for sulfates (Appendix VII B), using 0.50 g of the substance being examined. Any opalescence produced is not more intense than that of a reference using 2.0 ml of standard potassium sulfate solution (0.04%).

Iodate Dissolve 0.50 g in 10 ml of freshly boiled and cooled water, add 2 drops of dilute sulfuric acid and 0.2 ml of starch IS, allow to stand in dark, no blue colour is produced within 2 minutes.

Loss on drying When dried at 105°C for 4 hours, loses not more than 1.0% of its weight (Appendix VIII L).

Barium Dissolve 1.0 g in 20 ml of water, filter, divide the filtrate into two equal portions. Add 1 ml of dilute sulfuric acid to one portion and add 1 ml of water to the other portion. The two portions should be same clear within 15 minutes.

Heavy metals Dissolve 2.0 g in 23 ml of water, add 2 ml of acetate BS (pH 3.5), carry out the limit test for heavy metals (Appendix VIII H, method 1); not more than 0.001%.

Assay Dissolve about 0.3 g, accurately weighed, in 10 ml of water, add 35 ml of hydrochloric acid. Titrate with potassium iodate (0.05 mol/L) VS until a yellow colour is produced; add 5 ml of chloroform, continue the titration and shake thoroughly until the colour disappears in the chloroform layer. Each ml of potassium iodate (0.05 mol/L) VS is equivalent to 16.60 mg of KI.

Category Iodine replenisher.

from light.

Preparation Potassium Iodide Tablets

Potassium Iodide Tablets

Potassium Iodide Tablets contain not less than 90.0% and not more than 110.0% of the labelled amount of Potassium Iodide (KI).

Description White tablets.

Identification Dissolve a quantity of the powdered tablets with water and filter. The filtrate yields the reactions characteristic of potassium salts and iodides (Appendix III).

Other requirements Comply with the general requirements for tablets (Appendix I A).

Assay Weigh and powder 10 tablets. Weigh accurately a quantity equivalent to about 0.3 g of potassium iodide, carry out the Assay as described under Potassium Iodide, beginning at the words "dissolve in 10 ml of water...".

Category As described under Potassium Iodide.

Strength (1) 10 mg (2) 200 mg

Storage Preserve in tightly closed containers, and protected from light and stored in dry place.

Potassium Permanganate

KMnO₄ 158.03 [7722-64-7]

Potassium Permanganate contains not less than 99.3% of KMnO₄.

Description A dark purple slender prismatic crystal or granule with bluish metallic lustre; odourless; may explode on contact with certain organic or easily oxidizable substances. Freely soluble in boiling water; soluble in water.

Identification (1) Acidify 5 ml of an aqueous solution (1→1000) with dilute sulfuric acid, add dropwise hydrogen peroxide solution, the purple-red colour is discharged. (2) The above discoloured solution yields the reactions characteristic of potassium salts (Appendix III).

Chlorides Dissolve 2.0 g in 60 ml of hot water, heat on a water bath, add a quantity of ethanol (about 8 ml) dropwise with constant stirring to discharge the colour completely. Transfer the solution to a 100 ml volumetric flask, add water to volume, mix well and filter. Carry out the limit test for chlorides (Appendix VII A), using 25 ml of the filtrate. Any opalescence produced is not more intense than that of a reference using 5.0 ml of sodium chloride standard solution (0.010%).

Sulfates Carry out the limit test for sulfates (Appendix VII B), using 25 ml of the remaining filtrate obtained in test of Chloride. Any opalescence produced is not more intense than that of a reference using 2.0 ml of potassium sulfate standard solution (0.040%).

Assay Dissolve about 0.8 g, accurately weighed, in freshly distilled water in a 250 ml volumetric flask and dilute to volume, mix well. To 25 ml of oxalic acid (0.05 mol/L) VS, accurately measured, add 5 ml of sulfuric acid solution (1→2) and 50 ml of water; then add quickly from a burette about 23 ml of the test preparation, heat to 65°C and

keep it for 30 seconds. Perform a blank determination and make any necessary correction. Each ml of oxalic acid (0.05 mol/L) VS is equivalent to 3.161 mg of KMnO₄.

Category Disinfectant and antiseptic.

Storage Preserve in tightly closed containers.

Preparation Potassium Permanganate Tablets for External Use

Potassium Permanganate Tablets for External Use

Potassium Permanganate Tablets for External Use contain not less than 95.0% and not more than 105.0% of the labelled amount of potassium permanganate (KMnO₄).

Processing Mix thoroughly dried potassium permanganate with a quantity of finely powdered boric acid and compress into tablets.

Description Black violet tablets.

Identification Comply with the tests for Identification described under Potassium Permanganate.

Other requirements Comply with the general requirements for tablets, except disintegration test (Appendix I A).

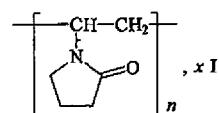
Assay Weigh accurately and powder 20 tablets. Weigh accurately a quantity of the powdered tablets equivalent to about 0.8 g of potassium permanganate, carry out the Assay as described under Potassium Permanganate. Each ml of oxalic acid (0.05 mol/L) VS is equivalent to 3.161 mg of KMnO₄.

Category As described under Potassium Permanganate.

Strength (1) 0.1 g (2) 0.3 g

Storage Preserve in tightly closed containers.

Povidone Iodine



[25655-41-8]

Povidone Iodine is 1-ethenyl-2-Pyrrolidinone homopolymer compound with iodine. It contains not less than 9.0% and not more than 12.0% of available iodine (I), calculated on the dried basis.

Description A yellowish-brown to reddish-brown amorphous powder.

Soluble in water or ethanol; insoluble in ether or chloroform.

Identification Carry out the test according to following methods, using a solution of 0.5 g in 5 ml of water. (1) Add 1 drop of the solution to a mixture of 1 ml of starch TS and 9 ml of water, a deep blue colour is produced.

(2) spread 0.5 ml of the solution over an area of about 7.5 cm × 2.6 cm on a glass plate, and allow it to air-dry overnight at room temperature in an atmosphere of low

readily in water.

Loss on drying Dry about 5 g, weighed accurately, at 105°C for 4 hours, weigh and continue to weigh, once every hour until the difference between two successive weightings at 1 hour intervals is not greater than 5.0 mg; it loses not more than 8.0% of its weight (Appendix VIII L).

Residue on ignition Not more than 0.1% (Appendix VIII N), using 1.0 g.

Heavy metals Carry out the limit test for heavy metals (Appendix VIII H, method 2), using the residue obtained in the Residue on ignition; not more than 0.002%.

Arsenic Mix 1.3 g with 0.5 g of calcium hydroxide and about 2 ml of water. Allow to dry, heat gently until it is thoroughly charred and then ignite at 600°C until the incineration is complete. Cool to room temperature, add 5 ml of hydrochloric acid and 23 ml of water and carry out the limit test for arsenic (Appendix VIII J, method 1); not more than 0.00015%.

Nitrogen content Weigh accurately about 0.50 g and carry out the method for determination of Nitrogen (Appendix VIII D, method 1); not less than 9.5% and not more than 11.5% of N, calculated on the dried basis.

Iodine ion Dissolve about 0.50 g, weighed accurately, in 100 ml of water in a 250 ml conical flask. Add dropwise sodium bisulfite TS until the colour of iodine has disappeared. Add accurately 25 ml of silver nitrate (0.1 mol/L) VS and 10 ml of nitric acid and mix well. Titrate the excess of silver nitrate with ammonium thiocyanate (0.1 mol/L) VS to light brick red colour, using 0.5 ml of ferric ammonium sulfate TS as the indicator. Perform a blank determination and make any necessary correction. Each ml of silver nitrate (0.1 mol/L) VS is equivalent to 12.69 mg of I, the percentage of iodide ion is obtained by subtracting the percentage of available iodine under Assay from the percentage of total iodine calculated on the dried basis. Not more than 6.6%, calculated on the dried basis.

Assay Dissolve 1 g, accurately weighed, in 120 ml of water and shake. Carry out the method for potentiometric titration (Appendix VII A), titrate with sodium thiosulfate (0.1 mol/L) VS. Each ml of sodium thiosulfate (0.1 mol/L) VS is equivalent to 12.69 mg of I.

Category Topical anti-infective.

Storage Preserve in tightly closed containers, protected from light, stored at a cool and dry place.

Preparation (1) Povidone Iodine Cream
(2) Povidone Iodine Gel
(3) Povidone Iodine Solution
(4) Povidone Iodine Suppositories

Povidone Iodine Cream

Povidone Iodine Ointment contains not less than 0.85% and not more than 1.15% (g/g) of povidone iodine, calculated on available iodine (I).

Description A brown-red cream.

Identification To 1 g add 20 ml of water, shake to dissolve povidone iodine. The solution complies with the test for Identification described under Povidone Iodine.

Other requirements Comply with the general requirements

with 120 ml of water, on a water bath at 50°C with shaking occasionally to dissolve povidone-iodine and cool to room temperature. Carry out the method for potentiometric titration (Appendix VII A). Titrate immediately with sodium thiosulfate (0.1 mol/L) VS until the brown colour disappears. Each ml of sodium thiosulfate (0.1 mol/L) VS is equivalent to 12.69 mg of I.

Category As described under Povidone Iodine.

Strength 10%

Storage Preserve in tightly closed containers, protected from light and stored at a cool place.

Povidone Iodine Gel

Povidone Iodine Gel contains not less than 8.5% and not more than 11.5% of the labelled amount of povidone iodine, calculated on available iodine (I).

Description A water soluble, reddish-brown, viscous liquid.

Identification (1) To about 5 g add 20 ml of water, stir to dissolve. The solution complies with the test for Identification described under Povidone Iodine Solution.

Acidity To about 4.0 g add 20 ml of water, stir to dissolve. pH 3.5-4.5 (Appendix VI H).

Viscosity Carry out the method for determination of Viscosity (Appendix VI G, method 2), using NDJ-1 rotating viscosimeter and No. 4 rotator with the rotation speed of 6 rpm, the kinetic viscosity at 25°C is 30-50 Pa · s.

Other requirements Complies with the general requirements for gel (Appendix I U).

Assay Transfer an accurately weighed quantity, equivalent to about 1.0 g of povidone iodine, to a beaker, add 120 ml of water, stir to dissolve. Carry out the method for potentiometric titration (Appendix VII A), titrate with sodium thiosulfate (0.1 mol/L) VS. Each ml of sodium thiosulfate (0.1 mol/L) VS is equivalent to 12.69 mg of I.

Category antiseptic-disinfectant.

Strength (1) 5 g : 0.25 g (containing 0.5% available iodine)
(2) 5 g : 0.5 g (containing 1% available iodine)

Storage Preserve in tightly closed containers, protected from light and stored in a cool place.

Povidone Iodine Solution

Povidone Iodine Solution contains not less than 8.5% and not more than 12.0% of the labelled amount of povidone iodine, calculated on available iodine (I).

Description A reddish-brown colour liquid.

Identification (1) To 1-5 drops add 10 ml of water and 1 drop of starch IS; a dark blue colour is produced.

(2) Transfer 10 ml to a 50 ml conical flask, avoiding contact with the neck of the flask. Cover the mouth of the flask with a piece of glass paper, and moisten it with 1 drop of

pH value 3.0-6.5 (Appendix VI H)

Content variation Comply with the requirements (Appendix X F).

Assay Transfer an accurately measured volume equivalent to about 1.25 g of povidone iodine to a beaker and dilute with water to 125 ml. Carry out the method for potentiometric titration (Appendix VII A), titrate with sodium thiosulfate (0.1 mol/L) VS. Each ml of sodium thiosulfate (0.1 mol/L) VS is equivalent to 12.69 mg of I.

Category As described under Povidone Iodine.

Strength (1) 1% (2) 2.5% (3) 5% (4) 7.5% (5) 10%

Storage Preserve in tightly closed containers, protected from light and stored at a cool place.

Povidone Iodine Suppositories

Each Povidone Iodine Suppository contains not less than 0.017 g and not more than 0.023 g of povidone iodine, calculated on the available iodine (I).

Description A brownish-red suppositories.

Identification To 1 suppository add 20 ml of water, shake to dissolve povidone-iodine. The solution complies with the tests for Identification described under Povidone-Iodine.

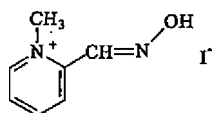
Other requirements Comply with the general requirements for suppositories (Appendix I D).

Assay To 5 suppositories in a iodine flask add 120 ml of water, stopper, shake to dissolve povidone iodine. Titrate immediately with sodium thiosulfate (0.1 mol/L) VS towards the end of titration, add 3 ml of starch TS and continue the titration to the disappearance of blue colour. Each ml of sodium thiosulfate (0.1 mol/L) VS is equivalent to 12.69 mg of I.

Category As described under Povidone Iodine.

Storage Preserve in tightly closed containers, protected from light.

Pralidoxime Iodide



$C_7H_9IN_2O$ 264.07

Pralidoxime Iodide is 2-formyl-1-methylpyridinium iodide oxime.

Description Yellow granular crystals or crystalline powder; odourless; taste, bitter; deteriorated easily on exposure to light. Soluble in water or hot ethanol; slightly soluble in ethanol; insoluble in ether.

Melting range 220-227°C, with decomposition (Appendix VI C).

Specific absorbance Protect from light throughout the

per ml in hydrochloric acid solution (9→1000) at 294 nm within 1 hour (Appendix IV A). The value of A (1%, 1 cm) is 464-494.

Identification Dissolve 0.2 g in 20 ml of water, carry out the following tests.

(1) To 5 ml of the solution add a few drops of potassium iodobismuthate TS; a red brown precipitate is produced.

(2) To 10 ml of the solution add 1 drop of ferric chloride TS; a yellow colour is produced. Add 1 more drop of ferric chloride TS; a brown precipitate is produced (distinction from pralidoxime chloride).

(3) The infrared absorption spectrum (Appendix IV C) is concordant with the reference spectrum of pralidoxime iodide (Appendix XVI).

Cyanides Complies with the limit test for cyanides (Appendix VII F, method 2), using 0.40 g. The absorbance produced is not greater than that of a reference using 1.0 ml of potassium cyanide standard solution (0.0005%).

Free iodine Dissolve 0.10 g in 3 ml of water, add 0.5 ml of starch IS; no blue or violet colour is produced.

Loss on drying When dried to constant weight at 105°C, loses not more than 0.5% of its weight (Appendix VIII L).

Residue on ignition Not more than 0.1% (Appendix VIII N), using 1.0 g.

Heavy metals Carry out the test for heavy metals (Appendix VIII H, method 2), using the residue obtained under the test for Residue on ignition; not more than 0.001%.

Total iodine Dissolve about 0.5 g, accurately weighed, in 50 ml of water, add 10 ml of dilute acetic acid and 10 drops of eosin sodium IS, titrate with silver nitrate (0.1 mol/L) VS, until the colour changes from rose red to violet red. Each ml of silver nitrate (0.1 mol/L) VS is equivalent to 12.69 mg of I. It contains not less than 47.6% and not more than 48.5% of I, calculated on the dried basis.

Category Antidote.

Storage Preserve in tightly closed containers, protected from light.

Preparation Pralidoxime Iodide Injection

Pralidoxime Iodide Injection

Pralidoxime Iodide Injection is a sterile solution of pralidoxime iodide in Water for Injection. It contains not less than 90.0% and not more than 105.0% of the labelled amount of pralidoxime iodide ($C_7H_9IN_2O$).

5% of glucose may be added to the injection as a stabilizing agent.

Description A clear, colourless or almost colourless liquid.

Identification Dilute 10 ml with water to produce 25 ml. The resulting solution complies with the tests (1) and (2) for Identification described under Pralidoxime Iodide.

pH value 3.5-5.0 (Appendix VI H).

Cyanide Carry out the limit test for cyanides (Appendix VII F, method 2), using 2.0 ml. The absorbance is not greater than that of a reference using 2.5 ml of potassium cyanide standard solution (0.00025%).

Free iodine To 4 ml add 0.5 ml of starch IS; no blue or

Decomposition products Protected from light throughout the procedure. Measure the absorbance of the solution obtained under Assay at 294 nm and 262 nm within 1 hour (Appendix IV A); the ratio of the absorbance at 294 nm to that at 262 nm is not less than 3.1.

Pyrogens Complies with the test for pyrogens (Appendix XI D), using 2 ml per kg of the rabbit's weight.

Other requirements Complies with the general requirements for injections (Appendix I B).

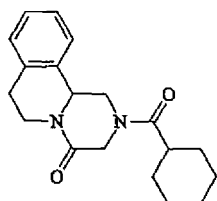
Assay Protected from light throughout the procedure. Transfer 5 ml, accurately measured, to a 250 ml volumetric flask, dilute with hydrochloric acid solution (9→1000) to volume and mix. Transfer 5 ml of the solution, accurately measured, to another 250 ml volumetric flask, dilute with hydrochloric acid solution (9→1000) to volume and mix. Measure the absorbance of the resulting solution at 294 nm within 1 hour (Appendix IV A). Calculate the content of $C_{19}H_{24}N_2O_2$, taking 479 as the value of A (1%, 1 cm).

Category As described under Pralidoxime Iodide.

Strength (1) 5 ml : 0.15 g (2) 20 ml : 0.5 g

Storage Preserve in well closed containers, protected from light.

Praziquantel



$C_{19}H_{24}N_2O_2$ 312.41

[55268-74-1]

Praziquantel is 2-(cyclohexylcarbonyl)-1,2,3,6,7,11b-hexahydro-4H-pyrazino[2,1-a]isoquinolin-4-one. It contains not less than 98.0% and not more than 102.0% of $C_{19}H_{24}N_2O_2$, calculated on the dried basis.

Description A white or almost white crystalline powder; taste, bitter. Freely soluble in chloroform; soluble in ethanol; insoluble in ether or water.

Melting range 136-141°C (Appendix VI C).

Identification (1) The light absorption of a solution of 0.5 mg per ml in ethanol exhibits maxima at 264 nm and 272 nm (Appendix IV A).

(2) The infrared absorption spectrum (Appendix IV C) is concordant with the reference spectrum of praziquantel (Appendix XVI).

Acidity Dissolve 0.50 g in 15 ml ethanol (neutral to methyl red IS), add 1 drop of methyl red IS and 0.10 ml of sodium hydroxide (0.01 mol/L) VS, a yellow colour is produced.

Related substances Carry out the method as described under Assay. Dissolve a quantity of the substance being examined, accurately weighed, in methanol to produce a solution of 1.2 mg per ml [solution (1)] and of 60 mg per ml [solution (2)]. Inject 10 μ l of solution (1) into the column. Adjust

10 μ l each of solution (1) and (2), accurately measured, into the column. Record the chromatogram for twice the retention time of principal peak. The sum of the areas of all peaks other than the principal peak in the chromatogram obtained with solution (2) is not greater than the area of the principal peak obtained with solution (1).

Loss on drying When dried to constant weight at 105°C, loses not more than 0.5% of its weight (Appendix VII L).

Residue on ignition Not more than 0.1% (Appendix VII N); use 1.0 g.

Heavy metals Carry out the limit test for heavy metals (Appendix VIII H, method 2). Using the residue obtained in the test for Residue on ignition; not more than 0.002%.

Assay Carry out the method for high performance liquid chromatography (Appendix V D), using a column packed with octadecylsilane bonded silica gel and a mixture of methanol-water (100 : 40) as the mobile phase. Detective wavelength is 263 nm. The resolution factor between the peaks of praziquantel and internal standard complies with related requirements.

Internal standard solution Dissolve a quantity of α -asarone in methanol to produce a solution of 0.4 mg per ml, mix well.

Procedure Dissolve about 100 mg of praziquantel CRS, accurately weighed, in 5 ml of the internal standard solution, measured accurately, shake to dissolve praziquantel. Dilute with methanol to 10 ml, mix well, as reference solution. Inject 10 μ l of the reference solution into the column and calculate the correction factor. Repeat the operation, using the substance being examined instead of praziquantel CRS, calculate the content of $C_{19}H_{24}N_2O_2$.

Category Anthelmintic.

Storage Preserve in tightly closed containers, protected from light.

Preparation Praziquantel Tablets

Praziquantel Tablets

Praziquantel Tablets contain not less than 93.0% and not more than 107.0% of the labelled amount of praziquantel ($C_{19}H_{24}N_2O_2$).

Description White tablets.

Identification To a quantity of the powdered tablets equivalent to about 10 mg of praziquantel add 20 ml of ethanol. Shake to dissolve praziquantel and filter, discard the initial filtrate. The light absorption of the successive filtrate exhibits maxima at 264 nm and 272 nm (Appendix IV A).

Dissolution Carry out the dissolution test (Appendix X C, method 2), using 900 ml of hydrochloric acid solution (9→1000) containing 2 mg of sodium lauryl sulfate per ml as the dissolution medium, adjust the rotational speed of paddle to 50 rpm. Withdraw 10 ml of the solution after exactly 60 minutes and filter. Measure the absorbance of the successive filtrate (for strength 0.2 g) at 263 nm, or dilute the successive filtrate with the dissolution medium to produce a solution of 0.2 mg per ml, measure the absorbance of the resulting solution (for strength 0.6 g) at 263 nm (Appendix IV A). Dissolve a quantity of praziquantel CRS, accurately weighed, in dissolution medium to produce a solution of 0.2 mg per ml. Repeat the operation. Calculate

than 75% the labelled amount is dissolved.

Other requirements Comply with the general requirements for tablets (Appendix I A).

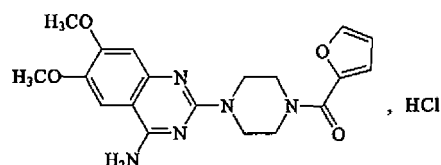
Assay Carry out the assay described under Praziquantel. Weigh accurately and pulverize 20 tablets. To a quantity of the powdered tablets equivalent to about 100 mg of praziquantel, accurately weighed, in a 10 ml volumetric flask, add accurately 5 ml of the internal standard solution, shake thoroughly, dilute with methanol to volume. Mix well and filter. Inject 10 μ l of the successive filtrate into the column, proceed as described under the Assay of Praziquantel and calculate the content of $C_{19}H_{21}N_5O_4$.

Category As described under Praziquantel.

Strength (1) 0.2 g (2) 0.6 g

Storage Preserve in tightly closed containers, protected from light.

Prazosin Hydrochloride



$C_{19}H_{21}N_5O_4 \cdot HCl$ 419.87

[19237-84-4]

Prazosin Hydrochloride is 1-(4-amino-6,7-dimethoxy-2-quinazolinyl)-4-(2-furoyl)-piperazine hydrochloride. It contains not less than 98.0% of $C_{19}H_{21}N_5O_4 \cdot HCl$, calculated on the dried basis.

Description A white or almost white crystalline powder; odourless; tasteless. Slightly soluble in ethanol; practically insoluble in water.

Identification (1) To about 0.1 g add an equal amount of sodium carbonate in a dry test tube, mix well. Ignite, fumes are evolved which turn a filter paper moistened with 1% 1,2-naphthoquinone-4-sodium sulfonate solution to violet.

(2) The light absorption of a 5 μ g per ml solution in ethanol exhibits a maximum at 251 nm (Appendix IV A).

(3) The infrared absorption spectrum (Appendix IV C) is concordant with the reference spectrum of prazosin hydrochloride (Appendix XVI).

(4) The aqueous solution yields the reactions characteristic of chlorides (Appendix III).

Acidity Dissolve 0.30 g in 20 ml of water, filter, the filtrate pH 3.0-4.5 (Appendix VI H).

Related substances Carry out the method for thin-layer chromatography (Appendix V B), using silica gel GF₂₅₄ as the coating substance and ethyl acetate-diethylamine (95 : 5) as the mobile phase. Apply separately to the plate 10 μ l each of two solutions of the substance being examined in a mixture of chloroform-methanol-diethylamine (10 : 10 : 1) containing (1) 5.0 mg per ml, (2) 50 μ g per ml. After developing and removal of the plate, dry it in air, examine under ultraviolet light (254 nm). Any spot other than the principal spot in the chromatogram obtained with solution (1) is not more intense than the principal spot obtained with solution (2).

Isoamyl alcohol Dissolve about 1.0 g in 10 ml of water,

and use the supernatant liquid. Carry out the method for gas chromatography (Appendix V E, method 4), using a column packed with porous polymer beads of divinyl benzene-ethyl vinyl benzene with a diameter of 0.25-0.18 mm, maintain the column temperature at 150°C. The content of isoamyl alcohol is not more than 0.1% (g/g).

Loss on drying When dried to constant weight at 105°C, loses not more than 1.0% of its weight (Appendix VIII L).

Residue on ignition Not more than 0.1% (Appendix VIII N); use 1.0 g.

Heavy metals Use the residue obtained in the test for Residue on ignition, carry out the limit test for heavy metals (Appendix VIII H, method 2); not more than 0.002%.

Assay Dissolve about 0.3 g, accurately weighed, in 20 ml of glacial acetic acid and 6 ml of mercuric acetate TS, add 1 drop of crystal violet IS. Titrate with perchloric acid (0.1 mol/L) VS until the colour change to blue. Perform a blank determination and make any necessary correction. Each ml of perchloric acid (0.1 mol/L) VS is equivalent to 41.99 mg of $C_{19}H_{21}N_5O_4 \cdot HCl$.

Category Antihypertensive.

Storage Preserve in tightly closed containers, protected from light.

Preparation Prazosin Hydrochloride Tablets

Prazosin Hydrochloride Tablets

Prazosin Hydrochloride Tablets contain not less than 90.0% and not more than 110.0% of the labelled amount of prazosin hydrochloride ($C_{19}H_{21}N_5O_4 \cdot HCl$).

Description White tablets.

Identification (1) Triturate a quantity of powdered tablets, equivalent to about 20 mg prazosin hydrochloride, with 1.5 ml of 10% sodium hydroxide solution for 5 minutes. Add 10 ml of chloroform, shake for 15 minutes, allow to stand. Separate the chloroform layer and filter, evaporate the filtrate to dryness. The residue complies with test (1) for Identification described under Prazosin Hydrochloride.

(2) The light absorption of the solution obtained in the Assay exhibits a maximum at 251 nm (Appendix IV A).

(3) The aqueous solution yields the reactions characteristic of chlorides (Appendix III).

Related substances Complies with the test described under Prazosin Hydrochloride but for solution (1) use the supernatant liquid obtained by shaking a quantity of the powdered tablets with a solution of chloroform-methanol-diethylamine (10 : 10 : 1) to produce a suspension containing 3.0 mg of prazosin hydrochloride per ml. For solution (2) dilute solution (1) with the same solvent to produce a solution containing 45 μ g of prazosin hydrochloride per ml.

Content uniformity Comply with the requirements for content uniformity (Appendix X E). Triturate 1 tablet in a mortar with 3 ml of water. Transfer to a 100 ml volumetric flask with about 80 ml of ethanol in portions. Shake thoroughly to dissolve prazosin hydrochloride, dilute with ethanol to volume, mix well and filter. Measure accurately a quantity of the successive filtrate, dilute with ethanol to produce a solution of 3 μ g per ml. Measure the absorbance of the resulting solution as described under Assay.

method 2), using 900 ml of 0.1 mol/L hydrochloride acid solution as the dissolution medium, adjust the rotational speed of the paddle to 75 rpm. Withdraw a quantity of the solution after exactly 30 minutes and filter. Measure the absorbance of the successive filtrate at 246 nm (Appendix IV A). Dissolve 20 mg of prazosin hydrochloride CRS, accurately weighed, with ethanol and dilute to 100 ml, mix well. Transfer accurately 2 ml to a 200 ml volumetric flask, dilute to volume with the dissolution medium, repeat the operation. Calculate the dissolution of $C_{19}H_{21}N_5O_4 \cdot HCl$ from each tablet. Not less than 75% of the labelled amount is dissolved.

Other requirements Comply with the general requirements for tablets (Appendix I A).

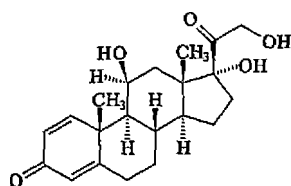
Assay Weigh accurately 20 tablets and powder finely. Transfer a quantity of the powdered tablets, accurately weighed, equivalent to about 15 mg of prazosin hydrochloride to a 100 ml volumetric flask, moisten with 3 ml of water, shake thoroughly, then add 60 ml of ethanol. Heat gently on a water bath and shake for 30 minutes, cool to room temperature, dilute with ethanol to volume, mix well. Filter, measure accurately 2 ml of the successive filtrate to another 100 ml volumetric flask, dilute with ethanol to volume, mix well. Measure the absorbance of the resulting solution at 251 nm (Appendix IV A). Calculate the content of $C_{19}H_{21}N_5O_4 \cdot HCl$, using a 3 µg per ml solution of prazosin hydrochloride CRS as the reference.

Category As described under Prazosin Hydrochloride.

Strength (1) 0.5 mg (2) 1 mg (3) 2 mg

Storage Preserve in tightly closed containers, protected from light.

Prednisolone



$C_{21}H_{28}O_5$ 360.45

[52438-85-4]

Prednisolone is 11β, 17α, 21-trihydroxypregna-1,4-diene-3,20-dione. It contains not less than 97.0% and not more than 102.0% of $C_{21}H_{28}O_5$, calculated on the dried basis.

Description A white or almost white crystalline powder; odourless, taste, slightly bitter; hygroscopic. Soluble in methanol or ethanol; sparingly soluble in acetone or dioxane; slightly soluble in chloroform; very slightly soluble in water.

Melting range 225-236°C, with decomposition (Appendix VI C).

Specific optical rotation +96° to +103°, in a solution of 10 mg per ml in dioxane (Appendix VI E).

Specific absorbance Measure the absorbance of a solution of 10 µg per ml in ethanol at 243 nm (Appendix IV A), the value of *A* (1%, 1cm) is 400-430.

Identification (1) Dissolve 10 mg in 1 ml of methanol, add

(2) Dissolve about 2 mg in 2 ml of sulfuric acid, a scarlet colour without fluorescence is produced gradually; add 10 ml of water, the colour disappears and a grey flocculent precipitate is produced.

(3) The infrared absorption spectrum (Appendix IV C) is concordant with the reference spectrum of prednisolone (Appendix XVI).

Related substances Carry out the method for thin-layer chromatography (Appendix V B), using silica gel G as the coating substance and a mixture of dichloromethane-ether-methanol-water (77 : 12 : 6 : 0.4) as the mobile phase. Apply separately to the plate 5 µl each of two solutions of the substance being examined in chloroform-methanol (9 : 1) containing (1) 3 mg per ml, (2) 60 µg per ml. After developing and removal of the plate, dry in air and then at 105°C for 10 minutes, cool and spray with alkaline tetrazolium blue TS. Not more than 3 secondary spots are obtained in the chromatogram of solution (1) and any secondary spot obtained with solution (1) is not more intense than the principal spot obtained with solution (2).

Loss on drying When dried to constant weight at 105°C, loses not more than 1.0% of its weight (Appendix VIII L).

Assay Carry out the method for high performance liquid chromatography (Appendix V D), using a column packed with an octadecylsilane bonded silica gel and using methanol-water (65 : 35) as the mobile phase. Detection wavelength is 240 nm. The number of theoretical plates of the column is not less than 1000, calculated with reference to the peak of prednisolone; the resolution factor between the peaks of prednisolone and internal standard is not less than 3.5.

Internal standard solution Prepare a solution of 1.5 mg per ml norethisterone CRS in methanol.

Procedure Dissolve a quantity of prednisolone CRS accurately weighed, in methanol to produce a solution of about 1 mg per ml in the reference solution. Measure accurately 5 ml each of reference solution and internal standard solution to a 50 ml volumetric flask, dilute with methanol to volume, mix well, inject 10 µl into the column and calculate the correction factor. Repeat the operations using a quantity of the substance being examined instead of prednisolone CRS, calculate the content of $C_{21}H_{28}O_5$.

Category Corticosteroid.

Storage Preserve in tightly closed containers, protected from light.

Preparation Prednisolone Tablets

Prednisolone Tablets

Prednisolone Tablets contain not less than 90.0% and not more than 110.0% of the labelled amount of prednisolone ($C_{21}H_{28}O_5$).

Description White tablets.

Identification To a quantity of finely powdered tablets equivalent to 50 mg of prednisolone add 30 ml of chloroform, stir until prednisolone is dissolved, filter and evaporate the filtrate to dryness on a water bath. The residue complies with tests (1) and (2) for Identification described under Prednisolone.

X E). Triturate 1 tablet with ethanol and transfer to a 50 ml volumetric flask, add ethanol to volume, shake thoroughly. Filter, discard the initial filtrate, transfer 5 ml of the successive filtrate, accurately measured, into another 50 ml volumetric flask, add ethanol to volume and mix well. Measure the absorbance of the resulting solution at 243 nm (Appendix IV A), calculate the content of $C_{21}H_{28}O_5$, taking 415 as the value of A (1%, 1 cm).

Other requirements Comply with the general requirements for tablets (Appendix I A).

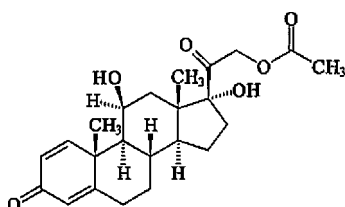
Assay Weigh accurately and pulverize 20 tablets. To an accurately weighed amount of the powder equivalent to 20 mg of prednisolone in a 100 ml volumetric flask add 75 ml of ethanol, shake for 30 minutes, add ethanol to volume and mix well. Filter, transfer accurately 5 ml of the successive filtrate into another 100 ml volumetric flask, dilute with ethanol to volume and mix well. Measure the absorbance of the resulting solution at 243 nm (Appendix IV A), Calculate the content of $C_{21}H_{28}O_5$, taking 415 as the value of A (1%, 1 cm).

Category As described under Prednisolone.

Strength 5 mg

Storage Preserve in tightly closed containers, protected from light.

Prednisolone Acetate



$C_{23}H_{30}O_6$ 402.49

[52-21-1]

Prednisolone Acetate is 11β , 17α , 21-trihydroxy-pregna-1,4-diene-3,20-dione-21-acetate. It contains not less than 96.0% and not more than 102.0% of $C_{23}H_{30}O_6$, calculated on the dried basis.

Description A white or almost white crystalline powder; odourless; taste, bitter.

Slightly soluble in ethanol or chloroform; practically insoluble in water.

Specific optical rotation $+112^\circ$ to $+119^\circ$, in a solution of about 10 mg per ml in dioxane (Appendix VI E).

Specific absorbance Measure the absorbance of a solution of 10 μ g per ml in dehydrated ethanol at 243 nm (Appendix IV A), the value of A (1%, 1 cm) is 355-385.

Identification (1) Dissolve about 20 mg in 1 ml of methanol by warming, add 1 ml of hot alkaline cupric tartrate TS; an orangish-red precipitate is produced.

(2) Dissolve about 2 mg in 2 ml of sulfuric acid, allow to stand for 5 minutes; a rose red colour is produced. On adding 10 ml of water, the colour disappears and a grey flocculent precipitate is produced.

(3) The retention time of principal peak of the substance being examined is identical with that of principal peak of the reference solution in the chromatogram obtained in Assay.

(4) The infrared absorption spectrum (Appendix IV C) is

acetate (Appendix XVI).

Related substances Carry out the method for thin-layer chromatography (Appendix V B), using silica gel G as the coating substance and a mixture of dichloromethane-ether-methanol-water (385 : 60 : 15 : 2) as the mobile phase. Apply separately to the plate 5 μ l each of two solutions of the substance being examined in chloroform-methanol (9 : 1) containing (1) 4 mg per ml, (2) 0.12 mg per ml. After developing and removal of the plate, dry it in air and then at 105°C for 10 minutes, cool and spray with alkaline tetrazolium blue TS. Any spot in the chromatogram obtained with solution (1) other than the principal spot is not more intense than the principal spot obtained with solution (2).

Loss on drying When dried to constant weight at 105°C , loses not more than 0.5% of its weight (Appendix VII L).

Assay Carry out the method for high performance liquid chromatography (Appendix V D), using a column packed with octadecylsilane bonded silica gel and a mixture of methanol-water (70 : 30) as the mobile phase. Detection wavelength is 240 nm and the number of theoretical plates of the column is not less than 3000, calculated with reference to the peak of prednisolone acetate. The resolution factor between the peaks of prednisolone acetate and internal standard complies with the related requirements.

Internal standard solution Prepare a solution of fluocinonide CRS of about 0.50 mg per ml in methanol.

Procedure Dissolve a quantity of prednisolone acetate CRS accurately weighed in methanol to produce a solution of about 0.50 mg per ml as the reference solution. Measure accurately 5 ml each of reference solution and internal standard solution to a 25 ml volumetric flask, dilute with methanol to volume, mix well, inject 5 μ l into the column and calculate the correction factor. Repeat the operations using a quantity of the substance being examined instead of prednisolone acetate CRS. Calculate the content of $C_{23}H_{30}O_6$.

Category Corticosteroid.

Storage Preserve in tightly closed containers, protected from light.

Preparation (1) Prednisolone Acetate Cream
(2) Prednisolone Acetate Injection
(3) Prednisolone Acetate Tablets

Prednisolone Acetate Cream

Prednisolone Acetate Cream contains not less than 90.0% and not more than 110.0% of the labeled amount of prednisolone acetate ($C_{23}H_{30}O_6$).

Description A white cream.

Identification (1) Dissolve 1 g in dehydrated ethanol, shake vigorously, filter and allow the filtrate to evaporate to dryness on a water bath. Add sulfuric acid TS to the residue and mix well, a red colour is produced. Add 10 ml to 15 ml of water, the red colour disappears and a white precipitate is produced.

(2) To 15 g add 70 ml of dehydrated ethanol, warm by heating in the water bath, shake well, cool in an ice bath and filter. Evaporate about 30 ml of filtrates on a water bath to dryness. Add 1 ml of methanol to the residue, allow it to dissolve by heating and add warm copper tartrate TS, a reddish-orange precipitate is produced.

Other requirements Complies with requirements for cream

Assay Reference preparation To 20 mg of prednisolone acetate CRS, weighed accurately, in a 100 ml volumetric flask add a quantity of dehydrated ethanol, shake and allow it to dissolve. Add dehydrated ethanol to volume and mix well.

Test preparation To about 4 g of the cream equivalent to 20 mg of prednisolone acetate, weighed accurately, in a beaker add about 30 ml of dehydrated ethanol, heat on a water bath, stir vigorously. Cool in an ice bath, filter and transfer the filtrate to a 100 ml volumetric flask. Repeat this operation for three times. Combine the filtrates, add dehydrated ethanol to volume and mix well.

Procedure To 1 ml each of two preparations, accurately measured, in separate dry test tubes with stopper add 9 ml of dehydrated ethanol and 2 ml of triphenyltetrazolium chloride TS, accurately measured, and mix well; then add 1 ml of tetramethylammonium hydroxide TS, accurately measured, and mix well. Allow to stand in dark place at 25°C for 40-50 minutes. Measure the absorbance at 485 nm (Appendix IV A). Calculate the content of $C_{23}H_{30}O_6$.

Category Corticosteroids.

Strength (1) 4 g : 0.02 g (2) 10 g : 0.05 g

Storage Preserve in tightly closed containers, stored at cold place.

Prednisolone Acetate Injection

Prednisolone Acetate Injection is a sterile suspension of prednisolone. It contains not less than 90.0% and not more than 110.0% of the labelled amount of prednisolone acetate ($C_{23}H_{30}O_6$).

Description A suspension of minute granules which deposit on standing, a homogeneous creamy white suspension is obtained on shaking.

Identification Complies with tests (1) for Identification described under Prednisolone Acetate.

pH value 4.2-7.0 (Appendix VI H).

Other requirements Complies with the general requirements for injections (Appendix I B)

Assay Reference preparation Dissolve 25 mg of prednisolone acetate CRS, weighed accurately, in a 100 ml volumetric flask with dehydrated ethanol, dilute to volume with dehydrated ethanol and mix well.

Test preparation Dilute 1 ml of the injection, accurately measured, equivalent to 25 mg of prednisolone acetate in a 100 ml volumetric flask with dehydrated ethanol to volume and mix well. Allow it stand to deposit, use supernatant liquid as the test solution.

Procedure To 1 ml each of above two preparations, accurately measured, in dry test tubes with stopper add 9 ml of dehydrated ethanol, accurately measured, and shake well. Use 10 ml of dehydrated ethanol as the blank solution. To each tube, add accurately 1 ml of triphenyltetrazolium chloride TS and 1 ml of tetramethylammonium hydroxide TS and mix well. Allow to stand in the dark place 25°C for 40-50 minutes. Measure the absorbance at 485 nm (Appendix IV A). Calculate the content of $C_{23}H_{30}O_6$.

Category As described under Prednisolone Acetate.

Strength (1) 1 ml : 25 mg (2) 5 ml : 125 mg

Prednisolone Acetate Tablets

Prednisolone Acetate Tablets contain not less than 90.0% and not more than 110.0% of the labelled amount of prednisolone acetate ($C_{23}H_{30}O_6$).

Description White tablets.

Identification Triturate an amount of finely pulverized tablets, equivalent to 0.1 g of prednisolone acetate, with 30 ml of chloroform in divided portions, filter, evaporate the filtrate to dryness on a water bath. The residue complies with tests (1), (2) and (3) for Identification described under Prednisolone Acetate.

Content uniformity Comply with the requirements (Appendix X E). Triturate 1 tablet with a quantity of dehydrated ethanol to dissolve prednisolone acetate, and dilute with dehydrated ethanol to produce a solution of 10 µg per ml, filter. Measure the absorbance of the filtrate at 243 nm (Appendix IV A). Calculate the content of $C_{23}H_{30}O_6$, taking 370 as the value of A (1%, 1 cm).

Other requirements Comply with the general requirements for tablets (Appendix I A).

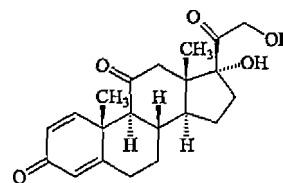
Assay Weigh accurately and powder finely 20 tablets. To a quantity of the powder, accurately weighed, equivalent to 20 mg of prednisolone acetate in a 100 ml volumetric flask, add 60 ml of dehydrated ethanol, shake thoroughly for 15 minutes, dilute with dehydrated ethanol to volume, mix well. Filter, transfer, accurately 5 ml of the successive filtrate to another 100 ml volumetric flask, dilute with dehydrated ethanol to volume and mix well. Measure the absorbance of the resulting solution at 243 nm (Appendix IV A). Calculate the content of $C_{23}H_{30}O_6$, taking 370 as the value of A (1%, 1 cm).

Category As described under Prednisolone Acetate.

Strength 5 mg

Storage Preserve in tightly closed containers, protected from light.

Prednisone



$C_{21}H_{26}O_5$ 358.43

[53-03-2]

Prednisone is 17α, 21-dihydroxypregna-1,4-diene-3,11,20-trione. It contains not less than 97.0% and not more than 102.0% of $C_{21}H_{26}O_5$, calculated on the dried basis.

Description A white or almost white, crystalline powder; odourless. Slightly soluble in chloroform or ethanol; practically insoluble in water.

Storage Preserve in tightly closed containers, protected from light. With decomposition: insert the

Specific optical rotation $+167^{\circ}$ to $+175^{\circ}$, in a solution of 5 mg per ml in dioxane (Appendix VI E).

Specific absorbance Dissolve an accurately weighed quantity in ethanol to produce a solution of 15 μ g per ml, measure the absorbance at 240 nm (Appendix IV A), the value of A (1%, 1 cm) is 405-435.

Identification (1) Dissolve about 5 mg in 2 ml of sulfuric acid, allow to stand for 5 minutes; an orange colour appears. Pour it to 10 ml of water; it changes to a yellow colour and then gradually changes to bluish-green.

(2) The infrared absorption spectrum (Appendix IV C) is concordant with the reference spectrum of prednisone (Appendix XVI).

Related substances Carry out the method for high performance liquid chromatography (Appendix V D), using a column packed with silica gel and a mixture of chloroform-methanol (98 : 2) as the mobile phase. Detection wavelength is 254 nm. The number of the theoretical plates of the column is not less than 2500, calculated with reference to the peak of prednisone and the resolution factor between the peaks of prednisone and adjacent impurity complies with the related requirements. Dissolve a quantity of the substance being examined, with mobile phase in a brown volumetric flask to produce a solution of about 1.25 mg per ml as the test solution (1). Measure accurately 1 ml of the test solution into a 100 ml brown volumetric flask and dilute to volume with mobile phase as the reference solution (2). Inject 20 μ l of solution (2) into the column, adjust the attenuation so that the peak height of the principal peak in the chromatogram is about 25%-30% of full scale of the chart. Inject separately 10 μ l of the solution (1) and (2) into the column and record the chromatogram for 2.5 times of the retention time of the principal peak. In the chromatogram of solution (1), the area of any secondary peak is not greater than the area of the principal peak in the chromatogram of solution (2), the sum of the areas of all secondary peaks is not greater than twice the area of the principal peak of solution (2).

Loss on drying When dried at 105°C , loses not more than 1.0% of its weight; use 0.5 g.

Assay Carry out the method for high performance liquid chromatography (Appendix V D), using a column packed with an octadecyl silane bonded silica gel and a mixture of water-tetrahydrofuran-methanol (688 : 250 : 62) as the mobile phase. The detection wavelength is 254 nm, number of theoretical plates of the column is not less than 3000, calculated with reference to the peak of prednisone. The resolution factor between the peaks of prednisone and internal standard complies with related requirement.

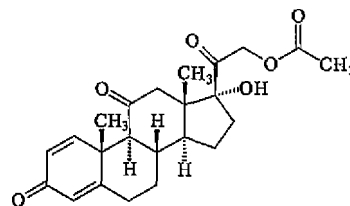
Internal standard solution Prepare a solution of acetanilide in dilute methanol (1 \rightarrow 2) with a concentration of about 0.11 mg per ml.

Procedure Prepare a solution in dilute methanol (1 \rightarrow 2) of an accurately weighed quantity of prednisone CRS of about 0.2 mg per ml. Transfer accurately 5 ml of the solution and 5 ml of internal standard solutions to a 50 ml volumetric flask, add dilute methanol (1 \rightarrow 2) to volume and mix well; inject 10 μ l into the column and record the chromatogram. Repeat the operation, using the substance being examined instead of prednisone CRS. Calculate the content of $\text{C}_{21}\text{H}_{28}\text{O}_5$.

Category Corticosteroid.

Storage Preserve in tightly closed containers, protected from light.

Prednisone Acetate



$\text{C}_{23}\text{H}_{28}\text{O}_6$ 400.47

Prednisone Acetate is 17 α , 21-dihydroxypregna-1,4-diene-3,11,20-trione-21-acetate. It contains not less than 97.0% and not more than 102.0% of $\text{C}_{23}\text{H}_{28}\text{O}_6$, calculated on the dried basis.

Description A white or almost white crystalline powder; odourless, taste, bitter.

Freely soluble in chloroform; sparingly soluble in acetone; slightly soluble in ethanol or ethyl acetate; insoluble in water.

Melting range $235\text{--}242^{\circ}\text{C}$, with decomposition (Appendix VI C).

Specific optical rotation $+183^{\circ}$ to $+190^{\circ}$, in a solution of 10 mg per ml in dioxane (Appendix VI E).

Specific absorbance Measure the absorbance of a solution of 10 μ g per ml in dehydrated ethanol at 238 nm (Appendix IV A), the value of A (1%, 1 cm) is 373-397.

Identification (1) Dissolve about 1 mg in 2 ml of ethanol, add 2 drops of 10% sodium hydroxide solution and 1 ml of triphenyl-tetrazolium chloride TS; a red colour is produced. (2) Dissolve about 5 mg in 1 ml of sulfuric acid, allow to stand for 5 minutes; an orange colour is produced. Pour the solution into 10 ml of water, the colour changes to yellow and subsequently to bluish-green.

(3) The retention time of principal peak of the substance being examined is identical with that of principal peak of the reference solution in the chromatogram obtained in Assay.

(4) The infrared absorption spectrum (Appendix IV C) is concordant with the reference spectrum of prednisone acetate (Appendix XVI).

Related substances Carry out the method for thin-layer chromatography (Appendix V B), using silica gel G as the coating substance and dichloromethane-ether-methanol-water (385 : 60 : 15 : 2) as the mobile phase. Apply separately to the plate 5 μ l each of two solutions of the substance being examined in chloroform-methanol (9 : 1) containing (1) 4.0 mg per ml, (2) 80 μ g per ml. After developing and removal of the plate, dry in air and then at 105°C for 10 minutes, cool and spray with alkaline tetrazolium blue TS. Any spot in the chromatogram obtained with solution (1) other than the principal spot is not more intense than the principal spot obtained solution (2).

Loss on drying When dried to constant weight at 105°C , loses not more than 0.5% of its weight (Appendix VIII L).

Assay Carry out the method for high performance liquid chromatography (Appendix V D), using a column packed with an octadecylsilane bonded silica gel and using methanol-water (58 : 42) as the mobile phase. The wavelength of the detector is 240 nm. The number of theoretical plates of the column is not less than 2000, calculated with reference to the

the peaks of prednisone acetate and internal standard complies with the related requirements.

Internal standard solution Prepare a solution of hydrocortisone CRS of about 0.30 mg per ml in methanol.

Procedure Dissolve a quantity of prednisone acetate CRS, accurately weighed, in methanol to produce a solution of about 0.40 mg per ml, as the reference solution. Measure accurately 10 ml each of reference solution and internal standard solution to a 25 ml volumetric flask, dilute with methanol to volume, mix well, inject 10 μ l into the column and record the peak area in the chromatogram. Repeat the operations using a quantity of the substance being examined instead of prednisone acetate CRS. Calculate the content of $C_{23}H_{28}O_6$.

Category Corticosteroid.

Storage Preserve in tightly closed containers, protected from light.

Preparation (1) Prednisone Acetate Eye Ointment
(2) Prednisone Acetate Tablets

Prednisone Acetate Eye Ointment

Prednisone Acetate Eye Ointment contains not less than 90.0% and not more than 110.0% of the labelled amount of prednisone acetate ($C_{23}H_{28}O_6$).

Description Light yellow eye ointment.

Identification Place 2 g of the eye ointment in a stoppered conical flask, add 30 ml of petroleum ether, shake thoroughly until the eye ointment base is dissolved. Filter, wash the residue with several portions of petroleum ether, then dissolve the residue in 10 ml of dehydrated ethanol by warming and stirring, cool in an ice bath and filter again. Evaporate the filtrate on a water bath to dryness, dissolve the residue in 5 ml of chloroform, the solution complies with test (2) for Identification described under Prednisone Acetate Tablets.

Other requirements Complies with the general requirements for eye preparation (Appendix I G).

Assay Reference preparation Place 25 mg of prednisone acetate CRS, accurately weighed, in a 100 ml volumetric flask, add dehydrated ethanol to volume and mix well.

Test preparation Place 5 g of the eye ointment equivalent to 25 mg of prednisone acetate, accurately weighed, in a beaker, add 30 ml of dehydrated ethanol, heat on a water bath and stir thoroughly, cool in an ice bath and filter into a 100 ml volumetric flask. Repeat the extraction twice more, combine all the filtrates in the same volumetric flask, add dehydrated ethanol to volume and mix well.

Procedure Transfer separately 1 ml each of the two preparations, accurately measured, to stoppered test tubes, add to each tube exactly 9 ml of dehydrated ethanol and 2 ml of triphenyltetrazolium chloride TS, mix well, add exactly 2 ml of tetramethylammonium hydroxide TS and mix well. Allow to stand in the dark at 25°C for 40 minutes and measure the absorbance at 485 nm (Appendix IV A). Calculate the content of $C_{23}H_{28}O_6$.

Category As described under Prednisone Acetate.

Strength 0.5%

Prednisone Acetate Tablets

Prednisone Acetate Tablets contain not less than 90.0% and not more than 110.0% of the labelled amount of prednisone acetate ($C_{23}H_{28}O_6$).

Description White tablets.

Identification To a quantity of powdered tablets equivalent to 0.1 g of prednisone acetate add 50 ml of chloroform, stir until prednisone acetate is dissolved and filter, use the filtrate for the following tests.

(1) Evaporate the filtrate to dryness on a water bath, the residue complies with tests (2) and (3) for Identification described under Prednisone Acetate.

(2) Dissolve prednisone acetate CRS in chloroform to produce a solution of 2 mg per ml as reference solution. Carry out the method for thin-layer chromatography (Appendix V B), using silica gel G as the coating substance and dichloromethane-ether-methanol-water (385 : 60 : 15 : 2) as the mobile phase. Apply separately to the plate 5 μ l each of the filtrate and the reference solution. After developing and removal of the plate, dry it in air and then at 105°C for 10 minutes, cool and spray with alkaline tetrazolium blue TS. The principal spots in the chromatogram obtained with the two solutions are identical in position and colour.

Content uniformity Comply with the requirements (Appendix X E). Moisten 1 tablet with 5 drops of dehydrated ethanol and triturate it with a quantity of dehydrated ethanol then transfer to a 50 ml volumetric flask with 40 ml of dehydrated ethanol in divided portions, shake thoroughly to dissolve prednisone acetate, dilute with dehydrated ethanol to volume, mix well, filter with a dry filter paper. Discard the initial filtrates. Measure accurately 5 ml of the successive filtrate to another 50 ml volumetric flask, mix well. Measure the absorbance of the resulting solution at 238 nm (Appendix IV A). Calculate the content of $C_{23}H_{28}O_6$, taking 385 as the value of A (1%, 1 cm).

Dissolution Carry out dissolution test (Appendix X C, method 2), using 600 ml of 0.25% sodium lauryl sulfate solution as the dissolution medium, adjust the rotational speed of paddle to 100 rpm, take a quantity solution after exactly 45 minutes and filter, using successive filtrate solution as test solution. Dissolve a quantity of prednisone acetate CRS, accurately weighed, in dehydrated ethanol and dilute to about 1 mg per ml. Withdraw 2 ml of the resulting solution, accurately measured, transfer to 200 ml volumetric flask, dilute with dissolution medium to volume and mix well as reference solution. Measure the absorbance of two solutions at 242 nm and 267 nm (Appendix IV A). By the difference between two absorbances, respectively. Calculate the dissolution of $C_{23}H_{28}O_6$ from each tablet. Not less than 70% of the labelled amount is dissolved.

Other requirements Comply with the general requirements for tablets (Appendix I A).

Assay Carry out the method for high performance liquid chromatography (Appendix V D), using a column packed with octadecylsilane bonded silica gel and a mixture of methanol-water (60 : 40) as the mobile phase. Detection wavelength is 240 nm, and the number of theoretical plates of the column is not less than 2000, calculated with reference to the peak of prednisone acetate.

Procedure Weigh accurately and powder 20 tablets. To a quantity, weighed accurately, equivalent to about 5 mg of

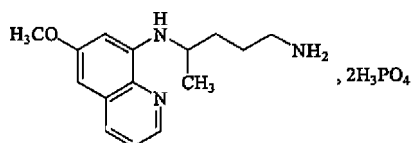
acetate dissolved, then dilute with methanol to volume, mix well and filter, take the successive filtrate as the test solution. Inject 20 μ l of the test solution into the column and record the chromatogram. Dissolve a quantity of prednisone acetate CRS, accurately weighed, with methanol to produce a solution of about 0.1 mg per ml as the reference solution. Repeat the operations using the reference solution instead of the test solution, calculate the content of $C_{23}H_{28}O_6$ with respect to the peak area obtained in the chromatogram by the external standard method.

Category As described under Prednisone Acetate.

Strength 5 mg

Storage Preserve in tightly closed containers, Protected from light.

Primaquine Phosphate



$C_{15}H_{21}N_3O \cdot 2H_3PO_4$ 455.34 [63-45-6]

Primaquine Phosphate is N^4 -(6-methoxy-8-quinoliny)-1,4-pentanediamine phosphate (1 : 2). It contains not less than 98.0% of $C_{15}H_{21}N_3O \cdot 2H_3PO_4$, calculated on the dried basis.

Description An orange-red crystalline powder; odourless; taste, bitter.

Soluble in water; insoluble in chloroform or ether.

Melting range 200-205°C, with decomposition (Appendix VI C).

Identification (1) Dissolve 10 mg in 5 ml of water, add 1 ml of 5% ceric ammonium sulfate solution in dilute nitric acid; a deep violet colour develops.

(2) The light absorption of a solution of 15 μ g per ml in 0.01 mol/L hydrochloric acid solution exhibits maxima at 265 nm and 282 nm; the absorbance is about 0.50-0.52 and 0.49-0.51, respectively (Appendix IV A).

(3) The infrared absorption spectrum (Appendix IV C) is concordant with the reference spectrum of primaquine phosphate (Appendix XVI).

(4) Dissolve about 50 mg in 5 ml of water, add 2 ml of sodium hydroxide TS, filter. The filtrate, neutralized with dilute nitric acid, yields the reactions characteristic of phosphates (Appendix III).

Acidity Dissolve 0.50 g in 50 ml of water, pH 2.5-3.5 (Appendix VI H).

Loss on drying When dried to constant weight at 105°C, loses not more than 0.5% of its weight (Appendix VIII L).

Related substances Carry out the method for thin-layer chromatography (Appendix V B), using silica gel GF₂₅₄ as the coating substance and a mixture of ethyl acetate-isopropanol-concentrate ammonia solution (43 : 35 : 5) as the mobile phase. Apply separately to the plate 10 μ l of each of the following solutions in water-methanol (1 : 1) containing (1) 10 mg per ml, (2) 0.2 mg per ml, (3) 0.1 mg per ml of the substance being examined. After developing and removal of the plate, dry it in air, examine under ultraviolet light (254 nm), not more than two secondary spots are

Any secondary spot obtained with solution (1) is not more intense than the principal spot obtained with solution (3); not more than one secondary spot in the chromatogram obtained with solution (1) is not more intense than the principal spot obtained with solution (2).

Assay Dissolve about 0.15 g, accurately weighed, in 40 ml of glacial acetic acid. Carry out the method for potentiometric titration (Appendix VII A), titrate with perchloric acid (0.1 mol/L) VS. Perform a blank determination and make any necessary correction. Each ml of perchloric acid (0.1 mol/L) VS is equivalent to 22.77 mg of $C_{15}H_{21}N_3O \cdot 2H_3PO_4$.

Category Antimalarial.

Storage Preserve in tightly closed containers, protected from light.

Preparation Primaquine Phosphate Tablets

Primaquine Phosphate Tablets

Primaquine Phosphate Tablets contain not less than 90.0% and not more than 110.0% of the labelled amount of primaquine phosphate ($C_{15}H_{21}N_3O \cdot 2H_3PO_4$).

Description Sugar coated tablets with orange red core.

Identification (1) Dissolve a quantity of the powdered tablets equivalent to about 60 mg of primaquine phosphate, in 10 ml of water with coating removed, filter. The filtrate complies with tests (1) and (4) for Identification described under Primaquine Phosphate.

(2) Dissolve a quantity of the powdered tablets in hydrochloric acid solution (0.01 mol/L) to produce a solution of 15 μ g per ml and filter. The filtrate exhibits maxima at 265 nm and 282 nm (Appendix IV A).

Content uniformity Comply with the requirements for content uniformity (Appendix X E). Triturate 1 tablet with hydrochloric acid solution (0.01 mol/L) in 100 ml volumetric flask, dilute with hydrochloric acid solution (0.01 mol/L) to volume, mix well and filter. Measure accurately 3 ml of the successive filtrate to another 25 ml volumetric flask, add hydrochloric acid solution (0.01 mol/L) to volume and mix well, carry out the method as described under Dissolution.

Dissolution Comply with the requirements for dissolution test (Appendix X C, method 1), using 900 ml hydrochloric acid solution (0.01 mol/L) as the dissolution medium, adjust the rotational speed of the paddle to 100 rpm. Withdraw 10 ml of the solution at 60 minutes and filter. A quantity of the successive filtrate, as test solution. Measure the absorbance of the resulting solution at 342 nm (Appendix IV A). Calculate the content of primaquine phosphate ($C_{15}H_{21}N_3O \cdot 2H_3PO_4$), from each other, taking 342 as the value of A (1%, 1 cm). Not less than 75% of the labelled amount is dissolved.

Other requirements Comply with the general requirements for tablets (Appendix I A).

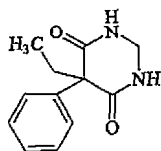
Assay Weigh and powder 50 tablets with coating removed. Weigh accurately a quantity of the powder equivalent to about 0.3 g of primaquine phosphate, carry out the method for dead-stop titration (Appendix VII A), titrate with sodium nitrite (0.05 mol/L) VS, the galvanometer sensitivity is changed to 10^{-8} A per unit scale. Each ml of sodium nitrite (0.05 mol/L) VS is equivalent to 22.77 mg of $C_{15}H_{21}N_3O$.

Category As described under Primaquine Phosphate.

Strength 13.2 mg

Storage Preserve in tightly closed containers, protected from light.

Primidone



$C_{12}H_{14}N_2O_2$ 218.26

[125-33-7]

Primidone is 5-ethyl-5-phenyl-4,6 (1*H*, 5*H*)-Pyrimidine-dione. It contains not less than 98.5% of $C_{12}H_{14}N_2O_2$, calculated on the dried basis.

Description A white crystalline powder; odourless; taste, slightly bitter.

Slightly soluble in ethanol; practically insoluble in water, acetone or benzene.

Melting range 280-284°C (Appendix VI C).

Identification (1) Warm 0.1 g with 5 ml of chromotropic acid TS on a water bath for 30 minutes; a purple colour is produced.

(2) Ignite 0.1 g with 0.1 g of anhydrous sodium carbonate, ammonia vapor is evolved which turns a moistened red litmus paper blue.

(3) The infrared absorption spectrum (Appendix IV C) is concordant with the reference spectrum of primidone (Appendix XVI).

Chlorides Shake 1.0 g with 50 ml of water for 5 minutes and filter. Carry out the limit test for chlorides (Appendix VIII A), using 25 ml of the filtrate. Any opalescence produced is not more intense than that of a reference using 7.0 ml of sodium chloride standard solution (0.014%).

Loss on drying When dried to constant weight at 105°C, loses not more than 0.5% of its weight (Appendix VIII L).

Residue on ignition Not more than 0.1% (Appendix VII N); use 2.0 g.

Heavy metals To the residue obtained in the test for Residue on ignition add 1 ml of nitric acid, evaporate to dryness and completely expel the nitrogen oxide vapour. Add 2 ml of hydrochloric acid and evaporate on a water bath to dryness. Add 5 ml of water and evaporate to dryness. Dissolve the residue in 15 ml of water and 4 ml of acetate BS (pH 3.5) by warming, add water to produce 50 ml and mix well. Carry out the limit test for heavy metals (Appendix VIII H, method 1), using 25 ml of the resulting solution; not more than 0.001%.

Zinc Transfer the remaining 25 ml of the solution obtained in the test for Heavy metals to a 50 ml Nessler cylinder, add 4 ml of hydrochloric acid solution (1 → 2) and 3 ml of potassium ferrocyanide TS, add water to volume and mix well. Any opalescence produced is not more intense than that of a reference using 2.0 ml of zinc standard solution [dissolve 44 mg of zinc sulfate ($ZnSO_4 \cdot 7H_2O$), accurately weighed, in water in a 100 ml volumetric flask, add water to volume and mix well. Measure accurately 10 ml to

the substance being examined. (0.002%).

Assay Carry out the determination of nitrogen (Appendix VII D, method 1), using 0.2 g, accurately weighed. Each ml of sulfuric acid (0.05 mol/L) VS is equivalent to 10.91 mg of $C_{12}H_{14}N_2O_2$.

Category Anti-epileptic agent.

Storage Preserve in tightly closed containers, Protected from light.

Preparation Primidone Tablets

Primidone Tablets

Primidone Tablets contain not less than 95.0% and not more than 105.0% of the labelled amount of primidone ($C_{12}H_{14}N_2O_2$).

Description White tablets.

Identification To a quantity of powdered tablets equivalent to about 0.25 g of primidone add 30 ml of ethanol, warm to dissolve primidone and filter. Evaporate the filtrate on a water bath to dryness, the residue complies with tests (1) and (2) for Identification described under Primidone.

Dissolution Comply with the requirements for dissolution test (Appendix X C, method 2), using 900 ml of water as the dissolution medium, adjust the rotational speed of the paddle to 50 rpm. Withdraw 10 ml of the solution at 60 minutes and filter. The successive filtrate as a test solution. Dissolve 25 mg primidone CRS in water in 100 ml volumetric flask, ultrasonicate to dissolve the primidone, cool to room temperature and add water to volume as a reference solution. Measure the absorbance of the resulting solution at 257 nm (Appendix IV A). Calculate the dissolution of $C_{12}H_{14}N_2O_2$ from each other, not less than 70% of the labelled amount is dissolved.

Other requirements Comply with the general requirements for tablets (Appendix I A).

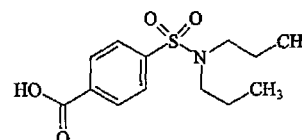
Assay Weigh accurately and powder 15 tablets. Weigh accurately a quantity equivalent to about 0.25 g of primidone, carry out the determination of nitrogen (Appendix VII D, method 1). Each ml of sulfuric acid (0.05 mol/L) VS is equivalent to 10.91 mg of $C_{12}H_{14}N_2O_2$.

Category As described under Primidone.

Strength (1) 50 mg (2) 100 mg (3) 250 mg

Storage Preserve in tightly closed containers, protected from light.

Probenecid



$C_{13}H_{19}NO_4S$ 285.36

[57-66-9]

Probenecid is 4-[(dipropylamino) sulfonyl]-benzoic acid. It contains not less than 98.5% of

Description A white crystalline powder; odourless; taste, slightly bitter.

Soluble in acetone; sparingly soluble in ethanol or chloroform; Practically insoluble in water; soluble in dilute sodium hydroxide solution; practically insoluble in dilute acids.

Melting range 198-201°C (Appendix VI C).

Identification (1) To about 5 mg add 0.2 ml of 0.1 mol/L sodium hydroxide solution and water to produce 2 ml (pH about 5.6-6.0), add 1 drop of ferric chloride TS; a creamy precipitate is produced.

(2) To about 0.1 g add a small quantity of sodium hydroxide, heat gently to fuse for a few minutes and cool. Add a few drops of nitric acid to the residue, dissolve and acidify with hydrochloric acid, then dilute with a small quantity of water and filter. The filtrate yields the reactions characteristic of sulfates (Appendix III).

(3) Add ethanolic hydrochloric acid [to 2 ml of hydrochloric acid solution (9→1000) add ethanol to produce 100 ml] to produce a solution of 20 µg per ml. The light absorption of the solution exhibits maxima at 225 nm and 249 nm; the absorbance at 249 nm is about 0.67 (Appendix IV A).

(4) The infrared absorption spectrum (Appendix IV C) is concordant with the reference spectrum of probenecid (Appendix XVI).

Acidity To 2.0 g add 100 ml of freshly boiled and cooled water, warm on a water bath for 5 minutes with shaking, cool and filter. To 50 ml of the filtrate add a few drops of phenolphthalein IS, titrate with sodium hydroxide (0.1 mol/L) VS. The sodium hydroxide (0.1 mol/L) VS consumed is not more than 0.25 ml.

Chlorides To 1.6 g add 100 ml of water and 1 ml of nitric acid, warm on a water bath for 5 minutes with shaking, cool and filter. Carry out the limit test for chlorides (Appendix VIII A), using 25 ml of the filtrate. Any opalescence produced is not more pronounced than that of a reference using 7.0 ml of sodium chloride standard solution (0.018%).

Sulfates Carry out the limit test for sulfates (Appendix VIII B), using 25 ml of the remaining filtrate obtained in the test for chlorides. Any opalescence produced is not more pronounced than that of a reference using 1.0 ml of potassium sulfate standard solution (0.025%).

Related substances Carry out the method for thin-layer chromatography (Appendix V B), using silica gel GF₂₅₄ as the coating substance and *n*-butanol-1.7% ammonia solution (15 : 3) as the mobile phase. Apply separately to the plate 20 µl each of two solutions of the substance being examined in a mixture of 1.7% ammonia solution-ethanol (1 : 9) containing (1) 10 mg per ml, (2) 50 µg per ml. After developing and removal of the plate, dry in air and examine under ultraviolet light (254 nm). Any spot in the chromatogram, other than the principal spot obtained with solution (1) is not more intense than the principal spot obtained with solution (2).

Loss on drying When dried to constant weight at 105°C, loses not more than 0.5% of its weight (Appendix VIII L).

Residue on ignition Not more than 0.1% (Appendix VIII N).

Heavy metals Dissolve 1.0 g in 10 ml of sodium hydroxide TS, add water to produce 25 ml, carry out the limit test for heavy metals (Appendix VIII H, method 3); not more than 0.001%.

Assay Dissolve about 0.6 g, accurately weighed in 50 ml of

drops of phenolphthalein IS, titrate with sodium hydroxide (0.1 mol/L) VS. Each ml of sodium hydroxide (0.1 mol/L) VS is equivalent to 28.54 mg of C₁₃H₁₉NO₄S.

Category Gout suppressant.

Storage Preserve in tightly closed containers, protected from light.

Preparation Probenecid Tablets

Probenecid Tablets

Probenecid Tablets contain not less than 95.0% and not more than 105.0% of the labelled amount of probenecid (C₁₃H₁₉NO₄S).

Description White tablets.

Identification (1) To a quantity of the powdered tablets equivalent to 0.25 g of probenecid add 30 ml of acetone to dissolve probenecid and filter. To the filtrate add dropwise a quantity of water until a precipitate is produced. Filter, wash the precipitate with several portions of water, dry at 105°C; it has a melting point of 198-201°C (Appendix VI C). The remaining precipitate complies with tests (1) and (2) for Identification described under Probenecid.

(2) The light absorption of the solution obtained in the Assay exhibits maxima at 225 nm and 249 nm (Appendix IV A).

Dissolution Carry out the dissolution test (Appendix X C, method 2), using 900 ml of simulated intestinal fluid as the dissolution medium, adjust the rotational speed of the paddle to 50 rpm. Withdraw 10 ml of the solution at 30 minutes and filter. Discard the initial filtrate, transfer accurately 5 ml of the successive filtrate, to a 100 ml volumetric flask, dilute with 0.4% sodium hydroxide solution to volume and mix well. Measure the absorbance at 244 nm (Appendix IV A) and calculate the dissolution of C₁₃H₁₉NO₄S from each tablet, taking 359 as the value of *A* (1%, 1 cm). Not less than 80% of the labelled amount dissolved.

Other requirements Comply with the general requirements for tablets (Appendix I A).

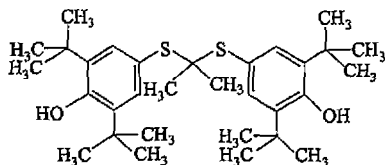
Assay Weigh accurately and powder 10 tablets. To an accurately weighed quantity equivalent to about 60 mg of probenecid in a 200 ml volumetric flask add 150 ml ethanol and 4 ml of hydrochloric acid solution (9→100), warm on a water bath at 70°C for 30 minutes, cool to room temperature, add ethanol to volume and mix well. Filter and discard the initial filtrate. Measure accurately 5 ml of the successive filtrate to a 100 ml volumetric flask, add 2 ml of hydrochloric acid solution (9→100), add ethanol to volume and mix well. Measure the absorbance of the resulting solution at 249 nm (Appendix IV A), calculated the content of C₁₃H₁₉NO₄S, taking 338 as the value of *A* (1%, 1 cm).

Category As described under probenecid.

Strength 0.25 g

Storage Preserve in tightly closed containers, protected from light.

Probucol



$C_{31}H_{48}O_2S_2$ 517.86

Probucol is 4,4' [(1-methylethylidene) bis (thio) bis [2,6-bis (1,1-dimethylethyl) phenol. It contains not less than 98.5% and not more than 102.0% of $C_{31}H_{48}O_2S_2$, calculated on the dried basis.

Description A white or almost white crystalline powder; odour, characteristic.

Very soluble in chloroform; soluble in ethanol; insoluble in water.

Melting range 124-127°C (Appendix VI C).

Identification (1) To about 5 mg, add 1 ml of *n*-hexane in a dry test tube and shake to dissolve. Add gently 0.5 ml of formaldehyde-sulfuric acid TS along the inner wall of the test tube, a yellowish-green colour is produced and then turns to brownish-red on standing between the two layers.

(2) The retention time of the principal peak of probucol in the substance being examined in the chromatogram obtained in the Assay is identical with the principal peak of probucol CRS in the chromatogram of the reference solution correspondingly.

(3) The infrared absorption spectrum (Appendix IV C) is concordant with the reference spectrum of probucol (Appendix XVI).

Related substances Carry out the method for high performance liquid chromatography (Appendix V D), using a column packed with silica gel and a mixture of dehydrated ethanol-*n*-hexane (1 : 4000) as mobile phase. Detection wavelength is 242 nm and the number of the theoretical plates of the column is not less than 4000, calculated with reference to the peak of probucol. Dissolve a quantity of the substance being examined in the mobile phase and dilute to produce a solution of 1 mg per ml as test solution. Measure accurately 1 ml of the solution, into a 100 ml volumetric flask, dilute with the mobile phase to volume and mix well as reference solution. Inject 20 μ l of the reference solution into the column. Adjust the attenuation so that the principal peak height in the chromatogram is 20%-25% of the full scale of the chart. Inject separately 20 μ l each of the test solution and the reference solution into the column, and record the chromatogram for twice the retention time of the principal peak. The sum of the areas of all peaks other than the principal peak in the chromatogram obtained with the test solution is not greater than the area of the principal peak in the chromatogram obtained with the reference solution.

Loss on drying When dried in vacuum to constant weight at 80°C, loses not more than 1.0% of its weight (Appendix VIII L).

Residue on ignition Not more than 0.1% (Appendix VIII N), using 1.0 g.

Heavy metals Carry out the limit test for heavy metals (Appendix VIII H, method 2), using the residue obtained in the test for Residue on ignition; not more than 0.002%.

with octadecylsilane bonded silica gel and a mixture of acetonitrile-water (85 : 15) as the mobile phase. Detection wavelength is 242 nm and the number of the theoretical plates of the column is not less than 2500, calculated with reference to the peak of probucol.

Procedure Dissolve about 25 g, accurately weighed, in a 50 ml volumetric flask with mobile phase and dilute to volume, mix well. Transfer accurately 3 ml of the solution, in a 10 ml volumetric flask, dilute with the mobile phase to volume and mix well. Inject 20 μ l of the solution into the column, record the chromatogram, and calculate the content obtained in the chromatogram. Repeat the operation, dissolving a quantity of probucol CRS instead of the substance being examined in the mobile phase and diluting to produce a solution of 0.15 mg per ml, calculate the content of $C_{31}H_{48}O_2S_2$.

Category Antihyperlipoproteinemic.

Storage Preserve in tightly closed containers, protected from light.

Preparation Probucol Tablets

Probucol Tablets

Probucol Tablets contain not less than 90.0% and not more than 110.0% of the labelled amount of probucol ($C_{31}H_{48}O_2S_2$).

Description Film coated tablets with white or almost white core.

Identification (1) To a quantity of the powdered tablets, obtained in Assay, equivalent to about 10 mg of probucol, add 2 ml of *n*-hexane, shake to dissolve probucol and filter. The filtrate complies with the test for Identification (1) described under Probucol.

(2) The retention time of the principal peak of probucol in the substance being examined in the chromatogram obtained in the Assay is identical with that of the principal peak of probucol CRS in the chromatogram of the reference solution.

(3) Dissolve a quantity of the powdered tablets, obtained in Assay, in dehydrated ethanol to produce a solution of 20 μ g per ml and filter. The light absorption of the filtrate exhibits a maximum at 242 nm (Appendix IV A).

Other requirements Comply with the general requirement for tablets (Appendix I A).

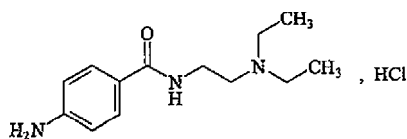
Assay Carry out the method for high performance liquid chromatography as described under Probucol in the Assay. Weigh accurately and powder 20 tablets. Weigh accurately a quantity of the powder equivalent to about 25 mg of probucol in a 50 ml volumetric flask, add a quantity of the mobile phase and ultrasonicate for 10 minutes to dissolve probucol. Cool to room temperature, dilute to volume with the mobile phase, mix well and filter. Measure accurately 3 ml of the successive filtrate, carry out the Assay described under Probucol, beginning at the words "in a 10 ml volumetric flask...". Calculate the content of $C_{31}H_{48}O_2S_2$.

Category As described under Probucol.

Strength (1) 0.125 g (2) 0.25 g

Storage Preserve in tightly closed containers, protected from light.

Procainamide Hydrochloride



$C_{13}H_{21}N_3O \cdot HCl$ 271.79

[614-39-1]

Procainamide Hydrochloride is 4-amino-*N*-(2-diethylaminoethyl) benzamide monohydrochloride. It contains not less than 99.0% of $C_{13}H_{21}N_3O \cdot HCl$, calculated on the dried basis.

Description A white to pale yellow crystalline powder; odourless; hygroscopic.

Freely soluble in water; soluble in ethanol; slightly soluble in chloroform; very slightly soluble in ether.

Melting range 165-169°C (Appendix VI C).

Identification (1) Dissolve 0.1 g in 5 ml of water, add 1 drop of ferric chloride TS and 1 drop of concentrated hydrogen peroxide solution, heat gently to boiling; a violet-red colour is produced, turns to dark brown and then to brownish black.

(2) The infrared absorption spectrum (Appendix IV C) is concordant with the reference spectrum of procainamide hydrochloride (Appendix XVI).

(3) The aqueous solution yields the reactions characteristic of chlorides (Appendix III).

Acidity Dissolve 1.0 g in 10 ml of water, pH 5.0-6.5 (Appendix VI H).

Loss on drying When dried to constant weight at 105°C, loses not more than 0.3% of its weight (Appendix VIII L).

Residue on ignition Not more than 0.1% (Appendix VIII N), use 1.0 g.

Heavy metals Carry out the limit test for heavy metals (Appendix VII H, method 2), using the residue obtained in Residue on ignition; not more than 0.001%.

Assay Weigh accurately about 0.55 g. Carry out the method for dead-stop titration (Appendix VII A). Titrate with sodium nitrite (0.1 mol/L) VS. Each ml of sodium nitrite (0.1 mol/L) VS is equivalent to 27.18 mg of $C_{13}H_{21}N_3O \cdot HCl$.

Category Local anesthetic.

Storage Preserve in tightly closed containers, protected from light.

Preparation (1) Procainamide Hydrochloride Injection
(2) Procainamide Hydrochloride Tablets

Procainamide Hydrochloride Injection

Procainamide Hydrochloride Injection is a sterile solution of procainamide hydrochloride in Water for Injection. It contains not less than 95.0% and not more than 105.0% of the labelled amount of procainamide hydrochloride ($C_{13}H_{21}N_3O \cdot HCl$).

Description A clear colourless liquid.

per ml water exhibits maxima at 280 nm (Appendix IV A).
(2) Yields the reactions characteristic of primary aromatic amines and chlorides (Appendix III).

pH value 3.5-6.0 (Appendix VI H).

Pyrogens Complies with the test for pyrogens (Appendix XI D), using 0.5 ml per kg of the rabbit's weight.

Other requirements Complies with the general requirements for injections (Appendix I B).

Assay Measure accurately 5 ml, add 40 ml of water and 10 ml of hydrochloric acid solution (1→2), heat to boiling quickly and cool immediately to room temperature. Carry out the method for dead-stop titration (Appendix VII A), titrate with sodium nitrite (0.1 mol/L) VS. Each ml of sodium nitrite (0.1 mol/L) VS is equivalent to 27.18 mg of $C_{13}H_{21}N_3O \cdot HCl$.

Category As described under Procainamide Hydrochloride.

Strength (1) 1 ml : 0.1 g (2) 2 ml : 0.2 g
(3) 5 ml : 0.5 g (4) 10 ml : 1 g

Storage Preserve in well closed containers, protected from light.

Procainamide Hydrochloride Tablets

Procainamide Hydrochloride Tablets contain not less than 95.0% and not more than 105.0% of the labelled amount of procainamide hydrochloride ($C_{13}H_{21}N_3O \cdot HCl$).

Description White to pale yellow tablets or sugar coated tablets.

Identification (1) Shake a quantity of powdered tablets with water, filter, discard the initial filtrate, dilute the successive filtrate with water to produce a solution of 5 µg per ml. The light absorption (Appendix IV A) exhibits a maximum at 280 nm.

(2) Shake a quantity of the powdered tablets equivalent to 0.1 g of procainamide hydrochloride with 5 ml of water and 0.5 ml of dilute hydrochloric acid, filter. The filtrate yields the reactions characteristic of primary aromatic amines (Appendix III).

(3) The above filtrate yields the reactions characteristic of chlorides (Appendix III).

Dissolution Carry out dissolution test (Appendix X C, method 1), using 900 ml of hydrochloric acid solution (9→1000) as dissolution medium, adjust the rotational speed of basket to 100 rpm. Withdraw 10 ml of the solution at 75 minutes and filter. Dilute 2 ml of the successive filtrate, accurately measured, with 0.1 mol/L sodium hydroxide solution to 50 ml, mix well. Measure the absorbance of the resulting solution at 273 nm (Appendix IV A), calculate the dissolution of $C_{13}H_{21}N_3O \cdot HCl$, taking 605 as the value of A (1%, 1 cm), from each tablet. Not less than 80% of the labelled amount is dissolved.

Other requirements Comply with the general requirements for tablets (Appendix I A).

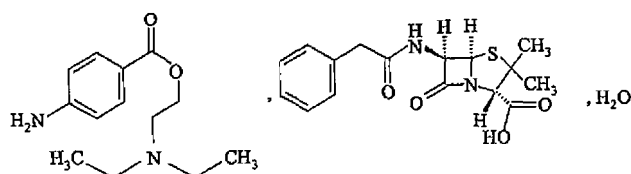
Assay Shake 10 tablets with 50 ml of water in a 100 ml volumetric flask, add water to volume, mix well, allow to stand. Measure accurately 20 ml of the supernatant liquid and carry out the method for dead-stop titration (Appendix VII A), titrate with sodium nitrite (0.1 mol/L) VS. Each ml of sodium nitrite (0.1 mol/L) VS is equivalent to 27.18

Category As described under Procainamide Hydrochloride.

Strength 0.25 g

Storage Preserve in tightly closed containers, protected from light.

Procaine Benzylpenicillin



$C_{13}H_{20}N_2O_2 \cdot C_{16}H_{18}N_2O_4S \cdot H_2O$ 588.72

Procaine Benzylpenicillin is 2-diethylaminoethyl-4-aminobenzoate (6R)-6-(2-phenylacetamido)-penicillanate monohydrate. It contains not less than 38.0% and not more than 43.0% of Procaine ($C_{13}H_{20}N_2O_2$), not less than 56.2% and not more than 59.6% of Penicillin ($C_{16}H_{18}N_2O_4S$), not less than 1000 Penicillin Units per mg, calculated on the anhydrous basis.

Description A white, microcrystalline powder; inactivated immediately by acid, alkaline, or oxidizing agents. Freely soluble in methanol; sparingly soluble in ethanol or chloroform; slightly soluble in water.

Identification (1) The retention time of two principal peak in the substance being examined in the chromatogram obtained in the Assay is identical with that the two principal peak of Procaine and Penicillin CRS in the chromatogram of the reference solution correspondingly.

(2) The infrared absorption spectrum (Appendix IV C) is concordant with the reference spectrum of procaine benzylpenicillin (Appendix XVI).

Acidity or alkalinity A suspension of 60 mg per ml in water, pH 5.0-7.5 (Appendix VI H).

Clarity and colour of solution To each of 5 portion add methanol to produce solutions of 60 mg per ml, the solutions are clear and colourless; any opalescence produced is not more pronounced than that of reference suspension 1 (Appendix IX B); any colour produced is not more intense than that of reference solution Y_2 or YG_2 (Appendix IX A, method 1).

Water Not less than 2.8% and not more than 4.0% (Appendix VIII M, method 1).

Consistence A suspension of 1.5 g per 5 ml in water passes readily through a No. 4 $\frac{1}{2}$ hypodermic needle without blockage.

Bacterial endotoxins Complies with the test for bacterial endotoxins (Appendix XI E). Less than 0.01 EU per 100 penicillin units.

Sterility Complies with the test for sterility (Appendix XI H), after being inactivated by penicillinase.

Assay Carry out the method for high performance liquid chromatography (Appendix V D), using a column packed with octadecylsilane bonded silica gel and a mixture of buffer solution (dissolve 14 g of potassium dihydrogen phosphate and 40% tetrabutylammonium hydroxide solution in 700 ml of water, adjust the pH with 1 mol/L potassium hydroxide

solution to 7.0 and dilute with water to 1000 ml, mix well)-water-acetonitrile (52 : 23 : 25), and adjust the pH with 1 mol/L potassium hydroxide solution or 10% dilute phosphoric acid to 7.5 ± 0.05 , as the mobile phase. Detection wavelength is 235 nm, dissolve phenoxymethylpenicillin CRS with the mobile phase to the solution that contained 2.4 mg of phenoxymethylpenicillin CRS, diluted the solution with the reference solution to a mixture of phenoxymethylpenicillin solution-reference solution (1 : 3), inject the resulting solution into column. The resolution factor between the peaks of penicillin and phenoxymethylpenicillin is not less than 2.0.

Procedure Dissolve about 70 mg of Procaine Benzylpenicillin, accurately weighed, with 30 ml of mobile phase in 50 ml volumetric flask, in ultrasonic bath, dilute with mobile phase to volume, mix well. Inject 10 μ l of the resulting solution into the column. Weighed accurately of penicillin CRS and procaine CRS, dissolve with mobile phase to the solution that contained 0.8 mg of penicillin and 0.54 mg of procaine per ml. Repeat the operation, using penicillin CRS and procaine CRS instead of the substance being examined. Calculate the content of $C_{13}H_{20}N_2O_2$ and $C_{16}H_{18}N_2O_4S$ with respect to the peak area obtained in the chromatogram by the external standard method. Each mg of $C_{16}H_{18}N_2O_4S$ is equivalent to 1780 Penicillin Unit.

Category Antibiotic.

Storage Preserve in hermetically sealed containers, stored in a dry place.

Preparation Procaine Benzylpenicillin for Injection

Procaine Benzylpenicillin for Injection

Procaine Benzylpenicillin for Injection is a sterile mixture of Procaine Benzylpenicillin and Benzylpenicillin Sodium (Potassium) containing suitable buffering and suspending agents. It contains not less than 59.0% and not more than 66.3% of Penicillin ($C_{16}H_{18}N_2O_4S$), not less than 29.1% and not more than 35.6% of Procaine ($C_{13}H_{20}N_2O_2$), not less than 1050 Penicillin Units and not more than 1180 Penicillin Units per mg, calculated on the anhydrous basis. It contains not less than 95.0% and not more than 105.0% of the labelled amount of Penicillin, calculated on the basis of the average weight of content.

Description A white powder.

Identification (1) The retention time of two principal peak in the substance being examined in the chromatogram obtained in the Assay is identical with that the two principal peak of Procaine and Penicillin CRS in the chromatogram of the reference solution correspondingly.

(2) Yields the flame reaction of sodium (potassium) salts (Appendix III).

Colour of solution Add methanol to each of 5 containers to produce solutions of about 67000 units per ml, any colour produced is not more intense than that of reference solution Y_4 or YG_4 (Appendix IX A, method 1).

Water Not more than 3.5% (Appendix VIII M, method 1 A).

Suspending time and consistence Add water to one containers to produce a suspension of 400000 Units per ml; shake thoroughly and allow to stand for 2 minutes; neither

sediment is produced nor the suspension is separated distinctly into layers. The suspension passes readily through a No. 4 $\frac{1}{2}$ hypodermic needle without blockage.

Acidity or alkalinity, Bacterial endotoxins and Sterility

Complies with the corresponding tests described under Procaine Benzylpenicillin.

Other requirements Complies with the general requirements for injections (Appendix I B).

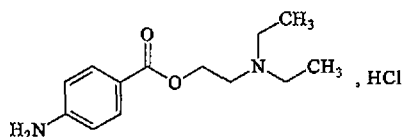
Assay Carry out the Assay described under Procaine Benzylpenicillin, using an accurately weighed quantity of the mixed contents obtained in the test for weight variation of contents.

Category As described under Procaine Benzylpenicillin.

Strength (1) 400000 Units [Procaine Benzylpenicillin 300000 Units, Benzylpenicillin Sodium (Potassium) 100000 Units]
(2) 800000 Units [Procaine Benzylpenicillin 600000 Units, Benzylpenicillin Sodium (Potassium) 200000 Units]

Storage Preserve in well closed containers, stored in a dry place.

Procaine Hydrochloride



$C_{13}H_{20}N_2O_2 \cdot HCl$ 272.77

[51-05-8]

Procaine Hydrochloride is 2-(diethylamino) ethyl 4-aminobenzoate monohydrochloride. It contains not less than 99.0% of $C_{13}H_{20}N_2O_2 \cdot HCl$, calculated on the dried basis.

Description White crystals or a crystalline powder; odourless; taste, slightly bitter with local numbness. Freely soluble in water; sparingly soluble in ethanol; slightly soluble in chloroform; practically insoluble in ether.

Melting point 154-157°C (Appendix VI C).

Identification (1) Dissolve 0.1 g in 2 ml of water, add 1 ml of 10% sodium hydroxide solution; a white precipitate is produced, changing to an oily substance on heating. Heat continuously, the vapor produced turns the moist red litmus paper to blue. Warm again until the oily substance disappears, cool, acidify with hydrochloric acid; a white precipitate is produced.

(2) The infrared absorption spectrum (Appendix IV C) is concordance with the reference spectrum of procaine hydrochloride (Appendix XVI).

(3) The aqueous solution yields the reactions characteristic of chlorides (Appendix III).

(4) Yields the reactions characteristic of primary aromatic amines (Appendix III).

Acidity Dissolve 0.40 g in 10 ml of water, add 1 drop of methyl red IS. If a red colour is developed, not more than 0.2 ml of sodium hydroxide (0.02 mol/L) VS is required for neutralization.

Clarity of solution A solution of 2.0 g in 10 ml of water is clear.

Loss on drying When dried to constant weight at 105°C, loses not more than 0.5% of its weight (Appendix VIII L).

Residue on ignition Not more than 0.1% (Appendix VIII N), use 1.0 g.

Iron To the residue obtained in the Residue on ignition, add 2 ml of hydrochloric acid and evaporate to dryness on a water bath. Add 4 ml of dilute hydrochloric acid, warm gently to dissolve, add 30 ml of water and 50 mg of ammonium persulphate, then carry out the limit test for iron (Appendix VIII G). Any colour produced is not more intense than that of the reference solution containing 1.0 ml of iron standard solution (0.0010%).

Heavy metals Dissolve 2.0 g in 15 ml of water, add 2 ml of acetate BS (pH 3.5) and water to 25 ml. Carry out the limit test for heavy metals (Appendix VIII H, method 1): not more than 0.001%.

Assay Weigh accurately about 0.6 g, carry out the method for dead-stop titration (Appendix VII A). Titrate at 15-25°C with sodium nitrite (0.1 mol/L) VS. Each ml of sodium nitrite (0.1 mol/L) VS is equivalent to 27.28 mg of $C_{13}H_{20}N_2O_2 \cdot HCl$.

Category Local anesthetic.

Storage Preserve in tightly closed containers, protected from light.

Preparation (1) Procaine Hydrochloride for Injection
(2) Procaine Hydrochloride Injection

Procaine Hydrochloride for Injection

Procaine Hydrochloride for Injection is a sterile powder of procaine hydrochloride. It contains not less than 95.0% and not more than 105.0% of the labelled amount of procaine hydrochloride ($C_{13}H_{20}N_2O_2 \cdot HCl$), calculated on the basis of the average weight of contents.

Description White crystals or a crystalline powder; odourless; taste, slightly bitter with local numbness.

Identification Complies with tests (1), (3) and (4) for Identification described under Procaine Hydrochloride.

Acidity Dissolve 0.40 g in 10 ml of water, add 1 drop of methyl red IS. If a red colour is developed, not more than 0.20 ml of sodium hydroxide (0.02 mol/L) VS is required for neutralization.

Clarity of solution A solution of 2.0 g in 10 ml of water is clear.

Loss on drying When dried to constant weight at 105°C, loses not more than 1.0% of its weight (Appendix VIII L).

Sterility Complies with the test for sterility (Appendix XI D), to each container add sterile water to produce a solution of 30 mg per ml.

Pyrogens Complies with the test for pyrogens (Appendix XI D), using 1 ml of a solution of 10 mg per ml in Sodium Chloride Injection per kg of rabbit's weight.

Other requirements Complies with the general requirements for injections (Appendix I B).

Assay Weigh accurately a quantity of the mixed contents obtained in the test for weight variation of contents, equivalent to 0.6 g of procaine hydrochloride, carry out the method for dead-stop titration (Appendix VII A), titrate

with sodium nitrite (0.1 mol/L) VS at 15-25°C. Each ml of sodium nitrite (0.1 mol/L) VS is equivalent to 27.28 mg of $C_{13}H_{20}N_2O_2 \cdot HCl$.

Category As described under Procaine Hydrochloride.

Strength (1) 0.15 g (2) 1 g

Storage Preserve in well closed containers, protected from light.

Procaine Hydrochloride Injection

Procaine Hydrochloride Injection is a sterile solution of procaine hydrochloride in Water for Injection made isotonic by the addition of sodium chloride. It contains not less than 95.0% and not more than 105.0% of the labelled amount of procaine hydrochloride ($C_{13}H_{20}N_2O_2 \cdot HCl$).

Description A clear, colourless liquid.

Identification Complies with test (3) and (4) for Identification described under Procaine Hydrochloride.

pH value 3.5-5.0 (Appendix VI H).

p-Aminobenzoic acid Carry out the method for thin-layer chromatography (Appendix V B), using silica gel H and sodium carboxymethylcellulose as the coating substances and a mixture of benzene-glacial acetic acid-acetone-methanol (14 : 1 : 1 : 4) as the mobile phase. Apply separately to the plate 10 μ l each of two solutions containing (1) 2.5 mg per ml of procaine hydrochloride obtained by diluting the injection with ethanol; and (2) 30 μ g per ml of p-aminobenzoic acid CRS in ethanol. After developing and removal of the plate, dry it in air and spray with 4-dimethyl-aminobenzaldehyde solution (mix 100 ml of 2% 4-dimethyl-aminobenzaldehyde ethanol solution with 5 ml of glacial acetic acid). The spot, corresponding to p-aminobenzoic acid in the chromatogram obtained with solution (1) is not more intense than the principal spot obtained with solution (2).

Other requirements Complies with the general requirements for injections (Appendix I B).

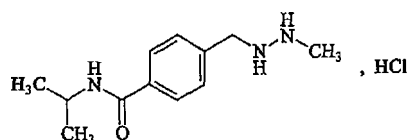
Assay Measure accurately a quantity equivalent to 0.1 g of procaine hydrochloride. Carry out the method for dead-stop titration (Appendix VII A). Titrate at 15-25°C with sodium nitrite (0.05 mol/L) VS. Each ml of sodium nitrite (0.05 mol/L) VS is equivalent to 13.64 mg of $C_{13}H_{20}N_2O_2 \cdot HCl$.

Category As described under Procaine Hydrochloride.

Strength (1) 2 ml : 40 mg (2) 10 ml : 100 mg
(3) 20 ml : 50 mg (4) 20 ml : 100 mg

Storage Preserve in well closed containers, protected from light.

Procarbazine Hydrochloride



$C_{12}H_{19}N_3O \cdot HCl$ 257.76

[366-70-1]

Procarbazine Hydrochloride is *N*-(1-methylethyl)-4-[(2-methylhydrazino) methyl]-benzamide monohydrochloride. It contains not less than 98.0% of $C_{12}H_{19}N_3O \cdot HCl$, calculated on the dried basis.

Description A white crystalline powder.

Freely soluble in water; sparingly soluble in ethanol; practically insoluble in ether.

Melting range 218-226°C, with decomposition (Appendix VI C).

Identification (1) Dissolve about 10 mg in water, add 1 ml of sodium carbonate TS and a few drops of potassium permanganate, the colour of potassium permanganate is discharged.

(2) The light absorption of a solution of 10 μ g per ml in hydrochloric acid solution (9 \rightarrow 1000) exhibits a maximum at 232 nm; the absorbance is about 0.49 (Appendix IV A).

(3) The aqueous solution yields the reactions characteristic of chlorides (Appendix III).

Acidity Dissolve 1.0 g in 100 ml of water, pH 3.0-4.0 (Appendix VI H).

Loss on drying When dried to constant weight at 105°C, loses not more than 1.0% of its weight (Appendix VIII L).

Assay Dissolve about 0.25 g, accurately weighed, in 50 ml of water and 3 ml of nitric acid. Add 20 ml of silver nitrate (0.1 mol/L) VS, accurately measured, and about 3 ml of dibutylphthalate, shake vigorously, then add 2 ml of ferric ammonium sulfate IS. Titrate with ammonium thiocyanate (0.1 mol/L) VS. Perform a blank determination and make any necessary correction. Each ml of silver nitrate (0.1 mol/L) VS is equivalent to 25.78 mg of $C_{12}H_{19}N_3O \cdot HCl$.

Category Antineoplastic.

Storage Preserve in tightly closed containers, protected from light.

Preparation Procarbazine Hydrochloride Enteric-coated Tablets

Procarbazine Hydrochloride Enteric-Coated Tablets

Procarbazine Hydrochloride Enteric-Coated Tablets contain not less than 93.0% and not more than 107.0% of the labelled amount of procarbazine hydrochloride ($C_{12}H_{19}N_3O \cdot HCl$).

Description Enteric-coated tablets with white cores.

Identification (1) To a quantity of powder equivalent to about 50 mg of procarbazine hydrochloride add 20 ml of water, shake thoroughly and filter; the filtrate complies with tests (1) and (3) for Identification described under Procarbazine Hydrochloride.

(2) To a quantity of the powder add hydrochloric acid solution (9 \rightarrow 1000) to produce a solution of 10 μ g of procarbazine hydrochloride per ml and filter. The light absorption of the filtrate exhibits a maximum at 232 nm (Appendix IV A).

Other requirements Comply with the general requirements for tablets (Appendix I A).

Assay R. v. c. i. 15 abls for strength 50 mg) or 25 tablets (for strength 25 mg). Weigh accurately and powder finely. Weigh accurately a quantity equivalent to about 0.25 g of procarbazine hydrochloride and complete the

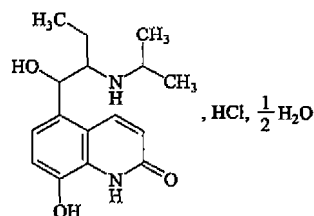
Assay as described under Procarbazine Hydrochloride. Each ml of silver nitrate (0.1 mol/L) VS is equivalent to 25.78 mg of $C_{16}H_{22}N_2O_3 \cdot HCl$.

Category As described under Procarbazine Hydrochloride.

Strength (1) 25 mg (2) 50 mg

Storage Preserve in tightly closed containers, protected from light.

Procaterol Hydrochloride



$C_{16}H_{22}N_2O_3 \cdot HCl \cdot \frac{1}{2} H_2O$ 335.83 [59828-07-8]

Procaterol Hydrochloride is 5-(1-hydroxy-2-isopropylaminobutyl)-8-hydroxy-quinolinone hydrochloride hemihydrate. It contains not less than 98.5% of $C_{16}H_{22}N_2O_3 \cdot HCl$, calculated on the anhydrous basis.

Description A white or almost white crystalline powder; odourless; taste, astringent. Soluble in water, formic acid or methanol; slightly soluble in ethanol; practically insoluble in ether.

Melting range 193-198°C, with decomposition (Appendix VI C).

Identification (1) Dissolve about 2 mg in 5 ml of water, add 1 drop of ferric chloride TS; a dark green colour is produced.

(2) The light absorption of a solution of 7 µg per ml in water exhibits maxima at 234 nm, 259 nm and 295 nm.

(3) The infrared absorption spectrum (Appendix IV C) is concordant with the reference spectrum of procaterol hydrochloride (Appendix XVI).

(4) Yields the reactions characteristic of chlorides (Appendix III).

Acidity Dissolve 0.10 g in 10 ml of water, pH 4.0-5.0 (Appendix VI H).

Clarity and colour of solution Dissolve 0.5 mg in 15 ml of water, the solution is clear and colourless; any colour produced is not more intense than that of reference solution Y₂ (Appendix IX A, method 1).

Related substances Carry out the method for high performance liquid chromatography (Appendix V D), using a column packed with octadecylsilane bonded silica gel and a mixture of phosphate buffer (dissolve 11.04 g of sodium dihydrogen phosphate in 1000 ml of water, adjust to pH 3.1 ± 0.05 with phosphoric acid)-methanol (83 : 17) as the mobile phase. Detection wavelength is 259 nm and the number of the theoretical plates of the column is not less than 2500, calculated with reference to the peak of procaterol hydrochloride. The resolution factor between the peaks of procaterol hydrochloride and adjacent impurities complies with the related requirements.

Procedure Dissolve a quantity of the substance being examined in mobile phase to produce a solution of 1 mg per

ml as the test solution. Transfer accurately 1 ml to a 100 ml volumetric flask, dilute to volume with the mobile phase as the reference solution. Inject 20 µl of the reference solution into the column. Adjust the attenuation so that the principal peak height in the chromatogram is about 20% full scale of the chart. Inject separately 20 µl of the test solution and the reference solution into the column, record the chromatogram for three times the retention time of the principal peak. The sum of the areas of all peaks other than the principal peak in the chromatogram obtained with the test solution is not greater than half of the area of the principal peak in the chromatogram obtained with the reference solution.

Water 2.5%-3.3% (Appendix VIII M, method 1 A).

Residue on ignition Not more than 0.1% (Appendix VIII N), using 1.0 g.

Heavy metals Carry out the limit test for heavy metals (Appendix VIII H, method 2), using the residue obtained in the test for Residue on ignition; not more than 0.001%.

Arsenic Mix 0.1 g with 1.0 g of calcium hydroxide, add a small amount of water and mix well. Dry, heat gently until thoroughly charred, and then ignite at 500-600°C until the incineration is completed. Dissolve the cooled residue in a mixture of 8 ml of hydrochloric acid and 20 ml of water. Carry out the limit test for arsenic (Appendix VIII J, method 2); not more than 0.0002%.

Assay To about 0.25 g, accurately weighed, add 2 ml of formic acid and heat to dissolve. Add 15 ml of perchloric acid (0.1 mol/L) VS, accurately measured, and 1 ml of acetic anhydride. Heat on a water bath for 30 minutes, cool. Add 60 ml of acetic anhydride and 0.5 ml of naphtholbenzein IS. Titrate with sodium acetate (0.1 mol/L) VS until the colour changes to yellow. Perform a blank determination and make any necessary correction. Each ml of perchloric acid (0.1 mol/L) VS is equivalent to 32.68 mg of $C_{16}H_{22}N_2O_3 \cdot HCl$.

Category β₂-adrenoceptor agonist.

Storage Preserve in tightly closed containers, protected from light.

Preparation Procaterol Hydrochloride Tablets

Procaterol Hydrochloride Tablets

Procaterol Hydrochloride Tablets contain not less than 93.0% and not more than 107.0% of the labelled amount of procaterol hydrochloride ($C_{16}H_{22}N_2O_3 \cdot HCl$).

Description white tablets.

Identification (1) To a quantity of the powdered tablets equivalent to about 0.25 mg of procaterol hydrochloride add 20 ml of hydrochloric acid solution (1 → 6), shake thoroughly to dissolve procaterol hydrochloride, and filter. To filtrate add 10 mg of crystalline sodium nitrite, shake to dissolve and add 1 ml of sodium hydroxide solution (1 → 5); an orange-yellow colour is produced.

(2) To a quantity of the powdered tablets equivalent to about 100 µg of procaterol hydrochloride add 20 ml of hydrochloric acid solution (9 → 1000), shake thoroughly to dissolve procaterol hydrochloride, and filter. The light absorption of the filtrate exhibits maxima at 259 nm and 295 nm.

Content uniformity Comply with the requirements for content uniformity (Appendix X E). Carry out the method

and use the internal standard solution as described under Assay.

Procedure Dissolve a quantity of procaterol hydrochloride CRS, accurately weighed, in mobile phase to produce a solution of 5 µg per ml (10 µg per ml if the strength is 50 µg, both calculated on the anhydrous basis). Accurately transfer 5 ml of this solution and 1 ml (2 ml if the strength is 50 µg) of the internal standard solution into a 10 ml volumetric flask, dilute with mobile phase to volume, mix well, as the reference solution. Transfer 1 tablet to a 10 ml volumetric flask, add 1 ml (2 ml if the strength is 50 µg) of the internal standard solution, accurately measured, add 5 ml of mobile phase, shake for 10 minutes to dissolve procaterol hydrochloride. Dilute with mobile phase to volume, mix well, and filter. Using the successive filtrate as the test solution. Carry out the method as described under Assay and calculate the content of $C_{16}H_{22}N_2O_3 \cdot HCl$ from each tablet. Comply with the requirements for content uniformity (Appendix X E).

Dissolution Carry out the dissolution test (Appendix X C, method 3), using 100 ml of hydrochloric acid solution (3 → 50000) as the dissolution medium, adjust the rotational speed of the paddle to 70 rpm. Withdraw 10 ml of the solution at 10 minutes and filter, using the successive filtrate as the test solution. Dissolve a quantity of procaterol hydrochloride CRS, accurately weighed, in dissolution medium to produce a solution of 0.25 µg per ml (0.50 µg per ml if the strength is 50 µg, both calculated on the anhydrous basis) as the reference solution. Carry out the method as described under Assay. Inject separately 20 µl of the test solution and the reference solution into the column. Calculate the dissolution of $C_{16}H_{22}N_2O_3 \cdot HCl$ from each tablet by the external standard method. Not less than 90% of the labelled amount is dissolved.

Other requirements Comply with the general requirements for tablets (Appendix I A).

Assay Carry out the method for high performance liquid chromatography (Appendix V D), using a column packed with octadecylsilane bonded silica gel and a mixture of phosphate buffer (dissolve 11.04 g of sodium dihydrogen phosphate in water to make 1000 ml, adjust to pH 3.1 ± 0.05 with phosphoric acid)-methanol (83 : 17) as the mobile phase. Detection wavelength is 259 nm and the number of the theoretical plates of the column is not less than 2000, calculated with reference to the peak of procaterol hydrochloride. The resolution factor between the peaks of procaterol hydrochloride and internal standard complies with the related requirements.

Internal standard solution Dissolve a quantity of paracetamol in mobile phase to produce a solution of 40 µg per ml.

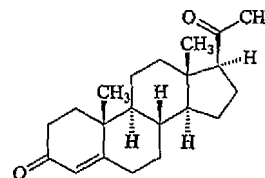
Procedure Dissolve a quantity of procaterol hydrochloride CRS, accurately weighed, in mobile phase to produce a solution of 50 µg per ml (calculated on the anhydrous basis). Accurately measure 5 ml of this solution and 10 ml of the internal standard solution into a 50 ml volumetric flask, dilute with mobile phase to volume, mix well. Inject 20 µl of the resulting solution into the column. Weigh accurately and powder 20 tablets. Weigh accurately a quantity of the powdered tablets equivalent to about 250 µg of procaterol hydrochloride into a 50 ml volumetric flask, add 10 ml of the internal standard solution, accurately measured, and a quantity of mobile phase, shake to dissolve procaterol hydrochloride. Dilute with mobile phase to volume, mix well, and filter. Inject 20 µl of the successive filtrate into the column. Calculate the content of $C_{16}H_{22}N_2O_3 \cdot HCl$.

Category As described under Procaterol Hydrochloride.

Strength (1) 25 µg (2) 50 µg

Storage Preserve in tightly closed containers, protected from light.

Progesterone



$C_{21}H_{30}O_2$ 314.47

[57-83-0]

Progesterone is pregn-4-ene-3,20-dione. It contains not less than 98.0% and not more than 103.0% of $C_{21}H_{30}O_2$, calculated on the dried basis.

Description A white or almost white crystalline powder; odourless, tasteless.

Very soluble in chloroform; soluble in ethanol, ether or vegetable oil; insoluble in water.

Melting point 128-131°C (Appendix VI C).

Specific optical rotation +186° to +198°, measured at 25°C in a solution of about 10 mg per ml in ethanol (Appendix VI E).

Identification (1) Dissolve 5 mg in 0.2 ml of methanol, add about 3 mg of finely powdered sodium nitroprusside, 50 mg of sodium carbonate and 50 mg of ammonium acetate, mix well and allow to stand for 10-30 minutes; a bluish violet colour is produced.

(2) Dissolve 0.5 mg in 1 ml of methanol, add 1 mg of isoniazid and 1 drop of dilute hydrochloric acid, a yellow colour is produced.

(3) The infrared absorption spectrum (Appendix IV C) is concordant with the reference spectrum of progesterone (Appendix XVI).

Related substances Carry out the method and the solution as described under Assay. Inject 5 µl of solution into the column. Adjust the attenuation so that the principal peak height in the chromatogram is full scale of the chart. Dissolve a quantity of the substance being examined, accurately weighed, in methanol to produce solutions of 8 mg per ml as solution (1) and 0.02 mg per ml as solution (2), inject separately 10 µl each of solution (1) and (2) into the column and record the chromatogram for 1.5 times of the retention time of the principal peak. Not more than one secondary peak in the chromatogram obtained with solution (1), secondary peak area are not greater than 3/4 of area of the principal peak in the chromatogram obtained with solution (2).

Loss on drying When dried to constant weight at 105°C, loses not more than 0.5% of its weight (Appendix VIII L).

Assay Carry out the method for high performance liquid chromatography (Appendix V D), using a column packed with octadecylsilane bonded silica gel and a mixture of methanol-water (65 : 35) as the mobile phase. Detection wavelength is 254 nm and the number of the theoretical plates of the column is not less than 1000, calculated with reference to the peak of progesterone. The resolution factor between the peaks of progesterone and internal standard complies with related requirements.

Internal standard solution Dissolve about 25 mg of

diethylstilbestrol CRS, accurately weighed, in methanol in a 25 ml volumetric flask and dilute to volume, mix well.

Procedure Dissolve about 25 mg of progesterone CRS, accurately weighed, in methanol and dilute to 25 ml, mix well as the reference solution. Transfer 5 ml each of the reference solution and the internal standard solution, both measured accurately, in a 25 ml volumetric flask, dilute with methanol to volume, mix well. Inject 5 μ l of the resulting solution into the column and record the chromatogram. Repeat the operation, using the substance

g f pr g CRS, h
content of $C_{21}H_{30}O_2$.

Category Progestin.

Storage Preserve in tightly closed containers, protected from light.

Preparation Progesterone Injection

Progesterone Injection

Progesterone Injection is a sterile oily solution of progesterone. It contains not less than 93.0% and not more than 107.0% of the labelled amount of progesterone ($C_{21}H_{30}O_2$).

Description A colourless to pale yellow clear oily liquid.

Identification The retention time of principal peak of the substance being examined is identical with that of principal peak of the reference solution in the chromatogram obtained in Assay.

Other requirements Complies with the general requirements for injections (Appendix I B).

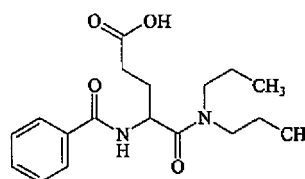
Assay Carry out the method as described under Assay in progesterone. Dissolve about 25 mg of progesterone CRS, accurately weighed, in methanol and dilute to 25 ml, mix well as the reference solution. Transfer accurately 5 ml each of the reference solution and the internal standard solution, in a 25 ml volumetric flask, dilute with methanol to volume, mix well. Inject 5-10 μ l of the resulting solution into the column and record the chromatogram. Transfer accurately the injection being examined equivalent to about 50 mg of progesterone with a pipet to contain to a 50 ml volumetric flask, wash the inner wall of the pipet with several portions of ether, add the washings to the same volumetric flask, dilute with ether to volume and mix well. Transfer accurately 5 ml of the ether solution, to a centrifuge tube with stopper, expel the ether in a water bath, then shake with 5 ml of methanol for 10 minutes and centrifuge for 15 minutes and repeat the extraction with 5 ml, 5 ml, 3 ml of methanol successively. Transfer the methanol layers to a 25 ml volumetric flask, add accurately 5 ml of the internal standard solution, dilute with methanol to volume and mix well. inject 5-10 μ l into the column. Calculate the content of $C_{21}H_{30}O_2$.

Category As described under Progesterone.

Strength (1) 1 ml : 5 mg (2) 1 ml : 10 mg
(3) 1 ml : 20 mg

Storage Preserve in well closed containers, protected from light.

Proglumide



$C_{18}H_{26}N_2O_4$ 334.42

[6620-60-6]

Proglumide is 4-(benzoylamino)-5-(dipropylamino)-5-oxo-pentanoic acid. It contains not less than 99.0% of $C_{18}H_{26}N_2O_4$, calculated on the dried basis.

Description A white crystalline powder; odourless; taste, slightly bitter. Freely soluble in ethanol or chloroform; very slightly soluble in water; soluble in sodium hydroxide TS.

Melting point 148.5-152°C (Appendix VI C).

Identification The infrared absorption spectrum (Appendix IV C) is concordant with the reference spectrum of proglumide (Appendix XVI).

Chloride To 2.0 g add 1 ml of nitric acid, dilute with water to 50 ml, shake thoroughly and filter. Carry out the limit test for chlorides (Appendix VIII A), using 25 ml of filtrate. Any opalescence produced is not more intense than that of a reference solution using 5 ml of sodium chloride standard solution (0.005%).

Loss on drying When dried to constant weight at 105°C, loses not more than 0.5% of its weight (Appendix VIII L).

Residue on ignition Not more than 0.1% (Appendix VIII N); use 1.0 g.

Heavy metals Carry out the limit test for heavy metals (Appendix VIII H, method 2), using the residue obtained in the test for Residue on ignition; not more than 0.001%.

Assay Weigh accurately about 0.3 g, add 30 ml of neutral ethanol (neutral to phenolphthalein IS) and 2 drops of phenolphthalein IS, titrate with sodium hydroxide (0.1 mol/L) VS. Each ml of sodium hydroxide (0.1 mol/L) VS is equivalent to 33.44 mg of $C_{18}H_{26}N_2O_4$.

Category Antacid.

Storage Preserve in tightly closed containers.

Preparation (1) Proglumide Capsules
(2) Proglumide Tablets

Proglumide Capsules

Proglumide Capsules contain not less than 95.0% and not more than 105.0% of the labelled amount of proglumide ($C_{18}H_{26}N_2O_4$).

Identification Weigh a quantity of powdered tablets equivalent to about 0.2 g of proglumide, add 20 ml of ethanol, shake thoroughly and filter, evaporate the filtrate to expel ethanol, dry the crystals at 105°C, the melting range of the crystals is 148-152°C (Appendix VI C).

Other requirements Comply with the general requirements for capsules (Appendix I E).

Assay Carry out the Assay as described under Proglumide, using an accurately weighed quantity (equivalent to about 0.4 g of proglumide) of the mixed contents obtained in the test for weight variation of content, add 30 ml of neutral ethanol (neutral to phenolphthalein IS), shake thoroughly to dissolve proglumide, add 2 drops of phenolphthalein IS, titrate with sodium hydroxide (0.1 mol/L) VS. Each ml of sodium hydroxide (0.1 mol/L) VS is equivalent to 33.44 mg of $C_{18}H_{26}N_2O_4$.

Category As described under Proglumide.

Strength 0.2 g

Storage Preserve in tightly closed containers.

Proglumide Tablets

Proglumide Tablets contain not less than 95.0% and not more than 105.0% of the labelled amount of proglumide ($C_{18}H_{26}N_2O_4$).

Description White tablets.

Identification Weigh a quantity of powdered tablets equivalent to about 0.2 g of proglumide, add 20 ml of ethanol, shake thoroughly and filter, evaporate the filtrate to expel ethanol, dry the crystals at 105°C, the melting range of the crystals is 147–152°C (Appendix VI C).

Dissolution Carry out the dissolution test (Appendix X C, method 2), using 900 ml of phosphate BS (pH 7.2) as the dissolution medium, adjust the rotational speed of the paddle to 100 rpm. Withdraw 10 ml of the solution after exactly 30 minutes and filter. Dilute 3 ml of the successive filtrate, accurately measured, with phosphate BS (pH 7.2) to 50 ml. Dissolve proglumide CRS in phosphate BS (pH 7.2) to produce a solution of about 13.3 µg per ml. Measure the absorbance of the resulting solutions at 223 nm (Appendix IV A). Calculate the dissolution of $C_{18}H_{26}N_2O_4$ from each tablet. Not less than 70% of the labelled amount is dissolved.

Other requirements Comply with the general requirements for tablets (Appendix I A).

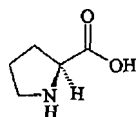
Assay Weigh accurately and powder 10 tablets. Weigh accurately a quantity of the powder equivalent to about 0.4 g of proglumide, add 30 ml of neutral ethanol (neutral to phenolphthalein IS), shake thoroughly to dissolve proglumide, add 2 drops of phenolphthalein IS, titrate with sodium hydroxide (0.1 mol/L) VS. Each ml of sodium hydroxide (0.1 mol/L) VS is equivalent to 33.44 mg of $C_{18}H_{26}N_2O_4$.

Category As described under Proglumide.

Strength 0.2 g

Storage Preserve in tightly closed containers, protected from light.

Proline



$C_5H_9NO_2$ 115.13

Proline is (S)-pyrrolidine-2-carboxylic acid. It

contains not less than 98.5% of $C_5H_9NO_2$, calculated on the dried basis.

Description White crystals or a crystalline powder; slightly odour; taste, slightly sweet. Freely soluble in water, soluble in ethanol, insoluble in ether or *n*-butanol.

Specific optical rotation -84.5° to -86.0° , in a solution of about 40 mg per ml in water (Appendix VI E).

Identification The infrared absorption spectrum (Appendix IV C) is concordant with the reference spectrum of Proline (Appendix XVI).

Acidity Dissolve 2.0 g in 20 ml of water, pH 5.9–6.9 (Appendix XVI H).

Transmittance of solution Dissolve 1.0 g in 10 ml of water, the transmittance at 430 nm is not less than 98.0% (Appendix IV A).

Chloride Carry out the limit test for chloride (Appendix VIII A), using 0.25 g. Any opalescence produced is not more pronounced than that of a reference solution using 5.0 ml of sodium chloride standard solution (0.02%).

Sulfate Carry out the limit test for sulfate (Appendix VIII B), using 1.0 g. Any opalescence produced is not more pronounced than that of a reference solution using 2.0 ml of potassium sulfate standard solution (0.02%).

Ammonium Carry out the limit test for ammonium (Appendix VIII K), using 0.10 g. Any colour produced is not more intense than that of a reference solution using 2.0 ml of ammonium chloride standard solution (0.02%).

Other amino acids Carry out the method for thin-layer chromatography (Appendix V B), using silica gel G as the coating substance and *n*-butanol-anhydrous ethanol-concentrated ammonia solution-water (8 : 8 : 1 : 3) as the mobile phase. Apply separately to the plate 2 µl each of two solutions of substance being examined in water containing (1) 50 mg per ml, (2) 0.25 mg per ml. After developing and removal of the plate, dry it in air, spray with ninhydrin acetone solution (1→50), heat at 80°C until the colour is produced and examine immediately. Any spot, other than the principal spot in the chromatogram, obtained with solution (1) is not more intense than the principal spot obtained with solution (2) (0.5%).

Loss on drying When dried at 105°C for 3 hours, loses not more than 0.3% of its weight (Appendix VIII L).

Residue on ignition Not more than 0.1% (Appendix VIII N).

Iron Carry out the limit test for iron (Appendix VIII G), using 1.0 g. Any colour produced is not more intense than that of a reference solution using 1.0 ml of iron standard solution (0.001%).

Heavy metals Dissolve 1.0 g in 23 ml of water, add 2 ml of acetate BS (pH 3.5). Carry out the limit test for heavy metals (Appendix VIII H, method 1): not more than 0.001%.

Arsenic Dissolve 2.0 g in 23 ml of water, add 5 ml of hydrochloric acid, carry out the limit test for arsenic (Appendix VIII J, method 1): not more than 0.001%.

Bacterial endotoxin Carry out the test for bacterial endotoxin (Appendix XI E): less than 0.01 EU per mg of proline (for parenteral administration).

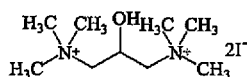
Assay Dissolve about 0.1 g, accurately weighed, in 50 ml of glacial acetic acid. Carry out the method for potentiometric titration (Appendix VII A), titrate with perchloric acid (0.1 mol/L) VS. Perform a blank

determination and make any necessary correction. Each ml of perchloric acid (0.1 mol/L) VS is equivalent to 11.51 mg of $C_9H_9NO_2$.

Category Amino acid.

Storage Preserve in tightly closed containers, protected from light.

Prolonium Iodide



$C_9H_{24}I_2N_2O$ 430.11

[123-47-7]

Prolonium Iodide is (2-hydroxy-1,3-propylenyl)-bis (trimethylammonium) diiodide. It contains not less than 99.0% of $C_9H_{24}I_2N_2O$, calculated on the dried basis.

Description A white or almost white powder; odourless; gradually changes to yellow on exposure to air. Very soluble in water; practically insoluble in ethanol or chloroform.

Identification (1) To about 20 mg add 1 ml of water, 1 ml of chloroform and 1 drop of a solution of 1% potassium dichromate in dilute sulfuric acid and shake, a rose red colour is produced in chloroform layer; a blue colour is produced in the aqueous layer on adding 2 drops of starch IS. (2) To about 0.1 g in a small beaker add 2 ml of 10% sodium hydroxide solution, a fishy odour is perceptible by heating; cover the beaker with a watch glass suspended with 1 drop of alkaline mercuric potassium iodide TS, a light brownish yellow precipitate is produced gradually. (3) The infrared absorption spectrum (Appendix IV C) is concordant with the reference spectrum of prolonium iodide (Appendix XVI).

Acidity or alkalinity A 1% aqueous solution, pH 5.5-7.5 (Appendix VI H).

Colour of solution The colour of a 2.0% aqueous solution is not more intense than that of reference solution Y_4 (Appendix IX A, method 1).

Free iodine Shake 0.50 g with 10 ml of water and 2 ml of starch IS in a test tube, no blue colour is observed.

Chloride To 0.1 g add 5 ml of water, 5 ml of concentrated ammonia solution and 10 ml of silver nitrate TS, shake well and filter. Wash the precipitate with 10 ml of water and combine the washings with the filtrate. To half of the solution add 10 ml of nitric acid (1→4), dilute with water to 50 ml. Carry out the limit test for chlorides (Appendix VIII A). Any opalescence produced is not more pronounced than that of a reference using 4.0 ml of sodium chloride standard solution (0.08%).

Loss on drying When dried at 105°C to constant weight, loses not more than 0.5% of its weight (Appendix VIII L).

Heavy metals Dissolve 1.0 g in a quantity of water, add 2 ml of acetate BS (pH 3.5) and water to make 25 ml. Carry out the limit test for heavy metals (Appendix VIII H, method 1); not more than 0.001%.

Assay Dissolve about 0.4 g, accurately weighed, in 20 ml of water, add 1.0 ml of potassium chromate IS and titrate with silver nitrate (0.1 mol/L) VS until an orange red precipitate is produced. Each ml of silver nitrate (0.1 mol/

L) VS is equivalent to 21.51 mg of $C_9H_{24}I_2N_2O$.

Category Used for ophthalmic disorder.

Storage Preserve in tightly closed containers, protected from light.

Preparation Prolonium Iodide Injection

Prolonium Iodide Injection

Prolonium Iodide Injection is a sterile solution of Prolonium Iodide in Water for Injection. It contains not less than 90.0% and not more than 110.0% of the labelled amount of prolonium iodide ($C_9H_{24}I_2N_2O$).

Description A colourless, clear liquid.

Identification Complies with tests (1) and (2) for identification described under prolonium iodide.

pH value 5.0-8.0 (Appendix VI H).

Free iodine To 2.0 ml add 0.5 ml of starch IS, no blue or violet colour is observed.

Other requirements Complies with the general requirements for injections (Appendix I B).

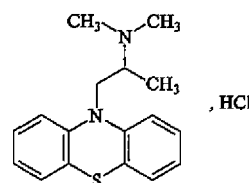
Assay Carry out the Assay described under Prolonium Iodide, using 2 ml, accurately measured, equivalent to about 0.4 g of prolonium iodide. Each ml of silver nitrate (0.1 mol/L) VS is equivalent to 21.51 mg of $C_9H_{24}I_2N_2O$.

Category As described under Prolonium Iodide.

Strength 2 ml : 0.4 g

Storage Preserve in well closed containers, protected from light.

Promethazine Hydrochloride



$C_{17}H_{20}N_2S \cdot HCl$ 320.89

Promethazine Hydrochloride is *N, N, α*-trimethyl-10*H*-phenothiazine-10-ethanamine monohydrochloride. It contains not less than 99.0% of $C_{17}H_{20}N_2S \cdot HCl$, calculated on the dried basis.

Description A white or almost white powder or granules; almost odourless; taste, bitter. Slowly changes to blue colour on long exposure to air. Very soluble in water; soluble in ethanol or chloroform; practically insoluble in acetone or ether.

Melting range 217-223°C, with decomposition (Appendix VI C).

Specific absorbance Measure the absorbance of a solution of 6 µg per ml in 0.01 mol/L hydrochloric acid solution at 249 nm (Appendix IV A), the value of *A* (1%, 1 cm) is 883-937.

Identification (1) Dissolve 5 mg in 5 ml of sulfuric acid, a cherry red colour is produced and deepens gradually on standing.

(2) Dissolve 0.1 g in 3 ml of water, add 1 ml of nitric acid, a red precipitate is produced, which dissolves on warming and the red solution changes to orange-yellow.

(3) The infrared absorption spectrum (Appendix IV C) is concordant with the reference spectrum of promethazine hydrochloride (Appendix XVI).

(4) The aqueous solution yields the reactions characteristic of chlorides (Appendix III).

Acidity Dissolve 0.50 g in 10 ml of water, pH 4.0-5.0 (Appendix VI H).

Clarity and Colour of Solution A solution of 1.0 g in 10 ml of water is clear and colourless; any opalescence produced is not more pronounced than reference suspension 1 (Appendix IX B), and its colour is not more intense than reference solution Y₂ (Appendix IX A, method 1).

Related substances Protect from light throughout the procedure. Carry out the method for thin-layer chromatography (Appendix V B), using silica gel GF₂₅₄ as the coating substance and a mixture of hexane-acetone-diethylamine (8.5 : 1 : 0.5) as the mobile phase. Apply separately to the plate 10 µl each of three solutions of the substance being examined in dichloromethane containing (1) 10 mg per ml, (2) 0.15 mg per ml, (3) 0.05 mg per ml. After developing and removal of the plate, dry it in air and examine under ultraviolet light 254 nm, not more than 3 secondary spots are observed in the chromatogram obtained with solution (1). The colour of any secondary spot is not more intense than the principal spot obtained with solution (3); not more than 1 secondary spot obtained in the chromatogram is more intense than the principal spot obtained with solution (2).

Loss on drying When dried to constant weight at 105°C, loses not more than 0.5% of its weight (Appendix VII L).

Residue on ignition Not more than 0.1% (Appendix VIII N).

Assay Dissolve by warming about 0.3 g, accurately weighed, in 10 ml of glacial acetic acid and 4 ml of mercuric acetate TS, cool to room temperature, add 1 drop of crystal violet IS, titrate with perchloric acid (0.1 mol/L) VS until the colour changes to blue. Perform a blank determination and make any necessary correction. Each ml of perchloric acid (0.1 mol/L) VS is equivalent to 32.09 mg of C₁₇H₂₀N₂S · HCl.

Category Antihistaminic agent.

Storage Preserve in tightly closed containers, protected from light.

Preparation (1) Promethazine Hydrochloride Injection
(2) Promethazine Hydrochloride Tablets

Promethazine Hydrochloride Injection

Promethazine Hydrochloride Injection is a sterile solution of Promethazine Hydrochloride in Water for Injection. It contains not less than 93.0% and not more than 107.0% of the labelled amount of promethazine hydrochloride (C₁₇H₂₀N₂S · HCl). It may also contain a quantity of Vitamin C.

Description A clear, colourless liquid.

Identification (1) Evaporate 0.2 ml to dryness, add 5 ml

of sulfuric acid, a cherry red solution is produced, which deepens gradually on standing.

(2) Complies with tests (2) and (4) Identification for described under Promethazine Hydrochloride.

(3) Use the test solution under related substance as the test solution. Dissolve a quantity of promethazine hydrochloride CRS in methanol-diethylamine (95 : 5) to produce a solution of 10 mg per ml as the reference solution. Carry out the method for thin-layer chromatography (Appendix V B), using silica gel GF₂₅₄ as the coating substance and a mixture of hexane-acetone-diethylamine (8.5 : 1 : 0.5) as the mobile phase. Apply separately to the plate 10 µl each of the test and reference solution. After developing and removal of the plate, dry it in air and examine under ultraviolet light 254 nm, the colour and position of the principal spot in the chromatography obtained with the test solution correspond to the principal spot obtained with the reference solution.

pH value 4.0-5.5 (Appendix VI H).

Related substances Protect from light throughout the procedure. Measure accurately 10 ml of the injection in 25 ml volumetric flask, dilute with methanol-diethylamine (95 : 5) to the volume and mix well as the test solution. Measure accurately a quantity of the successive filtrate, dilute separately with methanol-diethylamine (95 : 5) to produce the reference solutions (1) 0.05 mg per ml (2) 0.10 mg per ml (3) 0.20 mg per ml (4) 0.25 mg per ml. Comply with the test described under promethazine hydrochloride, beginning at the words "carry out the method for thin-layer chromatography...". The sum of impurities is not greater than 2.5%.

Other requirements Complies with the general requirements for injections (Appendix I B).

Assay Measure accurately 2 ml to a 100 ml volumetric flask, dilute with hydrochloric acid (9 → 1000) to volume and mix well. Measure accurately 10 ml of the solution to another 100 ml volumetric flask, dilute with water to volume and mix well. Measure the absorbance at 299 nm (Appendix IV A), calculate the content of C₁₇H₂₀N₂S · HCl, taking 108 as the value of A (1%, 1 cm).

Category As described under Promethazine Hydrochloride.

Strength 2 ml : 50 mg

Storage Preserve in well closed containers, protected from light.

Promethazine Hydrochloride Tablets

Promethazine Hydrochloride Tablets contain not less than 93.0% and not more than 107.0% of the labelled amount of promethazine hydrochloride (C₁₇H₂₀N₂S · HCl).

Description Sugar coated tablets with white to pale yellow core.

Identification (1) To a quantity of powdered tablets with the coating removed equivalent to about 0.2 g of promethazine hydrochloride, add 10 ml of water, shake to dissolve the promethazine hydrochloride and filter. Evaporate the filtrate to dryness on a water bath, the residue complies with the tests (1), (2) and (4) for Identification described under Promethazine Hydrochloride.

(2) Use the test solution under related substance as the test solution. Dissolve a quantity of promethazine hydrochloride CRS in methanol-diethylamine (95 : 5) to produce a solution of 10 mg per ml as the reference solution. Carry out

the method for thin-layer chromatography (Appendix V B), using silica gel GF₂₅₄ as the coating substance and a mixture of hexane-acetone-diethylamine (8.5 : 1 : 0.5) as the mobile phase. Apply separately to the plate 10 µl each of the test and reference solution. After developing and removal of the plate, dry it in air and examine under ultraviolet light 254 nm, the colour and position of the principal spot in the chromatography obtained with the test solution correspond to the principal spot obtained with the reference solution.

Related substances Protect from light throughout the procedure. Weigh and powder 10 tablets (for strength 25 mg) or 20 tablets (for strength 12.5 mg), with sugar coating removed, and dissolve the powder in methanol-diethylamine (95 : 5) in 25 ml volumetric flask. Dilute with methanol-diethylamine (95 : 5) to the volume, mix well and filter. Take the successive filtrate as the test solution. Measure accurately a quantity of the successive filtrate, dilute separately with methanol-diethylamine (95 : 5) to produce the reference solutions (1) 0.05 mg per ml (2) 0.10 mg per ml (3) 0.20 mg per ml (4) 0.25 mg per ml. Comply with the test described under promethazine hydrochloride, beginning at the words "carry out the method for thin-layer chromatography...". The sum of impurities is not greater than 2.5%.

Dissolution Carry out the dissolution test (Appendix X C, method 1), using 900 ml of hydrochloric acid (9→1000) as the dissolution medium, adjust the rotational speed of the basket to 100 rpm. Withdraw 10 ml of the solution after exactly 45 minutes and filter. Measure accurately 2.5 ml of the successive filtrate to a 10 ml volumetric flask, add water to volume and mix well. Measure the absorbance of the resulting solution at 249 nm (Appendix IV A). Calculate the dissolution of C₁₇H₂₀N₂S · HCl from each tablet, taking 910 as the value of A (1%, 1 cm), not less than 80% of the labelled amount is dissolved.

Other requirements Comply with the general requirements for tablets (Appendix I A).

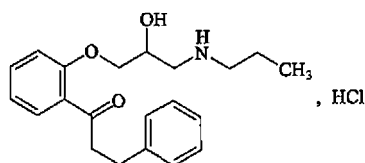
Assay Weigh accurately and powder 10 tablets with the coating removed. To a quantity of the powder equivalent to about 12.5 mg of promethazine hydrochloride, accurately weighed, in a 200 ml volumetric flask add a quantity of hydrochloric acid (9→1000). Shake for 15 minutes, dilute with hydrochloric acid (9→1000) to volume and mix well. Filter through a dry filter. Measure accurately 10 ml of the successive filtrate to a 100 ml volumetric flask, dilute with water to volume and mix well. Measure the absorbance of the solution at 249 nm (Appendix IV A), calculate the content of C₁₇H₂₀N₂S · HCl, taking 910 as the value of A (1%, 1 cm).

Category As described under Promethazine Hydrochloride.

Strength (1) 12.5 mg (2) 25 mg

Storage Preserve in tightly closed containers, protected from light.

Propafenone Hydrochloride



C₂₁H₂₇NO₃ · HCl 377.91

[34183-22-7]

Propafenone Hydrochloride is 3-phenyl-1-[2-[3-(propylamine)-2-hydroxy-propoxy] phenyl]-1-propanone hydrochloride. It contains not less than 99.0% of C₂₁H₂₇NO₃ · HCl, calculated on the dried basis.

Description A white crystalline powder; odourless; taste, bitter.

Slightly soluble in ethanol, chloroform or glacial acetic acid; very slightly soluble in water.

Melting point 171-174°C (Appendix VI C).

Identification (1) Dissolve about 20 mg in 4 ml of ethanol, add a few drops of dinitrophenyl hydrazine TS and shake, a golden yellow precipitate is immediately produced.

(2) The light absorption of a solution of 20 µg per ml in ethanol exhibits maxima at 210 nm, 248 nm and 304 nm (Appendix IV A).

(3) The infrared absorption spectrum (Appendix IV C) is concordant with the reference spectrum of propafenone hydrochloride (Appendix XVI).

(4) The aqueous solution yields the reactions characteristic of chlorides (Appendix III).

Clarity in methano solution Dissolve 0.10 g in 20 ml of methanol by warming in a water bath at about 60°C, cool to room temperature, the solution is clear. Any opalescence produced is not more pronounced than that of reference suspension 1 (Appendix IX B).

Loss on drying When dried at 105°C to constant weight, loses not more than 0.5% of its weight (Appendix VIII L).

Residue on ignition Not more than 0.1% (Appendix VIII N); use 2.0 g.

Heavy metals Carry out the limit test for heavy metals (Appendix VIII H, method 2), using the residue obtained in the test for Residue on ignition; not more than 0.001%.

Assay Dissolve about 0.3 g, accurately weighed, in 20 ml of glacial acetic acid by warming, add 5 ml of mercuric acetate TS and 1 drop of crystal violet IS. Titrate with perchloric acid (0.1 mol/L) VS until the solution becomes blue. Perform a blank determination and make any necessary correction. Each ml of perchloric acid (0.1 mol/L) VS is equivalent to 37.79 mg of C₂₁H₂₇NO₃ · HCl.

Category Antiarrhythmic.

Storage Preserve in tightly closed containers, protected from light.

Preparation (1) Propafenone Hydrochloride Capsules
(2) Propafenone Hydrochloride Injection
(3) Propafenone Hydrochloride Tablets

Propafenone Hydrochloride Capsules

Propafenone Hydrochloride Capsules contain not less than 90.0% and not more than 110.0% of the labelled amount of propafenone hydrochloride (C₂₁H₂₇NO₃ · HCl).

Identification (1) Dissolve a quantity of the contents equivalent to about 20 mg of propafenone hydrochloride, in 4 ml of ethanol, filter, add a few drops of 2,4-dinitrophenylhydrazine TS to the filtrate, shake, a golden yellow precipitate is produced.

(2) The light absorption of the solution obtained in the Assay exhibits three maxima at 210 nm, 248 nm and 304 nm (Appendix IV A).

(3) Dissolve a quantity of the contents in water, filter, the filtrate yields the reactions characteristic of chlorides (Appendix III).

Other requirements Comply with the general requirements for capsules (Appendix I E).

Assay To a quantity of the mixed contents obtained in the test for weight variation of contents equivalent to about 20 mg of propafenone hydrochloride in a 100 ml volumetric flask add a quantity of ethanol, shake thoroughly (if necessary, heat in a warm water bath to dissolve propafenone hydrochloride and cool), dilute with ethanol to volume and mix well. Filter, measure accurately 5 ml of the successive filtrate to a 50 ml volumetric flask, dilute with ethanol to volume and mix well. Measure the absorbance of the resulting solution at 248 nm (Appendix IV A). Calculate the content of $C_{21}H_{27}NO_3 \cdot HCl$, taking 220 as the value of A (1%, 1 cm).

Category As described under Propafenone Hydrochloride.

Strength (1) 100 mg (2) 150 mg

Storage Preserve in well closed containers, protected from light.

Propafenone Hydrochloride Injection

Propafenone Hydrochloride Injection is a sterile solution of Propafenone Hydrochloride in Water for Injection. It contains not less than 90.0% and not more than 110.0% of the labelled amount of propafenone hydrochloride ($C_{21}H_{27}NO_3 \cdot HCl$).

Description A colourless, clear liquid.

Identification (1) Evaporate 5 ml on a water bath to dryness, dissolve the residue in 4 ml of ethanol, add a few drops of dinitrophenylhydrazine TS and shake, a golden yellow precipitate is immediately produced.

(2) The light absorption of the solution obtained in the Assay exhibits maxima at 210 nm, 248 nm and 304 nm (Appendix IV A).

pH value 3.5-5.0 (Appendix VI H).

Bacterial endotoxin Carry out the test for bacterial endotoxin (Appendix XI E); less than 1.5 EU per mg of Propafenone hydrochloride.

Other requirements Complies with the general requirements for injections (Appendix I B).

Assay Dilute an accurately measured quantity with ethanol to produce a solution of about 20 µg per ml. Measure the absorbance at 248 nm (Appendix IV A) and calculate the content of $C_{21}H_{27}NO_3 \cdot HCl$, taking 220 as the value of A (1%, 1 cm).

Category As described under Propafenone Hydrochloride.

Strength (1) 5 ml : 17.5 mg (2) 5 ml : 35 mg
(3) 10 ml : 35 mg (4) 20 ml : 70 mg

Storage Preserve in well closed containers, protected from light.

Propafenone Hydrochloride Tablets

Propafenone Hydrochloride Tablets contain not less than 93.0% and not more than 107.0% of

the labelled amount of propafenone hydrochloride ($C_{21}H_{27}NO_3 \cdot HCl$).

Description White or almost white tablets.

Identification (1) To a quantity of the powdered tablets equivalent to about 20 mg of propafenone hydrochloride add 4 ml of ethanol and allow to stand. Decant the supernate liquid, add a few drops of dinitrophenyl hydrazine TS and shake; a golden yellow precipitate is immediately produced.

(2) Dissolve a quantity of the powdered tablets in ethanol to produce a solution of 20 µg per ml of propafenone hydrochloride and filter. The light absorption of the filtrate exhibits maxima at 210 nm, 248 nm and 304 nm (Appendix IV A).

(3) To a quantity of the powdered tablets add water to dissolve propafenone hydrochloride and filter. The filtrate yields the reactions characteristic of chlorides (Appendix III).

Other requirements Comply with the general requirements for tablets (Appendix I A).

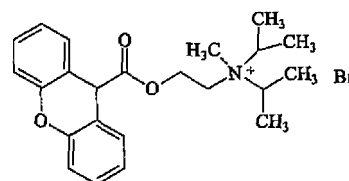
Assay Weigh accurately 20 tablets and powder finely. To a quantity of the powdered tablets, equivalent to about 50 mg of propafenone hydrochloride accurately weighed, in a 100 ml volumetric flask add a quantity of ethanol, shake thoroughly, dilute with ethanol to volume, mix well and filter. Measure accurately 5 ml of the successive filtrate to another 100 ml volumetric flask, dilute with ethanol to volume, mix well. Measure the absorbance of the resulting solution at 248 nm (Appendix IV A). Calculate the content of $C_{21}H_{27}NO_3 \cdot HCl$, taking 220 as the value of A (1%, 1 cm).

Category As described under Propafenone Hydrochloride.

Strength (1) 50 mg (2) 100 mg (3) 150 mg

Storage Preserve in tightly closed containers, protected from light.

Propantheline Bromide



$C_{23}H_{30}BrNO_3$ 448.40

[50-34-0]

Propantheline Bromide is *N*-methyl-*N*-(1-methylethyl)-*N*-[2-[(9*H*-xanthen-9-ylcarbonyl) oxy] ethyl]-2-propanaminium bromide. It contains not less than 98.5% and not more than 102.0% of $C_{23}H_{30}BrNO_3$, calculated on the dried basis.

Description A white or almost white crystalline powder; odourless; taste, extremely bitter. Slightly hygroscopic. Very soluble in water, ethanol or chloroform; insoluble in ether.

Melting range 157-164°C, with decomposition (Appendix VI C).

Identification (1) Dissolve 0.2 g in 5 ml of water, add 10 ml of sodium hydroxide TS, boil for 2 minutes, cool, add 5 ml of dilute hydrochloric acid and filter. Wash the residue with water, recrystallize from dilute ethanol. To about 10 mg of the crystals add 5 ml of sulfuric acid; a

bright yellow or orange yellow solution is produced with slightly green fluorescence.

(2) The light absorption of a solution of 50 µg per ml in ethanol exhibits maxima at 247 nm and 282 nm; the absorbance at 247 nm is about 0.61 (Appendix IV A).

(3) The infrared absorption spectrum (Appendix IV C) is concordant with the reference spectrum of Propantheline Bromide (Appendix XVI).

(4) The aqueous solution yields the reactions characteristic of bromides (Appendix III).

Related substances Carry out the method for thin layer chromatography (Appendix V B), using silica gel G as the coating substance and a mixture of dichloroethane-methanol-water-anhydrous formic acid (56 : 24 : 1 : 1) as the mobile phase. Apply separately to the plate 10 µl each of two solutions in chloroform containing (1) 40 mg per ml, (2) 0.20 mg per ml of the substance being examined. After developing and removal of the plate, dry it in air, examine under ultraviolet light at 254 nm. Any spot, other than the principal spot in the chromatogram obtained with solution (1) is not more intense than the principal spot obtained with solution (2).

Loss on drying When dried to constant weight at 105°C, loses not more than 1.0% of its weight (Appendix VII L).

Residue on ignition Not more than 0.1% (Appendix VII N).

Assay Dissolve about 0.3 g, accurately weighed, in 10 ml of glacial acetic acid TS, add 5 drops of crystal violet IS, titrate with perchloric acid (0.1 mol/L) VS until the colour changes to bluish-green. Perform a blank determination and make any necessary correction. Each ml of perchloric acid (0.1 mol/L) VS is equivalent to 44.84 mg of C₂₃H₃₀BrNO₃.

Category Anticholinergic.

Storage Preserve in tightly closed containers.

Preparation Propantheline Bromide Tablets

Propantheline Bromide Tablets

Propantheline Bromide Tablets contain not less than 90.0% and not more than 110.0% of the labelled amount of propantheline bromide (C₂₃H₃₀BrNO₃).

Description Sugar-coated tablets with white core.

Identification Triturate a quantity of the powdered uncoated tablets equivalent to about 0.15 g of propantheline bromide with 5 ml of water and filter, use the filtrate for the following tests:

(1) Complies with tests (1) for Identification described under Propantheline Bromide, beginning at words "add 10 ml of sodium hydroxide TS...".

(2) Yields the reactions characteristic of bromides (Appendix III).

Xanthanoic acid Shake the combined ether extracts obtained in the Assay with two 30 ml quantities of 1.5% of sodium chloride in 0.4% sodium hydroxide solution. Filter the combined aqueous extracts into a beaker and heat on a water bath until the odour of ether is no longer perceptible. Cool, transfer to a 100 ml volumetric flask, dilute with 0.4% sodium hydroxide to volume, and mix well. Measure the absorbance of the resulting solution at 250 nm (Appendix IV A); the absorbance is not more than 0.37.

Other requirements Comply with the general requirements

for tablets (Appendix I A).

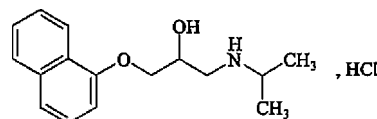
Assay Weigh accurately and powder 20 tablets with the coating removed. Transfer a quantity of the powdered tablets, accurately weighed, equivalent to about 75 mg of propantheline bromide to a sintered glass funnel, extract with four 10 ml quantities of ether and filter. Combine the ether extracts for the test for Xanthanoic acid. Extract the residue with successive quantities of 15 ml each of warm ethanol, transfer to a 100 ml volumetric flask, cool, dilute with ethanol to volume, mix. Measure accurately 5 ml to another 100 ml volumetric flask, dilute with ethanol to volume and mix well. Measure the absorbance of the resulting solution at 247 nm (Appendix IV A), calculate the content of C₂₃H₃₀BrNO₃, taking 121 as the value of A (1%, 1 cm).

Category As described under Propantheline Bromide.

Strength 15 mg

Storage Preserve in tightly closed containers.

Propranolol Hydrochloride



C₁₆H₂₁NO₂ · HCl 295.81

[318-98-9]

Propranolol Hydrochloride is 1-[(1-methylethyl)amino]-3-(1-naphthalenyloxy)-2-propanol hydrochloride. It contains not less than 99.0% of C₁₆H₂₁NO₂ · HCl, calculated on the dried basis.

Description A white or almost white crystalline powder; odourless; taste, slightly sweet then bitter. Soluble in water or ethanol; slightly soluble in chloroform.

Melting point 162-165°C (Appendix VI C).

Identification (1) The light absorption of a solution of 20 µg per ml in methanol exhibits maxima at 290 nm and 319 nm (Appendix IV A).

(2) The infrared absorption spectrum (Appendix IV C) is concordant with the reference spectrum of propranolol hydrochloride (Appendix XVI).

(3) The aqueous solution yields the reactions characteristic of chlorides (Appendix III).

Acidity Dissolve 0.10 g in 10 ml of water, pH 5.0-6.5 (Appendix VI H).

Free naphthol Dissolve 20 mg in 2 ml of ethanol and 2 ml of 10% sodium hydroxide solution, add 1 ml of diazotized sulfanilic acid TS, mix, allow to stand for 3 minutes. Any colour produced is not more intense than that of a reference solution containing 0.30 ml of ethanolic α-naphthol solution (20 µg per ml) (0.03%).

Loss on drying When dried to constant weight at 105°C, loses not more than 0.5% of its weight (Appendix VII L).

Residue on ignition Not more than 0.1% (Appendix VII N).

Assay Dissolve about 0.2 g, accurately weighed, in 20 ml of glacial acetic acid, add 5 ml of mercuric acetate TS and 1 drop of crystal violet IS. Titrate with perchloric acid (0.1 mol/L) VS until the colour changes to bluish-green. Perform a blank determination and make any necessary

correction. Each ml of perchloric acid (0.1 mol/L) VS is equivalent to 29.58 mg of $C_{16}H_{21}NO_2 \cdot HCl$.

Category β -Adrenergic blocker.

Storage Preserve in tightly closed containers.

Preparation (1) Propranolol Hydrochloride Injection
(2) Propranolol Hydrochloride Tablets

Propranolol Hydrochloride Injection

Propranolol Hydrochloride Injection is a sterile solution of Propranolol Hydrochloride in Water for Injection. It contains not less than 90.0% and not more than 110.0% of the labelled amount of propranolol hydrochloride ($C_{16}H_{21}NO_2 \cdot HCl$).

Description A clear, colourless liquid.

Identification (1) To a quantity, add a few drops of silicowolframic acid TS; a slightly pink precipitate is produced.

(2) The light absorption of the solution obtained in the Assay exhibits a maximum at 290 nm (Appendix IV A).

(3) Yields the reactions characteristic of chlorides (Appendix III).

pH value pH 3.0-4.0 (Appendix VI H).

Other requirements Complies with the general requirements for injections (Appendix I B).

Assay Dilute a quantity, accurately measured, with methanol to produce a solution containing about 20 μ g per ml and x well. Measure the absorbance of the resulting solution at 290 nm (Appendix IV A). Calculate the content of $C_{16}H_{21}NO_2 \cdot HCl$, taking 207 as the value of A (1%, 1 cm).

Category As described under Propranolol Hydrochloride.

Strength 5 ml : 5 mg

Storage Preserve in well closed containers, Protected from light.

Propranolol Hydrochloride Tablets

Propranolol Hydrochloride Tablets contain not less than 93.0% and not more than 107.0% of the labelled amount of propranolol hydrochloride ($C_{16}H_{21}NO_2 \cdot HCl$).

Description White tablets.

Identification (1) Shake a quantity of the powdered tablets equivalent to 0.1 g of propranolol hydrochloride with 20 ml of ethanol, filter, evaporate the filtrate to dryness. The residue complies with test (3) for Identification described under Propranolol Hydrochloride.

(2) The light absorption of the solution obtained in the Assay exhibits maxima at 290 nm, 306 nm and 319 nm (Appendix IV A).

Content uniformity Comply with the requirements for content uniformity (Appendix X E). Shake to disintegrate 1 tablet with 1 ml of water in a 50 ml volumetric flask, add 30 ml of methanol, carry out the procedure described under Assay, beginning at the words "shake for 5 minutes". Calculate the content of $C_{16}H_{21}NO_2 \cdot HCl$.

Dissolution Comply with the requirements for dissolution test (Appendix X C, method 1), using 1000 ml hydrochloric acid solution (1 \rightarrow 100) as the dissolution medium, adjust the rotational speed of the paddle to 100 rpm, withdraw a quantity of the solution after exactly 30 minutes and filter, use the successive filtrate as test solution. Measure the absorbance at 290 nm (Appendix IV A). Dissolve a quantity of Propranolol Hydrochloride CRS with the dissolution medium to produce a solution of 10 μ g per ml, repeat the test. Calculate the content of $C_{16}H_{21}NO_2 \cdot HCl$ from each tablet, Not less than 75% of the labelled amount is dissolved.

Other requirements Comply with the general requirements for tablets (Appendix I A).

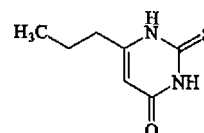
Assay Weigh accurately and powder 20 tablets. To a quantity of the powder equivalent to about 20 mg of propranolol hydrochloride, accurately weighed, in a 100 ml volumetric flask add 2 ml of water, shake for 5 minutes, dilute with methanol to volume, mix well, Filter, measure accurately 5 ml of the successive filtrate to a 50 ml volumetric flask, dilute with methanol to volume and mix well. Measure the absorbance at 290 nm (Appendix IV A). Calculate the content of $C_{16}H_{21}NO_2 \cdot HCl$, taking 207 as the value of A (1%, 1 cm).

Category As described under Propranolol Hydrochloride.

Strength 10 mg

Storage Preserve in tightly closed containers.

Propylthiouracil



$C_7H_{10}N_2OS$ 170.24

[51-52-5]

Propylthiouracil is 2,3-dihydro-6-propyl-2-thioxo-4 (1H)-pyrimidinone. It contains not less than 98.0% of $C_7H_{10}N_2OS$, calculated on the dried basis.

Description White crystals or a white crystalline powder; odourless; taste, bitter.

Sparingly soluble in ethanol; very slightly soluble in water; soluble in sodium hydroxide TS or ammonia TS.

Melting point 218-221°C (Appendix VI C).

Identification (1) Heat a quantity of the saturated aqueous solution to boil, add an equal quantity of a freshly prepared solution containing 0.4% of sodium nitroprusside, 0.4% of hydroxylamine hydrochloride and 0.8% of sodium carbonate; a greenish-blue colour is produced.

(2) Dissolve about 25 mg by adding bromine TS dropwise, heat until the colour disappears, cool and add barium hydroxide TS dropwise; a white precipitate is produced.

(3) The infrared absorption spectrum (Appendix IV C) is concordant with the reference spectrum of propylthiouracil (Appendix XVI).

Thiourea Dissolve 0.50 g in 50 ml of water by heating under reflux, cool and filter. Dilute 5.0 ml of the filtrate to 50 ml with water and mix well. Transfer 10 ml to Nessler cylinder (1) and add 1.0 ml of 0.010% thiourea solution. Transfer 10 ml of the filtrate and 1.0 ml of water to Nessler cylinder (2). Add 0.50 g of sodium acetate and 5.0 ml of silver

nitrate TS to each cylinder, heat in a water bath for 5 minutes. The colour produced in cylinder (2) is not more intense than that produced in cylinder (1).

Loss on drying When dried to constant weight at 105°C, loses not more than 0.5% of its weight (Appendix VIII L).

Residue on ignition Not more than 0.1%; use 1.0 g (Appendix VIII N).

Heavy metals Carry out the limit test for heavy metals, using the residue obtained in the test for Residue on ignition; not more than 0.002% (Appendix VIII H, method 2).

Assay To about 0.3 g, accurately weighed, add 5 ml of sodium hydroxide TS and 50 ml of water, heat to dissolve and cool. Add 2 drops of phenolphthalein IS, and add dropwise acetic acid until the red colour disappears. Add 1 ml of diphenylcarbazide IS, titrate with mercuric nitrate (0.05 mol/L) VS until the solution becomes purplish. Each ml of mercuric nitrate (0.05 mol/L) VS is equivalent to 17.02 mg of $C_7H_{10}N_2OS$.

Category Antithyroid agent.

Storage Preserve in tightly closed containers, protected from light.

Preparation Propylthiouracil Tablets

Propylthiouracil Tablets

Propylthiouracil Tablets contain not less than 93.0% and not more than 107.0% of the labelled amount of propylthiouracil ($C_7H_{10}N_2OS$).

Description White tablets; taste, bitter.

Identification To a quantity of the powdered tablets equivalent to about 0.2 g of propylthiouracil add 10 ml of ethanol, heat under reflux for 20 minutes, filter while hot and evaporate the filtrate on a water bath to dryness. The residue complies with tests (1) and (2) for Identification described under Propylthiouracil.

Dissolution Carry out the dissolution test (Appendix X C, method 1), using 900 ml of water as the dissolution medium, adjust the rotational speed of the paddle to 100 rpm. Withdraw 10 ml of the solution after exactly 30 minutes and filter. Measure accurately a quantity of the successive filtrate and dilute with water to produce a solution of about 5 µg of propylthiouracil per ml as the test solution. Measure the absorbance of the test solution at 274 nm (Appendix IV A). Dissolve about 25 mg of propylthiouracil CRS, weighed accurately, in 20 ml of ethanol in a 100 ml volumetric flask and dissolve propylthiouracil by ultrasonical treatment, cool to room temperature, dilute to volume with water and mix well. Measure accurately a quantity of the solution and dilute with water to produce a solution of about 5 µg of propylthiouracil per ml as the reference solution. Repeat the operations using the reference solution instead of the test solution, calculate the dissolution of $C_7H_{10}N_2OS$ from each tablet. Not less than 80% of the labelled amount is dissolved.

Other requirements Comply with the general requirements for tablets (Appendix I A).

Assay Weigh accurately and powder 20 tablets. To a quantity equivalent to about 0.3 g of propylthiouracil, accurately weighed, add 5 ml of sodium hydroxide TS and 50 ml of water, heat gently and cool to room temperature. Carry out the Assay described under Propylthiouracil, beginning at the words "Add 2 drops of phenolphthalein

IS...". Each ml of mercuric nitrate (0.05 mol/L) VS is equivalent to 17.02 mg of $C_7H_{10}N_2OS$.

Category As described under propylthiouracil.

Strength (1) 50 mg (2) 100 mg

Storage Preserve in tightly closed containers, protected from light.

Protamine Sulfate

Protamine Sulfate is the sulfate of an alkaline protein obtained from fresh, mature sperm of suitable species of fish. Each mg of Protamine Sulfate, calculated on the dried basis, neutralizes not less than 100 Units of anticoagulant activity of Heparin Sodium (mucous).

Description A white or almost white powder; the aqueous solution exhibits an acid reaction to litmus paper. Freely soluble in water; insoluble in ethanol or ether.

Identification (1) Dissolve about 5 mg in 1 ml of water by warming, add 1 drop of 10% sodium hydroxide solution and 2 drops of cupric sulfate TS; the supernatant liquid exhibits violet-red colour.

(2) Dissolve about 1 mg in 2 ml of water, add 5 drops of a 0.1% α -naphthol solution in 70% ethanol and 5 drops of sodium hypochlorite TS, then make alkaline with sodium hydroxide TS; a pink colour is produced.

(3) Yields the reactions characteristic of sulfates (Appendix III).

Nitrogen content Carry out the method for determination of nitrogen (Appendix XIII D, method 2); not less than 21.0% and not more than 25.0% of N, calculated on the dried basis.

Loss on drying When dried to constant weight at 105°C, loses not more than 7.0% of its weight (Appendix VIII L).

Bacterial endotoxin Carry out the test for bacterial endotoxin (Appendix XI E); less than 6.0 EU per mg of protamine sulfate.

Assay Carry out the biological assay of protamine sulfate (Appendix XIII J), the estimated potency is not less than 90% and not more than 110% of the labelled potency.

Category Heparin antagonist.

Storage Preserve in tightly closed containers, stored in a cool place.

Preparation Protamine Sulfate Injection

Protamine Sulfate Injection

Protamine Sulfate Injection is a sterile solution of Protamine Sulfate made isotonic by the addition of sodium chloride. It has a potency of not less than 90% and not more than 115% of the labelled potency, calculated on the basis that each mg of protamine sulfate neutralizes 100 Units of heparin sodium (mucous).

Description A clear, colourless liquid.

Identification Complies with the tests for Identification as described under Protamin Sulfate.

Bacterial endotoxin Complies with the test as described under Protamine Sulfate.

Other requirements Complies with the general requirements for injections (Appendix I B).

Assay Carry out the biological assay of protamine sulfate (Appendix XII J), it complies with the requirements for potency.

Category As described under Protamine Sulfate.

Strength (1) 5 ml : 50 mg (2) 10 ml : 100 mg

Storage Preserve in well closed containers, stored in a cool place.

Protamine Zinc Insulin Injection

Protamine Zinc Insulin Injection is a sterile suspension of Insulin (pig or cattle) with Protamine and Zinc Chloride in Water for Injection. It has a potency of not less than 86% and not more than 120% of the labelled potency. It contains 1.0-1.5 mg of Protamine and 0.2-0.25 mg of Zinc per 100 Units; and it may contain 1.4-1.8 g of Glycerol, 0.22-0.28 g of Phenol and 0.15-0.25 g of disodium hydrogen phosphate per 100 ml.

Description A white or almost white suspension; dispersed uniformly on shaking.

Identification (1) Adjust the pH of the injection with acid to 2.5-3.5, a clear, colourless liquid is formed. (2) To the injection per ml add 0.2 ml of 0.1 mol/L hydrochloric acid solution, allow to stand for a minute, complies with test (2), (3) for Identification described under Insulin.

pH value 6.9-7.3 (Appendix VI H).

Nitrogen content Measure accurately a volume equivalent to about 200 Units, carry out the method for determination of nitrogen (Appendix VII D, method 2); not more than 1.2 mg of N per 100 Units.

Zinc Measure accurately a volume equivalent to about 16 µg of Zinc, carry out the determination of Zinc as described under Insulin, add 2 ml of boric acid-potassium chloride BS (pH 9.0) and 0.4 ml of 0.01 mol/L hydrochloric acid solution (contain 250 Units per ml), allow to stand for 10 minutes, and then add 1 ml of Zincon solution, not less than 0.2 mg and not more than 0.25 mg of Zn per 100 Units.

Prolongation of insulin effect Complies with the test for prolongation of insulin effect (Appendix XII H).

Bacterial endotoxin Carry out the test for bacterial endotoxin (Appendix XI E); less than 0.8 EU per unit.

Other requirements Complies with the general requirements for injections (Appendix I B).

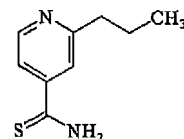
Assay To an accurately measured volume, add 0.2 ml of 0.1 mol/L hydrochloric acid solution per ml and allow to stand for a minute, carry out the biological assay of insulin (Appendix XII G), it complies with the requirement for potency.

Category As described under Insulin.

Strength (1) 10 ml : 400 Units (2) 10 ml : 800 Units

Storage Preserve in well closed containers, stored in a cold place, avoid freezing.

Protionamide



$C_9H_{12}N_2S$ 180.28

[14222-60-7]

Protionamide is 2-propylthioisonicotinamide. It contains not less than 99.0% of $C_9H_{12}N_2S$, calculated on the dried basis.

Description Yellow crystals or a crystalline powder; odour, slightly characteristic.

Soluble in methanol, ethanol or acetone; slightly soluble in ether; practically insoluble in water.

Melting range 139-143°C (Appendix VI C).

Identification (1) Heat gently about 50 mg with 3 ml of hydrochloric acid solution (9 → 100), fumes are evolved which stain moistened lead acetate TP black.

(2) The light absorption of a solution of about 20 µg per ml in ethanol exhibits a maximum at 291 nm; the absorbance is about 0.78 (Appendix IV A).

(3) The infrared absorption spectrum (Appendix IV C) is concordant with the reference spectrum of protionamide (Appendix XVI).

Acidity Dissolve 2.0 g in 20 ml of ethanol by warming, add 20 ml of water and cool; shake to precipitate protionamide. Add 2 drops of cresol red IS, titrate with sodium hydroxide (0.1 mol/L) VS; the volume of sodium hydroxide (0.1 mol/L) VS required is not more than 0.20 ml.

Related substances Protect from light in the procedure. Carry out the method for thin layer chromatography (Appendix V B), using silica gel GF₂₅₄ as the coating substance, a mixture of chloroform-methanol (90 : 10) as the mobile phase. Apply separately to the plate 10 µl each of two solutions in methanol containing (1) 50 mg, (2) 0.50 mg of the substance being examined per ml. After developing and removal of the plate, dry in air and examine under ultra-violet light at 254 nm. Any spot other than the principal spot in the chromatogram obtained with solution (1) is not more intense than the principal spot obtained with solution (2).

Loss on drying When dried to constant weight at 105°C, loses not more than 0.5% of its weight (Appendix VII L).

Residue on ignition Not more than 0.1% (Appendix VIII N); use 1.0 g.

Heavy metals Carry out the limit test for heavy metals, using the residue obtained in the test for Residue on ignition (Appendix VIII H, method 2); not more than 0.002%.

Assay Dissolve about 0.15 g, accurately weighed, in 25 ml of glacial acetic acid, add 0.4 ml of naphtholbenzein IS. Titrate with perchloric acid (0.1 mol/L) VS until the colour changes to green. Perform a blank determination and make any necessary correction. Each ml of perchloric acid (0.1 mol/L) VS is equivalent to 18.03 mg of $C_9H_{12}N_2S$.

Category Antituberculosis drug.

Storage Preserve in tightly closed containers.

Preparation Protionamide Enteric-coated Tablets

Protionamide Enteric-coated Tablets

Protionamide Enteric-coated Tablets contain not less than 90.0% and not more than 110.0% of the labelled amount of protionamide ($C_9H_{12}N_2S$).

Description Enteric coated tablets with yellow core.

Identification (1) To a quantity of powdered tablets equivalent to 20 mg of protionamide in a test tube, add 2 ml of hydrochloric acid solution (9→100), heat gently. Fumes are evolved which stain moistened lead acetate TP black.

(2) Dissolve a quantity of powdered tablets in ethanol to produce a solution of 20 μ g of protionamide per ml, filter. The light absorption of the filtrate exhibits a maximum at 291 nm (Appendix IV A).

Other requirements Comply with the general requirements for tablets (Appendix I A).

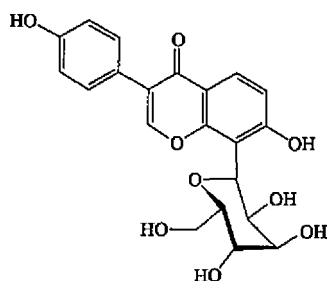
Assay Weigh accurately and powder 20 tablets with coating removed. Dissolve an accurately weighed quantity, equivalent to 0.3 g of protionamide, in 20 ml of acetone in an iodine flask. Add 50 ml of silver nitrate (0.1 mol/L) VS, accurately measured, mix well and allow to stand for 15 minutes. Add 50 ml of water, 3 ml of nitric acid, 5 ml of nitrobenzene and 2 ml of ferric ammonium sulfate IS; titrate with ammonium thiocyanate (0.1 mol/L) VS. Perform a blank determination and make any necessary correction. Each ml of silver nitrate (0.1 mol/L) VS is equivalent to 9.014 mg of $C_9H_{12}N_2S$.

Category As described under Protionamide.

Strength 0.1 g

Storage Preserve in tightly closed containers, protected from light.

Puerarin



$C_{21}H_{20}O_9$ 416.38

Puerarin is 8- β -D-Glucopyranol-4',7-dihydroxyisoflavone, extracted from dry roots of *Pueraria Lobata* (Willd.) Ohwi, a leguminous plant. It contains not less than 97.0% of $C_{21}H_{20}O_9$, calculated on the dried basis.

Description A white to slightly yellow crystalline powder. Soluble in methanol; sparingly soluble in ethanol; slightly soluble in water; insoluble in trichloromethane or ether.

Identification (1) Dissolve 10 mg in 10 ml of water, add 2-3 drops of 0.5% ferric chloride solution and mix well; add 2-3 drops of 0.5% potassium ferricyanide solution, a blue-

green colour is produced.

(2) The light absorption of a solution of 10 μ g per ml in ethanol exhibits a maximum at 250 nm (Appendix IV A).

(3) The infrared absorption spectrum (Appendix IV C) is concordant with the reference spectrum of Puerarin (Appendix XVI).

Acidity Dissolve 20 mg in 20 ml of water, pH 3.5-5.5 (Appendix VI H).

Clarity and colour of solution Dissolve 10 mg in 10 ml of water, the solution is clear and colourless; any opalescence produced is not more pronounced than that of reference suspension I (Appendix IX B); any colour produced is not more intense than that of reference solution Y_1 (Appendix IX A, Method 1).

Related substances Dissolve a quantity in mobile phase to produce a solution of 0.40 mg per ml as test solution. Dilute a quantity of the test solution, accurately measured, with mobile phase to produce a solution of 10 μ g per ml as reference solution. Carry out the method as described under the Assay. Inject 10 μ l of the reference solution into the column, adjust the attenuation so that the principle peak height in the chromatogram is above 20% full scale of the chart. Inject 10 μ l each of the test solution and the reference solution into the column separately, and record the chromatograms for four times the retention time of the principle peak. The sum of the areas of all peaks other than the principal peak obtained with the test solution is not greater than the area of the principle peak in the chromatogram obtained with the reference solution.

Loss on drying When dried to constant weight at 105°C, loses not more than 5.0% of its weight (Appendix VIII L).

Assay Carry out the method for high performance liquid chromatography (Appendix V D), using a column packed with octadecylsilane bonded silica gel and a mixture of methanol-0.1% citric acid solution (25 : 75) as mobile phase. Detection wavelength is 250 nm and the number of theoretical plates of the column is not less than 2500, calculated with reference to the peak of puerarin. Resolution factors between the peaks of puerarin and other peaks comply with the related requirements.

Procedure Dissolve a quantity, accurately weighed, in mobile phase to produce a solution of 0.05 mg per ml. Inject 20 μ l of the solution into the column. Repeat the operation, using puerarin CRS instead of the substance being examined, calculate the content of $C_{21}H_{20}O_9$ with respect to the peak area obtained in the chromatogram by the external standard method.

Category Vasodilators.

Storage Preserve in a tightly closed containers, protect from light.

Preparation (1) Puerarin Injection
(2) Puerarin and Glucose Injection
(3) Puerarin and Sodium Chloride Injection

Puerarin and Glucose Injection

Puerarin and Glucose Injection is a sterile solution of Puerarin and Glucose in Water for Injection. It contains not less than 93.0% and not more than 107.0% of the labelled amount of puerarin ($C_{21}H_{20}O_9$); not less than 95.0% and not more than 105.0% of the labelled amount of glucose ($C_6H_{12}O_6 \cdot H_2O$).

Description A clear, colourless or almost colourless liquid.

Identification (1) To 1 ml, add 2-3 drops of 0.5% ferric chloride solution and mix well, add 2-3 drops of 0.5% potassium ferricyanide solution and mix well; a bluish-green colour is produced.

(2) Drop slowly 5 ml of the injection to the warmly heated alkaline cupric tartrate TS, a red precipitate of cuprous oxide is produced.

(3) The retention time of principal peak of the substance being examined in the chromatogram obtained in the Assay is identical with that of principal peak of puerarin CRS.

pH value 3.5-5.5 (Appendix VI H).

Colour of solution Any colour produced is not more intense than that of the reference solution Y_1 (Appendix IX A).

5-Hydroxymethylfurfural Take the injection as test solution. Weigh accurately a quantity of 5-hydroxymethylfurfural CRS and dissolve in mobile phase to produce a solution of 10 μ g per ml as reference solution. Carry out the method as described under the Assay for puerarin, the detection wavelength is 284 nm. Inject 20 μ l of the reference solution into the column. Adjust the attenuation so that the principal peak height in the chromatogram is 10%-20% full scale of the chart. Inject separately 20 μ l of the test solution and the reference solution into the column, and record the chromatograms. The peak area of 5-hydroxymethylfurfural in the chromatogram obtained with the test solution is not greater than the area of the principle peak in the chromatogram obtained with the reference solution.

Related substances Dilute a quantity of the injection with mobile phase to produce a solution of 0.4 mg per ml as test solution. Measure accurately a quantity of the test solution, add mobile phase to produce a solution of 12 μ g per ml as reference solution. Carry out the method as described under the Assay for puerarin. Inject 20 μ l of the reference solution into the column, adjust the attenuation so that the principal peak height in the chromatogram is above 20% full scale of the chart. Inject 20 μ l each of the test solution and the reference solution into the column separately, and record the chromatograms for 4 times the retention time of the principle peak. The sum of the areas of all peaks other than the principal peak obtained with the test solution is not greater than the area of the principle peak in the chromatogram obtained with the reference solution.

Heavy metals Measure a quantity of the injection, equivalent to about 3 g of glucose, evaporate to about 20 ml and cool. Add 2 ml of acetate BS (pH 3.5) and sufficient water to 25 ml. Carry out the limit test for heavy metals (Appendix VIII H, method 1); not more than 0.0005%, calculated with reference to the content of glucose.

Bacterial endotoxin Complies with the test for Bacterial Endotoxin (Appendix XI E); less than 0.5 EU per ml.

Other requirements Complies with the general requirements for injections (Appendix I B).

Assay

Puerarin Measure accurately a quantity of the injection, add mobile phase to produce a solution of 0.05 mg per ml. Carry out the method as described under Puerarin for the Assay. Calculate the content of $C_{21}H_{20}O_9$ with respect to the peak area obtained in the chromatogram by the external standard method.

Glucose Carry out the determination of Specific optical rotation (Appendix VI E). Calculate the content of $C_6H_{12}O_6 \cdot H_2O$ (g), taking the resulting of optical rotation multiplied by 2.0852.

Category As described under Puerarin.

Strength (1) 100 ml : puerarin 0.2 g and glucose 5.0 g
(2) 150 ml : puerarin 0.3 g and glucose 7.5 g
(3) 250 ml : puerarin 0.3 g and glucose 12.5 g
(4) 250 ml : puerarin 0.5 g and glucose 12.5 g

Storage Preserve in well closed containers, protect from light.

Puerarin and Sodium Chloride Injection

Puerarin and Sodium Chloride Injection is a sterile solution of Puerarin and Sodium Chloride in Water for Injection. It contains not less than 93.0% and not more than 107.0% of the labelled amount of puerarin ($C_{21}H_{20}O_9$); not less than 95.0% and not more than 105.0% of the labelled amount of Sodium Chloride (NaCl).

Description A clear, colourless or almost colourless liquid.

Identification (1) To 1 ml add 2-3 drops of 0.5% ferric chloride solution and mix well, add 2-3 drops of 0.5% potassium ferricyanide solution and mix well, a blue-green colour is produced.

(2) The retention time of principal peak of the substance being examined in the chromatogram obtained in the Assay is identical with that of principal peak of puerarin CRS.

(3) Yields the reactions characteristics of sodium salts and chlorides (Appendix III).

pH value 3.5-5.5 (Appendix VI H).

Colour of solution Any colour produced is not more intense than that of the reference solution Y_1 (Appendix IX A).

Related substances Carry out the method as described under the Assay for puerarin. Dilute a quantity of the injection with mobile phase to produce a solution of 0.4 mg per ml as the test solution. Measure accurately a quantity of the test solution, add mobile phase to produce a solution of 12 μ g per ml as the reference solution. Carry out the method as described under the Assay for puerarin. Inject 20 μ l of the reference solution into the column, adjust the attenuation so that the principal peak height in the chromatogram is above 20% full scale of the chart. Inject 20 μ l each of the test solution and the reference solution into the column separately, and record the chromatograms for 4 times the retention time of the principle peak. The sum of the areas of all peaks other than the principal peak obtained with the test solution is not greater than the area of the principle peak in the chromatogram obtained with the reference solution.

Heavy metals Measure 20 ml, add 2 ml of acetate BS (pH 3.5) and sufficient water to 25 ml. Carry out the limit test for heavy metals (Appendix VIII H, method 1); not more than 0.0001%.

Bacterial endotoxin Carry out the test for Bacterial Endotoxin (Appendix XI E); less than 0.5 EU per ml.

Other requirements Complies with the general requirements for injections (Appendix I B).

Assay

Puerarin Measure accurately a quantity of the injection, add mobile phase to produce a solution of 0.05 mg per ml. Carry out the method as described under Puerarin for the assay. Calculate the content of $C_{21}H_{20}O_9$ with respect to the peak area obtained in the chromatogram by the external standard method.

Sodium Chloride Measure accurately 10 ml, add 40 ml of

water and 5 ml of 2% dextrin solution, add 5-8 drops of fluorescein IS, titrate with silver nitrate (0.1 mol/L) VS. Each ml of silver nitrate (0.1 mol/L) VS is equivalent to 5.844 mg of NaCl.

Category As described under Puerarin.

Strength (1) 100 ml : puerarin 0.2 g and Sodium Chloride 0.9 g
(2) 250 ml : puerarin 0.4 g and Sodium Chloride 2.25 g
(3) 1 : puerarin 0.6 g and Sodium Chloride 2.25 g

Storage Preserve in well closed containers, protect from light.

Puerarin Injection

Puerarin Injection is a sterile solution of Puerarin in Water for Injection. It contains not less than 90.0% and not more than 110.0% of the labelled amount of puerarin ($C_{21}H_{20}O_9$).

Description A clear, colourless to slightly yellow liquid.

Identification Complies with the tests (1) and (2) for Identification described under Puerarin.

Colour of solution Not more intense than that of the reference solution Y₂ (Appendix IV A, method 1).

pH value 3.5-5.5 (Appendix VI H).

Related substance Dilute a quantity of the injection with mobile phase to produce a solution of 0.40 mg per ml as test solution. Measure accurately a quantity of the test solution, add mobile phase to produce a solution of 12 µg per ml as reference solution. Carry out the method as described under the Assay. Inject 10 µl of the reference solution into the column, adjust the attenuation so that the principal peak height in the chromatogram is above 20% full scale of the chart. Inject 10 µl each of the test solution and the reference solution into the column separately, and record the chromatograms for 4 times the retention time of the principle peak. The sum of the areas of all peaks other than the principal peak obtained with the test solution is not greater than the area of the principle peak in the chromatogram obtained with the reference solution.

Pyrogens Dilute 5 ml with Sodium Chloride Injection to 25 ml as test solution. Complies with the test for pyrogens (Appendix XI D), using 5 ml of the test solution per kg of rabbit's weight. Inject slowly while administration.

Other requirements Complies with the general requirements for injections (Appendix I B).

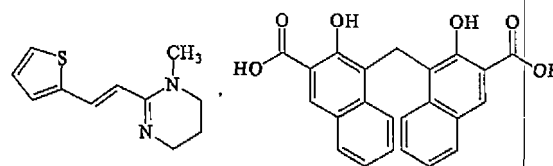
Assay Measure accurately a quantity of the injection, add mobile phase to produce a solution of 0.05 mg per ml. Carry out the method as described under Puerarin for the Assay. Calculate the content of $C_{21}H_{20}O_9$ with respect to the peak area obtained in the chromatogram by the external standard method.

Category As described under Puerarin.

Strength (1) 2 ml : 50 mg (2) 2 ml : 100 mg

Storage Preserve in well closed containers, protected from light.

Pyrantel Pamoate



$C_{11}H_{14}N_2S \cdot C_{23}H_{16}O_6$ 594.68

[22204-24-6]

Pyrantel Pamoate is (*E*)-1,4,5,6-tetrahydro-1-methyl-2-[2-(2-thienyl)ethenyl]pyrimidine-4,4'-methylene-bis[3-hydroxy-2-naphthalenecarboxylic acid (1:1)]. It contains not less than 97.0% and not more than 103.0% of $C_{11}H_{14}N_2S \cdot C_{23}H_{16}O_6$, calculated on the dried basis.

Description A pale yellow powder; odourless; tasteless. Sparingly soluble in dimethylformamide; very slightly soluble in ethanol; practically insoluble in water.

Specific absorbance Protect from light throughout the procedure.

Dissolve about 20 mg, accurately weighed, in 8 ml of a mixture of dioxane and 0.1% ammonia solution (1:1). Dilute with hydrochloric acid solution (9→1000) to 100 ml, and mix well, filter. Accurately measure 5 ml of the successive filtrate, dilute with a hydrochloric acid solution (9→1000) to 50 ml. Measure the absorbance of the resulting solution at 311 nm (Appendix IV A), the value of *A* (1%, 1 cm) is 302-324.

Identification (1) Dissolve about 10 mg in 5 ml of a mixture of dioxane-0.1% concentrated ammonia solution (1:1), add 2 ml of dilute hydrochloric acid; a yellow precipitate is produced.

(2) To about 20 mg add 1 ml of sulfuric acid and shake; a red colour is produced.

(3) The retention times of principal peaks of the substance being examined in the chromatogram obtained in the Assay are identical with those of principal peaks of pyrantel pamoate CRS.

(4) The infrared absorption spectrum (Appendix IV C) is concordant with the reference spectrum of pyrantel pamoate (Appendix XVI).

Chlorinated compounds Carry out the method for oxygen flask combustion (Appendix VII C), using 25 mg, with 10 ml of 0.4% sodium hydroxide solution as the absorbing liquid until absorption is complete. Carry out the limit test for chlorides (Appendix VIII A), using the resulting solution. Any opalescence produced is not more pronounced than that of a reference using 3.5 ml of sodium chloride standard solution (0.14%).

Pyrantel Accurately weigh a quantity of pyrantel, dried in vacuum for 3 hours at 60°C, dissolve in the mobile phase and dilute to produce a solution of 52 µg per ml. Carry out the method described under Assay. Inject 20 µl of the resulting solution into the column and record the chromatogram. Calculate the content of $C_{11}H_{14}N_2S$ by the external standard method. Not less than 63.4% and not more than 67.3%, calculated on the dried basis.

Loss on drying When dried to constant weight at 105°C, loses not more than 0.5% of its weight (Appendix VIII L).

Residue on ignition Not more than 0.1% (Appendix VIII N); use 1.0 g.

Heavy metals Carry out the limit test for heavy metals (Appendix VII H, method 2), using the residue obtained in the test for Residue on ignition; not more than 0.002%.

Assay Carry out the method for high performance liquid chromatography (Appendix V D), using a column packed with silica and a mixture of acetonitrile-water-acetic acid-diethylamine (94 : 2.5 : 2.5 : 1) as the mobile phase. Detection wavelength is 288 nm and the number of theoretical plates of the column is generally not less than 8000, calculated with reference to the peak of pyrantel. The resolution factor between peaks of pyrantel and pamoate is more than 10.

Procedure Dissolve a quantity of the substance being examined, accurately weighed, in the mobile phase to produce solutions of 80 µg per ml. Inject 20 µl of the resulting solution into the column. Repeat the operation, using the pyrantel pamoate CRS instead of the substance being examined. Calculate the content of $C_{11}H_{14}N_2S \cdot C_{23}H_{16}O_6$.

Category Anthelmintics.

Storage Preserve in tightly closed containers, protected from light.

Preparation (1) Pyrantel Pamoate Granules
(2) Pyrantel Pamoate Tablets

Pyrantel Pamoate Granules

Pyrantel Pamoate Granules contain not less than 93.0% and not more than 107.0% of the labelled amount of pyrantel pamoate ($C_{11}H_{14}N_2S \cdot C_{23}H_{16}O_6$).

Description A pale yellow powder or granules; taste sweet.

Identification (1) Comply with the tests (1) and (2) for Identification described under Pyrantel Pamoate, using a quantity of the powdered granules.

(2) The light absorption of the solution obtained in the assay exhibits a maximum at 311 nm (Appendix IV A).

Other requirements Comply with the general requirements for granules (Appendix I N).

Assay Protect from light throughout the procedure. Weigh accurately a quantity of mixed contents obtained in the test for weight variation of contents equivalent to about 20 mg of pyrantel pamoate, carry out the Assay described under Pyrantel Pamoate Tablets, calculate the content of $C_{11}H_{14}N_2S \cdot C_{23}H_{16}O_6$, taking 313 as the value of A (1%, 1cm).

Category As described under Pyrantel Pamoate.

Strength 1 g : 0.15 g

Storage Preserve in tightly closed containers, stored in a dry place and protected from light.

Pyrantel Pamoate Tablets

Pyrantel Pamoate Tablets contain not less than 93.0% and not more than 107.0% of the labelled amount of pyrantel pamoate ($C_{11}H_{14}N_2S \cdot C_{23}H_{16}O_6$).

Description Pale yellow tablets.

Identification To a quantity of the powdered tablets equivalent to about 40 mg of pyrantel pamoate add 20 ml of a

mixture of dioxane-0.1% concentrated ammonia solution (1 : 1) to dissolve pyrantel pamoate and filter. To 5 ml of the filtrate add 2 ml of dilute hydrochloric acid; a yellow precipitate is produced. Evaporate 10 ml of the filtrate to dryness, to the residue add 1 ml of sulfuric acid and shake; a red colour is produced.

Other requirements Comply with the general requirements for tablets (Appendix I A).

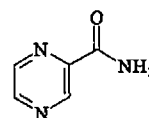
Assay Protect from light throughout the procedure. Weigh accurately and powder 10 tablets. Weigh accurately a quantity equivalent to about 20 mg of pyrantel pamoate to a 100 ml volumetric flask, add 8 ml of a mixture of dioxane-0.1% concentrated ammonia solution (1 : 1), shake to dissolve pyrantel pamoate, dilute to volume with hydrochloric acid solution (9→1000), mix well. Filter, measure accurately 5 ml of the successive filtrate to a 50 ml amber volumetric flask, dilute to volume with hydrochloric acid solution (9→1000), mix. Measure the absorbance of the resulting solution at 311 nm (Appendix IV A). Calculate the content of $C_{11}H_{14}N_2S \cdot C_{23}H_{16}O_6$, taking 313 as the value of A (1%, 1 cm).

Category As described under Pyrantel Pamoate.

Strength 0.3 g

Storage Preserve in tightly closed containers, protected from light.

Pyrazinamide



$C_5H_5N_3O$ 123.12

[98-96-4]

Pyrazinamide is pyrazine carboxylamide. It contains not less than 99.0% of $C_5H_5N_3O$, calculated on the dried basis.

Description A white or almost white crystalline powder; odourless or almost odourless; taste, slightly bitter. Sparingly soluble in water; slightly soluble in ethanol; very slightly soluble in ether.

Melting range 188-192°C (Appendix VI C).

Identification (1) Heat a quantity with 5 ml of sodium hydroxide TS, the characteristic odour of ammonia is perceived, the vapour turns moistened red litmus paper to blue.

(2) Dissolve 0.1 g in 10 ml of water, add 1 ml of ferrous sulfate TS, an orange-red colour is produced; make the solution alkaline with sodium hydroxide TS, the solution turns to blue.

(3) The light absorption of a solution of 10 µg per ml in water exhibits a maximum at 268 nm (Appendix IV A).

(4) The infrared absorption spectrum (Appendix IV C) is concordant with the reference spectrum of pyrazinamide (Appendix XVI).

Related substances Carry out the method for thin layer Chromatography (Appendix V B), using silica gel GF₂₅₄ as the coating substance and a mixture of *n*-butanol-acetic acid glacial-water (60 : 20 : 20) as mobile phase. Apply separately to the plate 20 µl each of two solution in a mixture solution of chloroform-methanol (9 : 1) containing (1) 20 mg (2) 0.04 mg of the substance being examined per ml. After

developing and removal of the plate, dry it in air and examine under ultraviolet light at 254 nm. Any spot in the chromatogram other than the principal spot obtained with solution (1) is not more intense than the principal spot obtained with solution (2).

Loss on drying When dried in vacuum over phosphorous pentoxide to constant weight, loses not more than 0.5% of its weight (Appendix VIII L).

Sulfate Carry out the limit test for sulfates (Appendix VIII B), using 0.30 g. Any opalescence produced is not more pronounced than that of a reference using 1.0 ml of potassium sulfate standard solution (0.033%).

Carboxylic acid Dissolve 0.10 g in 10 ml of water with heating, add 0.5 ml of 0.05 mol/L potassium bromate and 0.5 g of potassium iodide, extract this solution with 1 ml of chloroform. The colour in chloroform layer is not more intense than that of a blank reagent prepared in the same manner.

Residue on ignition Not more than 0.1% (Appendix VIII N).

Heavy metals Dissolve 0.50 g in 2 ml of acetate BS (pH 3.5) and 23 ml of water with heating. Carry out the limit test for heavy metals (Appendix VIII H, method 1); not more than 0.002%.

Assay Weigh accurately 0.25 g to a distillation flask, add 200 ml of water and 50 ml of 40% solution of sodium hydroxide along the inner wall of the flask to form a layer, connect the distillation apparatus. To 40 ml of 4% boric acid solution contained in a suitable receiver add 10 drops of a mixture of methyl-red and bromocresol-green indicator solution, rotate gently the distillation flask to mix the content. Boil vigorously to complete the distillation of ammonia. Titrate the absorbing solution with hydrochloric acid (0.1 mol/L) VS. Perform a blank determination and make any necessary correction. Each ml of hydrochloric acid (0.1 mol/L) VS is equivalent to 12.31 mg of $C_5H_5N_3O$.

Category Tuberculostatic.

Storage Preserve in tightly closed containers, protected from light.

Preparation (1) Pyrazinamide Capsules
(2) Pyrazinamide Tablets

Pyrazinamide Capsules

Pyrazinamide Capsules contain not less than 93.0% and not more than 107.0% of the labelled amount of Pyrazinamide ($C_5H_5N_3O$).

Description Capsules containing white powder.

Identification (1) Dissolve a quantity of the mixed contents obtained in the test for weight variation of contents equivalent to about 0.2 g of pyrazinamide in 20 ml of ethanol with gentle heating and shaking, filter, evaporate the filtrate to dryness. The residue complies with the tests (1) and (2) for Identification described under Pyrazinamide. (2) The light absorption of the solution under Assay exhibits a maximum at 268 nm (Appendix IV A).

Dissolution Comply with the dissolution test (Appendix XI C, method 1), using 900 ml of water as the dissolution medium, adjust the rotation speed of the paddle to 100 rpm. Withdraw 5 ml of the solution after exactly 30 minutes and filter. Dilute a quantity of the successive filtrate, measured accurately, with water to produce a solution of 10 μ g per

ml. Dissolve pyrazinamide CRS in water to produce a solution of about 10 μ g per ml. Measure the absorbances of the resulting solutions at 268 nm (Appendix IV A). Calculate the dissolution of $C_5H_5N_3O$ from each capsule. Not less than 70% of the labelled amount is dissolved.

Other requirements Comply with the general requirements for capsules (Appendix I E).

Assay Take an accurately weighed quantity of the mixed contents obtained in test for Weight variation of content equivalent to about 0.1 g of pyrazinamide to a 200 ml volumetric flask, add a quantity of water, shake to dissolve pyrazinamide, then dilute to volume with water, mix well, stand and filter. Measure accurately 5 ml of the successive filtrate to a 250 ml volumetric flask and dilute to volume with water, mix well, measure the absorbance of the solution at 268 nm (Appendix IV A). Calculate the content of $C_5H_5N_3O$, taking 650 as the value of A (1%, 1 cm).

Category As described under pyrazinamide.

Strength 0.25 g

Storage Preserve in tightly closed containers, protected from light.

Pyrazinamide Tablets

Pyrazinamide Tablets contain Pyrazinamide not less than 95.0% and not more than 105.0% of the labelled amount of Pyrazinamide ($C_5H_5N_3O$).

Description White tablets.

Identification (1) Dissolve a quantity of the powdered tablets equivalent to about 0.2 g of pyrazinamide in 20 ml of ethanol with gentle heating and shaking, filter, evaporate the filtrate to dryness. The residue complies with the tests (1) and (2) for Identification described under Pyrazinamide. (2) The light absorption of the solution under Assay exhibits a maximum at 268 nm (Appendix IV A).

Dissolution Carry out the dissolution test (Appendix X C, method 2), using 900 ml of water as the dissolution medium, adjust the rotational speed of paddle to 50 rpm. Withdraw 5 ml of solution after 45 minutes and filter. Dilute a quantity of successive filtrate, accurately measured, with water to the solution containing 10 μ g per ml. Dissolve a quantity of pyrazinamide CRS in water to produce a solution of 10 μ g per ml. Measure the absorbances of two solutions at 268 nm (Appendix IV A). Calculate the dissolution of $C_5H_5N_3O$ from each tablet not less than 75% of the labelled amount is dissolved.

Other requirements Comply with the general requirements for tablets (Appendix I A).

Assay Weigh accurately and powder 20 tablets. Weigh a quantity, weighed accurately, equivalent to about 0.1 g of pyrazinamide, to a 200 ml volumetric flask, add a quantity of water, shake to dissolve pyrazinamide, then dilute to volume with water, mix well, stand and filter. Measure accurately 5 ml of the successive filtrate to a 250 ml volumetric flask and dilute to volume with water, mix well, measure the absorbance of the solution at 268 nm (Appendix IV A). Calculate the content of $C_5H_5N_3O$, taking 650 as the value of A (1%, 1 cm).

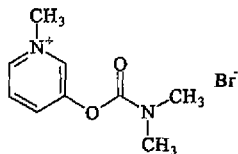
Category As described under Pyrazinamide.

Strength (1) 0.25 g (2) 0.5 g

Storage Preserve in tightly closed containers, protected

from light.

Pyridostigmine Bromide



$C_9H_{13}BrN_2O_2$ 261.2

[155-97-5]

Pyridostigmine Bromide is 3-hydroxy-1-methylpyridinium bromide dimethylcarbamate. It contains not less than 98.5% of $C_9H_{13}BrN_2O_2$, calculated on the dried basis.

Description A white or almost white crystalline powder; taste, bitter; deliquescent. Very soluble in water, ethanol and chloroform; Very slightly soluble in ether of petroleum ether.

Melting range 153-157°C (Appendix VI C).

Specific absorbance Dissolve an accurately weighed quantity, in water to produce a solution of 25 µg per ml. Measure the absorbance at 269 nm (Appendix IV A). The value of A (1%, 1 cm) is 180-190.

Identification (1) Add 1-2 drops of sodium hydroxide TS to about 0.1 g, an orange colour is produced gradually, the colour changes to yellow on heating and fumes are evolved which turn moistened red litmus TP to blue.

(2) The infrared spectrum (Appendix IV C) is concordant with the reference spectrum of pyridostigmine bromide (Appendix XVI).

(3) The aqueous solution yields the reactions characteristic of bromides (Appendix III).

Loss on drying When dried to constant weight at 105°C, loses not more than 2.0% of its weight (Appendix VIII L).

Residue on ignition Not more than 0.1% (Appendix VIII N).

Assay Dissolve about 0.25 g, accurately weighed, in 20 ml of glacial acetic acid. Add 5 ml of mercuric acetate TS, and 3 drops of quinaldine red IS, titrate with perchloric acid (0.1 mol/L) VS until the solution is colourless. Perform a blank determination and make any necessary correction. Each ml of perchloric acid (0.1 mol/L) VS is equivalent to 26.11 mg of $C_9H_{13}BrN_2O_2$.

Category Anticholinesterase drug.

Storage Preserve in tightly closed containers, protected from light.

Preparation Pyridostigmine Bromide Tablets

Pyridostigmine Bromide Tablets

Pyridostigmine Bromide Tablets contain not less than 93.0% and not more than 107.0% of the labelled amount of pyridostigmine bromide ($C_9H_{13}BrN_2O_2$).

Description Sugar coated tablets with white core.

Identification (1) Weigh a quantity of the powdered tablets

with sugar coating removed equivalent to about 0.15 g of pyridostigmine bromide, add 20 ml of chloroform, shake thoroughly, separate the chloroform layer. Filter and evaporate the filtrate to dryness. The residue complies with tests (1) and (3) for identification described under pyridostigmine bromide.

(2) The light absorption of the solution obtained in the Assay exhibits a maximum at 269 nm (Appendix IV A).

Dissolution Carry out the dissolution test (Appendix X C, method 2), using 900 ml of water as the dissolution medium, adjust the rotational speed of paddle to 100 rpm. Withdraw a quantity of solution after 60 minutes and filter. Dilute a quantity of successive filtrate, accurately measured, with water to produce a solution containing 26.7 µg per ml. Measure the absorbance of the resulting solution at 269 nm (Appendix IV A). Calculate the dissolution of $C_9H_{13}BrN_2O_2$ from each tablet, not less than 80% of the labelled amount is dissolved, taking 186 as the value of A (1%, 1 cm).

Other requirements Comply with the general requirements for tablets (Appendix I A).

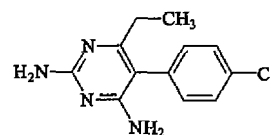
Assay Weigh and powder 20 tablets with coating removed. To an accurately weighed quantity of the powdered tablets, equivalent to 0.15 g of pyridostigmine bromide in a 250 ml volumetric flask add about 150 ml of water, shake thoroughly, dilute with water to volume, mix well, filter. Transfer 5 ml of the successive filtrate, accurately measured, to a 100 ml volumetric flask, dilute with water to volume, mix well. Measure the absorbance at 269 nm (Appendix IV A). Calculate the content of $C_9H_{13}BrN_2O_2$, taking 186 as the value of A (1%, 1 cm).

Category As described under Pyridostigmine Bromide.

Strength 60 mg

Storage Preserve in tightly closed containers, protected from light.

Pyrimethamine



$C_{12}H_{13}ClN_4$ 248.71

[58-14-0]

Pyrimethamine is 5-(4-chlorophenyl)-6-ethyl-2,4-pyrimidine diamino. It contains not less than 99.0% of $C_{12}H_{13}ClN_4$.

Description A white, crystalline powder; odourless; tasteless. Slightly soluble in ethanol or chloroform; practically insoluble in water.

Specific absorbance Measure the absorbance of a solution of 13 µg per ml in 0.1 mol/L hydrochloric acid solution at 272 nm (Appendix IV A), the value of A (1%, 1 cm) is 309-329.

Identification (1) The light absorption of the solution obtained in the test for Specific absorbance, exhibits a maximum at 272 nm and a minimum at 261 nm (Appendix IV A).

(2) The infrared absorption spectrum (Appendix IV C) is concordant with the reference spectrum of pyrimethamine (Appendix XVI).

(3) Ignite 0.1 g with 0.5 g of anhydrous sodium carbonate and cool. Extract the residue with water, filter, add nitric acid dropwise to the filtrate until it turns litmus paper red; the solution yields that reactions characteristic of chlorides (Appendix III).

Acidity or alkalinity Boil 0.30 g with 15 ml of water, cool and filter, to the filtrate add 2 drops of methyl red IS, no red colour is produced; add 0.10 ml of hydrochloric acid (0.05 mol/L) VS; a red colour is produced.

Related substances Carry out the method for thin-layer chromatography (Appendix V B), using silica gel GF₂₅₄ as the coating substance and mixture of toluene-glacial acetic acid-*n*-propanol-chloroform (25 : 10 : 10 : 2) as the mobile phase. Apply separately to the plate 10 µl of each of two solutions in the mixture of chloroform-methanol (9 : 1) containing (1) 20 mg (2) 50 µg of the substance being examined per ml. After developing and removal of the plate, dry it in air and examine under ultraviolet light (254 nm). Any spot in the chromatogram other than the principal spot obtained with solution (1) is not more intense than the principal spot obtained with solution (2).

Residue on ignition Not more than 0.1% (Appendix VIII N).

Assay Dissolve about 0.15 g, accurately weighed, in 20 ml of glacial acetic acid by heat and allow to cool. Add 2 drops of quinaldine red IS, titrate with perchloric acid (0.1 mol/L) VS until the solution becomes almost colourless. Perform a blank determination and make any necessary correction. Each ml of perchloric acid (0.1 mol/L) VS is equivalent to 24.87 mg of C₁₂H₁₃ClN₄.

Category Antimalarial agent.

Storage Preserve in tightly closed containers, protected from light.

Preparation Pyrimethamine Tablets

Pyrimethamine Tablets

Pyrimethamine Tablets contain not less than 90.0% and not more than 110.0% of the labelled amount of pyrimethamine (C₁₂H₁₃ClN₄).

Description White tablets.

Identification (1) To a quantity of the powdered tablets equivalent to about 5 mg of pyrimethamine, add 2 ml of dilute sulfuric acid and heat, cool and filter. Add 2 drops of mercuric potassium iodide TS to the filtrate, a creamy-white precipitate is produced.

(2) The light absorption of the solution obtained in the Assay exhibits a maximum at 272 nm and a minimum at 261 nm (Appendix IV A).

(3) Comply with the test (3) for Identification described under Pyrimethamine, using a quantity of the powdered tablets equivalent to about 0.1 g of pyrimethamine.

Content uniformity Comply with the requirements for content uniformity (Appendix X E). Dissolve 1 tablet in a 100 ml volumetric flask with a quantity of 0.1 mol/L hydrochloric acid solution by ultrasonic treatment, cool. Dilute to volume with 0.1 mol/L hydrochloric acid solution, mix well and filter. Transfer 5 ml of the successive filtrate, accurately measured in 25 ml volumetric flask, dilute to volume with 0.1 mol/L hydrochloric acid solution, mix well. Measure the absorbance at 272 nm (Appendix IV A), calculate the content of C₁₂H₁₃ClN₄, taking 319 as the value of A (1%, 1 cm).

Dissolution Carry out the dissolution test (Appendix X C, method 2), using 500 ml of 0.1 mol/L hydrochloric acid solution as the dissolution medium, adjust the rotational speed of the paddle to 75 rpm. Withdraw the solution after exactly 45 minutes and filter. Measure the absorbance at 272 nm (Appendix IV A), using the successive filtrate. Calculate the dissolution of C₁₂H₁₃ClN₄ from each tablet, taking 319 as the value of A (1%, 1 cm). Not less than 75% of the labelled amount is dissolved.

Other requirements Comply with the general requirements for tablets (Appendix I A).

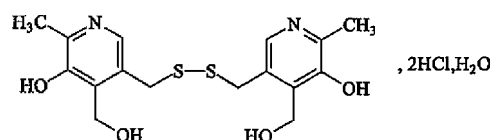
Assay Weigh accurately and powder 20 tablets. To a quantity of the powder equivalent to about 25 mg of pyrimethamine, accurately weighed, in a 100 ml volumetric flask add 70 ml of 0.1 mol/L hydrochloric acid solution, warm and shake thoroughly. Cool, add 0.1 mol/L hydrochloric acid solution to volume, mix well and filter. Measure accurately 5 ml of the successive filtrate to a 100 ml volumetric flask, add 0.1 mol/L hydrochloric acid solution to volume and mix well. Measure the absorbance at 272 nm (Appendix IV A). Calculate the content of C₁₂H₁₃ClN₄, taking 319 as the value of A (1%, 1 cm).

Category As described under Pyrimethamine.

Strength 6.25 mg

Storage Preserve in tightly closed containers, protected from light.

Pyritinol Hydrochloride



C₁₆H₂₀N₂O₄S · 2HCl · H₂O 459.40 [1098-97-1]

Pyritinol Hydrochloride is 3,3-(Dithiobismethylene) bis [5-hydroxy-6-methyl-4-pyridine methanol] dihydrochloride monohydrate. It contains not less than 97.0% and not more than 103.0% of C₁₆H₂₀N₂O₄S · 2HCl, calculated on the anhydrous basis.

Description A white or almost white crystalline powder; odourless; taste bitter and astringent.

Freely soluble in water; sparingly soluble in ethanol; insoluble in acetone, chloroform or ether.

Identification (1) Heat carefully on a straight fire to melt about 50 mg in a test tube, an odour of hydrogen sulfide is perceptible.

(2) The infrared absorption spectrum (Appendix IV C) is concordant with reference spectrum of Pyritinol Hydrochloride (Appendix XVI).

(3) The aqueous solution yields the reactions characteristic of chlorides (Appendix III).

Acidity Dissolve 0.1 g in 10 ml of water, pH 2.0-3.5 (Appendix VI H) (used for injection).

Clarity and colour of solution Dissolve 1.0 g in 10 ml of water, the solution is clear and colourless; any opalescence produced is not more pronounced than that of reference suspension I (Appendix IX B); any colour produced is not more intense than that of reference solution Y₇, OY₇ or YG₅ (for oral use), or Y₂ or YG₂ (used for injection) (Appendix

IX A, method 1).

Water Not more than 4.5% of its weight (Appendix VIII M, method 1 A).

Residue on ignition Not more than 0.1% (Appendix VIII N) use 1.0 g.

Heavy metals Carry out the limit test for heavy metals (Appendix VIII H, method 2), using the residue obtained in the test for residue on ignition, not more than 0.001%.

Sterility Comply with the test for sterility (Appendix XI H) (used for injection).

Assay Dissolve a quantity, accurately weighed, with 0.01 mol/L hydrochloric acid solution to produce a solution of 10 µg per ml. Measure the absorbance of the resulting solution at 295 nm (Appendix IV A), calculate the content of $C_{16}H_{20}N_2O_4S_2 \cdot 2HCl$, taking 403 as the value of A (1%, 1 cm).

Category Nootropic.

Storage Preserve in tightly closed containers, protected from light.

Preparation (1) Pyritinol Hydrochloride Capsules
(2) Pyritinol Hydrochloride for Injection
(3) Pyritinol Hydrochloride Tablets

Pyritinol Hydrochloride Capsules

Pyritinol Hydrochloride Capsules contain not less than 93.0% and not more than 107.0% of the labelled amount of pyritinol hydrochloride ($C_{16}H_{20}N_2O_4S_2 \cdot 2HCl \cdot H_2O$).

Description Capsules containing white or almost white powder.

Identification The contents of capsules comply with tests for Identification (1) described under Pyritinol Hydrochloride. (2) Shake a quantity of the contents of capsules with water and filter. The filtrate yields the reactions characteristic of chloride (Appendix III).

Other requirements Comply with the general requirements for capsules (Appendix I E).

Assay Dissolve a quantity of the mixed contents obtained in the test for weight variation of contents, equivalent to about 0.1 g of Pyritinol Hydrochloride, in 0.01 mol/L hydrochloric acid solution and dilute to 100 ml, mix well and filter. Measure accurately 2 ml of the successive filtrate to a 200 ml volumetric flask, dilute to volume with 0.01 mol/L hydrochloric acid solution, mix well. Measure the absorbance of the resulting solution at 295 nm (Appendix IV A). Calculate the content of $C_{16}H_{20}N_2O_4S_2 \cdot 2HCl \cdot H_2O$, taking 388 as the value of A (1%, 1 cm).

Category As described under pyritinol hydrochloride.

Strength 0.1 g

Storage preserve in tightly closed containers, protected from light.

Pyritinol Hydrochloride for Injection

Pyritinol Hydrochloride for Injection is a sterile powder of Pyritinol Hydrochloride. It contains

not less than 93.0% and not more than 107.0% of the labelled amount of anhydrous Pyritinol Hydrochloride ($C_{16}H_{20}N_2O_4S_2 \cdot 2HCl$), calculated with reference to the average weight of contents.

Description A white or almost white crystalline powder; odourless; taste, bitter and astringent.

Identification Complies with the tests for Identification (1) and (3) described under Pyritinol Hydrochloride.

Clarity and colour of solution Add 2 ml of water to each of 5 containers (calculated with reference to the labelled amount as 0.2 g), the solution is clear and colourless; any opalescence produced is not more pronounced than that of reference suspension I (Appendix IX B); any colour produced is not more intense than that of reference solution Y₂ or YG₂ (Appendix IX A, method 1).

Acidity A 1% aqueous solution, pH 2.0-3.5 (Appendix VI H).

Water Not more than 5.0% of its weight. (Appendix VIII M, method 1 A).

Other requirements Complies with the general requirements for injections (Appendix I B).

Assay Weigh accurately a quantity of the mixed contents obtained in the test for weight variation of contents, carry out the Assay described under Pyritinol Hydrochloride.

Category As described under Pyritinol Hydrochloride.

Strength (1) 0.1 g (2) 0.2 g

Storage Preserve in well closed containers, protected from light.

Pyritinol Hydrochloride Tablets

Pyritinol Hydrochloride Tablets contain not less than 93.0% and not more than 107.0% of the labelled amount of Pyritinol hydrochloride ($C_{16}H_{20}N_2O_4S_2 \cdot 2HCl \cdot H_2O$).

Description White or almost white tablets or sugar coated tablets with white or almost white core.

Identification A quantity of the powdered tablets complies with tests for Identification (1) and (3) described under Pyritinol Hydrochloride.

Other requirements Comply with the general requirements for tablets (Appendix I A).

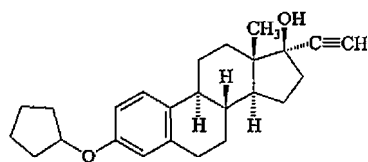
Assay Powder 20 tablets, with sugar coat removed. Dissolve a quantity, accurately weighed, equivalent to about 0.1 g of Pyritinol hydrochloride in a 100 ml volumetric flask in 0.01 mol/L hydrochloric acid, dilute to volume, mix well and filter. Measure accurately 2 ml of the successive filtrate to a 200 ml volumetric flask, dilute with 0.01 mol/L hydrochloric acid to volume, mix well. Measure the absorbance of the resulting solution at 295 nm (Appendix IV A). Calculate the content of $C_{16}H_{20}N_2O_4S_2 \cdot 2HCl \cdot H_2O$, taking 388 as the value of A (1% 1 cm).

Category As described under Pyritinol hydrochloride.

Strength 0.1 g

Storage Preserve in tightly closed containers, protect from light.

Quinestrol



$C_{25}H_{32}O_2$ 364.50

[152-43-2]

Quinestrol is 3-(cyclopentyloxy)-17 α -pregna-1,3,5 [10]-trien-20-yn-17-ol. It contains not less than 97.5% and not more than 102.5% of $C_{25}H_{32}O_2$, calculated on the dried basis.

Description White or almost white crystals or a crystalline powder.

Soluble in ethanol, acetone, ethyl acetate or chloroform; practically insoluble in water.

Melting range 106-112°C (Appendix VI C).

Specific optical rotation 0° to +5°, in a solution of about 10 mg per ml in dioxane (Appendix VI E).

Identification (1) Dissolve 2 mg in 2 ml of sulfuric acid, an orange red colour is produced, and a yellowish-green fluorescence is exhibited under ultraviolet light. Add 2 ml of water, a red precipitation is produced.

(2) The light absorption of a solution obtained in the Assay exhibits a maximum at 280 nm (Appendix IV A).

(3) The infrared absorption spectrum (Appendix IV C) is concordant with the reference spectrum of quinestrol (Appendix XVI).

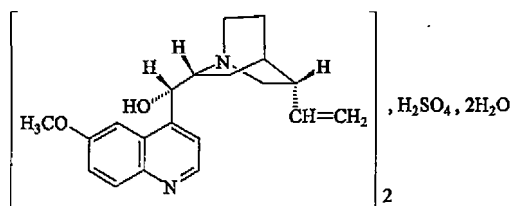
Loss on drying When dried to constant weight at 80°C, loses not more than 5.5% of its weight (Appendix VIII L).

Assay To 50 mg, accurately weighed, in a 50 ml volumetric flask add absolute ethanol and dilute to volume and mix well. Transfer 5 ml, accurately measured, to another 50 ml volumetric flask, dilute with absolute ethanol to volume and mix well. Measure the absorbance at 280 nm (Appendix IV A). Weigh a quantity of quinestrol CRS to produce a solution of 100 μ g per ml of absolute ethanol instead of the substance being examined. Calculate the content of $C_{25}H_{32}O_2$.

Category Progestogen.

Storage Preserve in tightly closed containers.

Quinidine Sulfate



$(C_{20}H_{24}N_2O_2)_2 \cdot H_2SO_4 \cdot 2H_2O$ 782.96 [6591-63-5]

Quinidine Sulfate is (9S)-6'-methoxydeoxycinchonane-9-ol sulfate (2 : 1) (salt), dihydrate. It contains not less than 99.0% of $(C_{20}H_{24}N_2O_2)_2 \cdot$

H_2SO_4 , calculated on the dried basis.

Description White, fine needle crystals; odourless; taste, very bitter; discoloured gradually on exposure to light. Freely soluble in boiling water; soluble in chloroform or ethanol; sparingly soluble in water; practically insoluble in ether.

Specific optical rotation +275° to +290°, in a solution of 20 mg per ml in 0.1 mol/L hydrochloric acid solution (Appendix VI E).

Identification (1) Dissolve 20 mg in 20 ml of water, acidify 10 ml of the solution with dilute sulfuric acid; a blue fluorescence is produced. Add a few drops of hydrochloric acid solution, a fluorescence is disappeared.

(2) Add 1-2 drops of bromine TS and 1 ml of ammonia TS to 5 ml of the solution obtained under (1); an emerald-green colour is produced.

(3) The aqueous solution yields the reactions characteristic of sulfates (Appendix III).

Acidity An aqueous solution of 10 mg per ml, pH 6.0-7.0 (Appendix VI H).

Chloroform-Ethanol-insoluble matter Dissolve 2.0 g in 15 ml of a mixture of chloroform-dehydrated ethanol (2 : 1), heat at 50°C for 10 minutes, cool, filter with a sintered glass filter and wash the filter with five 10 ml portions of a mixture of chloroform-dehydrated ethanol (2 : 1), dried at 105°C for 1 hour, the residue is not more than 0.1% of its weight.

Related substances Carry out the method for thin layer chromatography (Appendix V B), using silica gel H as the coating substance and chloroform-acetone-diethylamine (5 : 4 : 1) as the mobile phase. Apply separately to the plate 10 μ l of each of two solutions in dilute ethanol containing (1) 6 mg; (2) 0.06 mg of the substance being examined per ml. After developing 15 cm and removal of the plate, dry it and spray with glacial acetic acid, and examine under ultraviolet light at 365 nm, spray with potassium iodoplatinate TS. Any spot, other than the quinidine and dihydroquinidine principal spot in the chromatogram obtained with the solution (1) is not more intense than the principal spot obtained with the solution (2).

Loss on drying When dried to constant weight at 120°C, loses not more than 5.0% of its weight (Appendix VIII L).

Residue on ignition Not more than 0.1% (Appendix VIII N).

Assay Dissolve 0.2 g, accurately weighed, in 5 ml of glacial acetic acid, add 20 ml of acetic anhydride and a drop of crystal violet IS. Titrate with perchloric acid (0.1 mol/L) VS until the colour changes to green. Each ml of perchloric acid (0.1 mol/L) VS is equivalent to 24.90 mg of $(C_{20}H_{24}N_2O_2)_2 \cdot H_2SO_4$.

Category Antiarrhythmic agent.

Storage Preserve in tightly closed containers, protected from light.

Preparation Quinidine Sulfate Tablets

Quinidine Sulfate Tablets

Quinidine Sulfate Tablets contain not less than 93.0% and not more than 107.0% of the labelled amount of Quinidine Sulfate $(C_{20}H_{24}N_2O_2)_2 \cdot H_2SO_4 \cdot 2H_2O$.

Description Sugar-coated with white core.

Identification Powder the tablets with the sugar coating removed. Weigh accurately a quantity of the powder equivalent to about 20 mg of Quinidine Sulfate, add 20 ml of water, mix well and filter. The filtrate complies with the tests for Identification described under Quinidine Sulfate.

Dissolution Carry out the dissolution test (Appendix X C, method 1), using 900 ml of 0.1 mol/L hydrochloric acid as the dissolution medium, adjust the rotational speed of the basket to 100 rpm. Withdraw 10 ml of the solution after exactly 45 minutes and filter. Measure 2 ml of the successive filtrate and dilute with the dissolution medium to 10 ml. Measure the absorbance of the resulting solution at 347 nm (Appendix IV A). Calculate the dissolution of $(C_{20}H_{24}N_2O_2)_2 \cdot H_2SO_4$ from each tablet, taking 149 as the value of A (1%, 1 cm) and multiply by 0.9540; not less than 80% of the labelled amount is dissolved.

Other requirements Comply with the general requirements for tablets (Appendix I A).

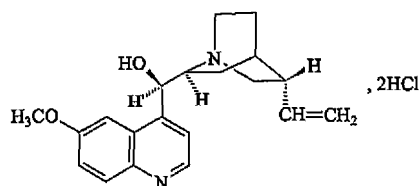
Assay Weigh accurately and powder 10 tablets with the sugar coating removed. To an accurately weighed quantity of the powdered tablets equivalent to about 0.2 g of quinidine sulfate add 20 ml of acetic anhydride, warm to dissolve quinidine sulfate. Add 1 drop of crystal violet IS. Titrate with perchloric acid (0.1 mol/L) VS until the solution changes to green. Perform a blank determination and make any necessary correction. Each ml of perchloric acid (0.1 mol/L) VS is equivalent to 26.10 mg $(C_{20}H_{24}N_2O_2)_2 \cdot H_2SO_4 \cdot 2H_2O$.

Category As described under Quinidine Sulfate.

Strength 0.2 g

Storage Preserve in tightly closed containers, protected from light.

Quinine Dihydrochloride



$C_{20}H_{24}N_2O_2 \cdot 2HCl$ 397.34

[60-93-5]

Quinine Dihydrochloride is 6'-methoxy-(8 α -9R)-chinchonan-9-ol dihydrochloride. It contains not less than 99.0% of $C_{20}H_{24}N_2O_2 \cdot 2HCl$, calculated on dried basis.

Description A white powder; odourless; taste, very bitter; discoloured slowly on exposure to light; the aqueous solution exhibits an acid reaction. Very soluble in water, soluble in ethanol, slightly soluble in chloroform, very slightly soluble in ether.

Specific optical rotation -223° to -229° in a solution of 30 mg per ml in 0.1 mol/L hydrochloric acid solution (Appendix VI E).

Identification (1) Dissolve about 20 mg in 20 ml of water, add dilute sulfuric acid dropwise to 10 ml of the solution, a blue fluorescence is produced. (2) Add 3 drops of bromine TS and 1 ml of ammonia TS to 5 ml of above solution, a emerald green colour is produced. (3) The infrared absorption spectrum (Appendix IV C) is

concordant with the reference spectrum of quinine dihydrochloride (Appendix XVI).

(4) The aqueous solution yields the reactions characteristic of chlorides (Appendix III).

Acidity Dissolve 0.30 g in 10 ml of water, pH 2.0-3.0 (Appendix VI H).

Sulfates Carry out the limit test for sulfates (Appendix VIII B), using 1.0 g. Any opalescence produced is not more pronounced than that of a reference solution using 5.0 ml of potassium sulfate standard solution (0.05%).

Other cinchona alkaloids Carry out the method for thin-layer chromatography (Appendix V B), using silica gel G as the coating substance and a mixture of toluene-ether-diethylamine (20 : 12 : 5) as the mobile phase. Apply separately to the plate 5 μ l of each of two solutions in methanol containing (1) 10 mg of the substance being examined per ml and (2) 0.25 mg of anchonidine CRS per ml. After developing and removal of the plate, allow it to dry in air and repeat twice the developing. Dry the plate at $105^\circ C$ for 30 minutes, allow it to cool and spray with potassium iodoplatinate TS. Any spot, other than the principal spot, obtained with solution (1) is not more intense than the principal spot obtained with solution (2) (2.5%).

Loss on drying When dried to constant weight at $105^\circ C$, loses not more than 3.0% of its weight (Appendix VIII L).

Residue on ignition Not more than 0.15% (Appendix VIII N).

Bariums Dissolve 0.20 g in 10 ml of water, add 1 ml of dilute sulfuric acid. The solution remains clear for at least 15 minutes.

Assay Dissolve about 0.15 g, accurately weighed, in 5 ml of acetic anhydride and 3 ml of mercuric acetate TS, add 1 drop of crystal violet IS, titrate with perchloric acid (0.1 mol/L) VS, until the colour changes to bluish green. Perform a blank determination and make any necessary correction. Each ml of perchloric acid (0.1 mol/L) VS is equivalent to 19.87 mg of $C_{20}H_{24}N_2O_2 \cdot 2HCl$.

Category Antimalarial.

Storage Preserve in tightly closed containers, protected from light.

Preparation Quinine Dihydrochloride Injection

Quinine Dihydrochloride Injection

Quinine Dihydrochloride Injection is a sterile solution of Quinine Dihydrochloride in Water for Injection. It contains not less than 95.0% and not more than 105.0% of the labelled amount of quinine dihydrochloride ($C_{20}H_{24}N_2O_2 \cdot 2HCl$).

Description A clear, colourless or pale yellow liquid.

Identification Complies with the tests (1), (2) and (4) for Identification described under Quinine Dihydrochloride.

pH value Not lower than 2.5 (Appendix VI H).

Colour Not more intense than the colour of the reference solution (using 10 ml of Potassium Dichromate Standard Solution, add water to 20 ml) in equal volume.

Other requirements Complies with the general requirements for injections (Appendix I B).

Assay Measure accurately a quantity of the injection equivalent to about 15 mg of quinine dihydrochloride per ml

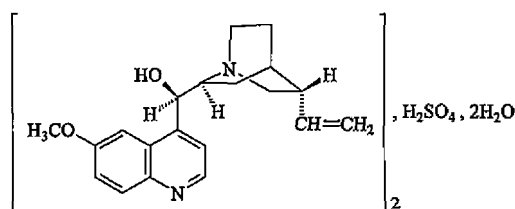
in water, and transfer 10 ml, accurately measured, to a separator, add water to produce 20 ml, alkaliify with ammonia TS and extract with chloroform in portions, first time use 25 ml, then use 10 ml each time until the extraction of quinine is completed. Wash each portion of chloroform extract twice with 5 ml of water, then extract the washings with 10 ml of chloroform. Combine the chloroform extracts, evaporate to expel the chloroform on a water bath, add 2 ml of dehydrated ethanol, evaporate to dryness, dry for an hour at 105°C and cool. Dissolve the residue in a mixture of 5 ml of acetic anhydride and 10 ml of glacial acetic acid, add 1 drop of crystal violet IS, titrate with perchloric acid (0.1 mol/L) VS until the colour changes to blue. Perform a blank determination and make any necessary correction. Each ml of perchloric acid (0.1 mol/L) VS is equivalent to 19.87 mg of $C_{20}H_{24}N_2O_2 \cdot 2HCl$.

Category As described under Quinine Dihydrochloride.

Strength (1) 1 ml : 0.25 g (2) 1 ml : 0.5 g
(3) 2 ml : 0.25 g (4) 2 ml : 0.5 g
(5) 10 ml : 0.25 g

Storage Preserve in tightly closed containers, protected from light.

Quinine Sulfate



$(C_{20}H_{24}N_2O_2)_2 \cdot H_2SO_4 \cdot 2H_2O$ 782.96 [6119-70-6]

Quinine Sulfate is (8α, 9R)-6'-methoxy-cinchonan-9-ol sulfate (2 : 1) (salt) dihydrate. It contains not less than 99.0% of $(C_{20}H_{24}N_2O_2)_2 \cdot H_2SO_4$, calculated on the dried basis.

Description White, fine needle crystals; light and soft; readily compressible; odourless; taste, very bitter; the colour changes gradually on exposure to light; the aqueous solution exhibits neutral reaction.

Freely soluble in a mixture of chloroform-dehydrated ethanol (2 : 1); slightly soluble in water, ethanol, chloroform or ether.

Specific optical rotation -237° to -244° , in a solution of 20 mg per ml in 0.1 mol/L hydrochloric acid solution (Appendix VI E).

Identification (1) Dissolve 20 mg in 20 ml of water, acidify 10 ml of the solution with dilute sulfuric acid, a blue fluorescence is produced.

(2) Add 3 drops of bromine TS and 1 ml of ammonia TS to 5 ml of the solution obtained under (1), an emerald green colour is produced.

(3) Add hydrochloric acid to acidify 5 ml of the solution obtained under (1), then add 1 ml of barium chloride TS, a white precipitate is produced.

(4) The infrared absorption spectrum (Appendix IV C) is concordant with the reference spectrum of quinine sulfate (Appendix XVI).

Acidity Dissolve 0.20 g in 20 ml of water, pH 5.7-6.6 (Appendix VI H).

Chloroform-ethanol-insoluble substances Dissolve 2.0 g in 15 ml of a mixture of chloroform-dehydrated ethanol (2 : 1), heat at 50°C for 10 minutes, filter with a previously weighed sintered glass crucible and wash the residue with 10 ml each of the same solvent for 5 times and dried to constant weight at 105°C, the residue is not more than 2 mg.

Other cinchona alkaloids Carry out the method for thin-layer chromatography (Appendix V B), using silica gel G as the coating substance and a mixture of chloroform-acetone-diethylamine (5 : 4 : 1.25) as the mobile phase. Apply separately to the plate 5 μl of each of two solutions in dilute ethanol containing (1) 10 mg, (2) 50 μg of the substance being examined per ml. After developing and removal of the plate, dry it in warm air and spray with potassium iodoplatinate TS. Any spots, other than the principal spot, obtained with solution (1) is not more intense than the principal spot obtained with solution (2).

Loss on drying When dried to constant weight at 105°C, loses not more than 5.0% of its weight (Appendix VII L).

Residue on ignition Not more than 0.1% (Appendix VII N).

Assay Dissolve 0.2 g, accurately weighed, in 10 ml of glacial acetic acid, add 5 ml of acetic anhydride and 1-2 drops of crystal violet IS. Titrate with perchloric acid (0.1 mol/L) VS until the colour changes to bluish green. Perform a blank determination and make any necessary correction. Each ml of perchloric acid (0.1 mol/L) VS is equivalent to 24.90 mg of $(C_{20}H_{24}N_2O_2)_2 \cdot H_2SO_4$.

Category Antimalarial.

Storage Preserve in tightly closed containers, protected from light.

Preparation Quinine Sulfate Tablets

Quinine Sulfate Tablets

Quinine Sulfate Tablets contain not less than 95.0% and not more than 105.0% of the labelled amount of quinine sulfate $[(C_{20}H_{24}N_2O_2)_2 \cdot H_2SO_4 \cdot 2H_2O]$.

Description Sugar coated tablets with white core.

Identification (1) To a quantity of powdered tablets with sugar coating removed equivalent to about 50 mg of quinine sulfate add 5 ml of water, shake and filter. The filtrate complies with tests (1) (2) (3) for Identification described under quinine sulfate.

(2) To a quantity of powdered tablets obtained under (1) add 0.1 mol/L hydrochloric acid solution to produce a solution of 10 mg per ml and filter. The optical rotation of the filtrate (Appendix VI E) exhibits levorotation (distinguish from quinidine tablets).

Other requirements Comply with the general requirements for tablets (Appendix I A).

Assay Weigh accurately and powder 10 tablets after removing sugar coating. Weigh accurately a quantity equivalent to about 0.3 g of quinine sulfate to a separator, add 0.5 g of sodium chloride and 10 ml of 0.1 mol/L sodium hydroxide solution and mix well. Add 50 ml of chloroform, accurately measured, shake for 10 minutes, allow to separate into two layers. Filter the chloroform layer, measure accurately 25 ml of the successive filtrate, add 5 ml of acetic anhydride and 2 drops of dimethyl yellow IS, titrate with perchloric acid (0.1 mol/L) VS until the colour

containing (1) 10 mg per ml, (2) 0.25 mg per ml (3) 0.15 mg per ml, (4) 0.10 mg per ml, (5) 0.05 mg per ml. After developing and removal of the plate, dry it in air, visualize in iodine vapour and observe immediately. The intensity of any secondary spot, in the chromatogram obtained with solution (1) is compared with that of the principal spots obtained with solution (2), (3), (4), (5), the total amount of impurities is not more than 2.5%.

Loss on drying When dried at 60 °C for 4 hours in vacuum over phosphorus pentoxide, loses not more than 1.0% of its weight (Appendix VIII L).

Residue on ignition Not more than 0.1% (Appendix VIII N); use 1.0 g.

Heavy metals Carry out the limit test for heavy metals (Appendix VIII H, method 2), using the residue obtained in Residue on ignition; not more than 0.002%.

Assay Carry out the method for high-performance liquid chromatography (Appendix V D), using a column packed with octadecylsilane bonded silica gel and a mixture of methanol-0.77% ammonium acetate solution (285 : 115) as the mobile phase. Detection wavelength is 320 nm and the number of theoretical plates of the column is not less than 1000, calculated with reference to the peak of ranitidine hydrochloride. The resolution factor between peaks of ranitidine hydrochloride and internal standard complies with the related requirements.

Internal standard solution Dissolve a quantity of indomethacin in methanol to produce a solution of about 0.30 mg per ml.

Procedure Dissolve a quantity of ranitidine hydrochloride, accurately weighed, in 50% methanol solution to produce a solution of 0.15 mg per ml. Transfer 2 ml each of the test solution and the internal standard solution, both measured accurately, in a 50 ml volumetric flask, dilute with 50% methanol solution to volume, mix well. Inject 10-15 µl of the resulting solution into the column. Repeat the operation, using the substance being examined instead of ranitidine hydrochloride CRS, calculate the content of $C_{13}H_{22}N_4O_3S$.

Category Histamine H_2 receptor antagonist.

Storage Preserve in tightly closed containers, protected from light, stored in cool, dark and dry place.

Preparation (1) Ranitidine Hydrochloride Capsules
(2) Ranitidine Hydrochloride Injection
(3) Ranitidine Hydrochloride Tablets

Ranitidine Hydrochloride Capsules

Ranitidine Hydrochloride Capsules contain not less than 93.0% and not more than 107.0% of the labelled amount of ranitidine ($C_{13}H_{22}N_4O_3S$).

Identification (1) A quantity of the contents equivalent to about 0.2 g of ranitidine complies with test (1) for Identification described under ranitidine hydrochloride.

(2) The solution obtained in Assay exhibits absorption maxima at 228 nm and 314 nm (Appendix IV A).

(3) Shake the contents with water and filter. The filtrate yields reactions characteristic of chlorides (Appendix III).

Related substances Carry out the related substances described under Ranitidine Hydrochloride Tablets, using the contents of capsules, the total amount of impurities is not more than 4.0%.

Other requirements Comply with the general requirements for capsules (Appendix I E).

Assay Mix well the mixed contents obtained in the test for weights variation of contents and dissolve a quantity of the contents, accurately weighed, equivalent to about 25 mg of ranitidine in a 100 ml volumetric flask with water, dilute to volume with water, mix well and filter, carry out the Assay described under Ranitidine Hydrochloride Tablets, using 5 ml, accurately measured, of the successive filtrate, beginning at the words "To 5 ml, accurately measured, of the dilute solution...". Calculate the content of $C_{13}H_{22}N_4O_3S$.

Category As described under Ranitidine Hydrochloride.

Strength (1) 75 mg (2) 100 mg (3) 150 mg
(calculated on $C_{13}H_{22}N_4O_3S$)

Storage Preserve in tightly closed containers, protected from light, stored in dry place.

Ranitidine Hydrochloride Injection

Ranitidine Hydrochloride Injection is a sterile solution of Ranitidine Hydrochloride in Water for Injection. It contains not less than 93.0% and not more than 107.0% of the labelled amount of ranitidine hydrochloride ($C_{13}H_{22}N_4O_3S$).

Description A clear, slightly yellow or pale yellow liquid.

Identification (1) Transfer 2 ml of the injection to a test tube, evaporate to dryness on a water bath, heat gently, the evolved vapour turns the moistened lead acetate test paper to black.

(2) Complies with the tests (2) and (4) for Identification described under ranitidine hydrochloride.

Related substances Prepare the test solution containing 10 mg per ml of methanol. Dilute a quantity of the test solution, accurately measured with methanol to produce solutions containing 0.05 mg, 0.10 mg, 0.15 mg and 0.20 mg per ml respectively as the reference solution (1), (2), (3) and (4). Carry out the method for thin layer chromatography (Appendix V B), using silica gel G as the coating substance and a mixture of ethyl acetate-isopropanol-concentrated ammonia solution-water (25 : 15 : 5 : 1) as the mobile phase. Apply separately to the plate 10 µl each of the 5 solutions. After developing and removal of the plate, dry in air, visualize in iodine vapour and observe immediately. The total amount of impurities is not more than 6.0% in comparison with the colour intensity of the principal spot in the chromatogram obtained with the reference solutions (1), (2), (3) and (4).

pH value 6.5-7.5 (Appendix VI H).

Pyrogens Complies with the test for pyrogens (Appendix XI D), using 1 ml per kg of rabbit's weight.

Other requirements Complies with the general requirements for injections (Appendix I B).

Assay Measure accurately a quantity equivalent to 25 mg of ranitidine into a 100 ml volumetric flask, dilute with water to volume and mix well. Carry out the assay described under Ranitidine Hydrochloride Tablets, using 5 ml, accurately measured, beginning at the words "To 5 ml, accurately measured, of the dilute solution...". Calculate the content of $C_{13}H_{22}N_4O_3S$.

Category As described under Ranitidine Hydrochloride.

Strength (1) 2 ml : 50 mg (2) 5 ml : 50 mg
(calculated on $C_{13}H_{22}N_4O_3S$)

Storage Preserve in well closed containers, protected from light.

Ranitidine Hydrochloride Tablets

Ranitidine Hydrochloride Tablets contain not less than 93.0% and not more than 107.0% of the labelled amount of ranitidine ($C_{13}H_{22}N_4O_3S$).

Description Sugar coated or film coated tablets with almost white or slightly yellow core.

Identification (1) Weigh and powder a quantity of tablets with coating removed equivalent to about 0.2 g of ranitidine. It complies with test (1) for Identification described under Ranitidine Hydrochloride.

(2) The solution obtained in Assay exhibits absorption maxima at 228 nm and 314 nm (Appendix IV A).

(3) Shake the powder obtained in test (1) for Identification with water and filter. The filtrate yields the reactions characteristic of chlorides (Appendix III).

Related substances Prepare the test solution containing 10 mg per ml of methanol. Dilute a quantity of the test solution, accurately measured with methanol to produce solutions containing 0.05 mg, 0.10 mg, 0.15 mg and 0.20 mg per ml respectively as the reference solution (1), (2), (3) and (4). Carry out the method for thin layer chromatography (Appendix V B), using silica gel G as the coating substance and a mixture of ethyl acetate-isopropanol-concentrated ammonia solution-water (25 : 15 : 5 : 1) as the mobile phase. Apply separately to the plate 10 μ l each of the 5 solutions. After developing and removal of the plate, dry it in air, visualize in iodine vapour and observe immediately. The total amount of impurities is not more than 4.0% in comparison with the colour intensity of the principal spot in the chromatogram obtained with the reference solutions (1), (2), (3) and (4).

Dissolution Carry out the dissolution test (Appendix X C, method 2), using 900 ml of water as the dissolution medium, adjust the rotational speed of the paddle to 50 rpm. Withdraw the solution after exactly 45 minutes and filter, dilute 2 ml of the successive filtrate with water to 20 ml, mix well. Measure the absorption of the resulting solution at 314 nm (Appendix IV A). Calculate the dissolution of $C_{13}H_{22}N_4O_3S$ from each tablet, taking 495 as the value of A (1%, 1 cm). Not less than 80% of the labelled amount is dissolved.

Other requirements Comply with the general requirements for tablets (Appendix I A).

Assay Weigh accurately and powder 10 tablets. Triturate a quantity of powder, accurately weighed, equivalent to about 25 mg of ranitidine with water in a mortar, allow it to disintegrate completely. Transfer the mixture to a 100 ml volumetric flask, wash the mortar with a small amount of water in portions. Combine the washings with the mixture in the volumetric flask, dilute with water to volume, mix well and filter, transfer 5 ml of the successive filtrate, accurately measured, to a 250 ml volumetric flask, dilute with water to volume and shake well. Measure accurately 5 ml of the dilute solution in a 100 ml volumetric flask, dilute with water to volume and mix well. Measure the absorbance of the resulting solution at 314 nm (Appendix IV A), calculate the content of $C_{13}H_{22}N_4O_3S$, taking 495 as the value of A (1%, 1 cm).

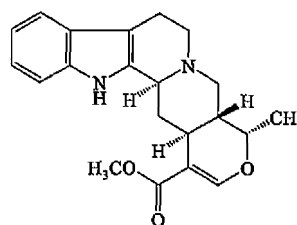
Category As described under Ranitidine Hydrochloride.

Strength (1) 75 mg (2) 150 mg

(calculated on $C_{15}H_{22}N_4O_3S$)

Storage Preserve in tightly closed containers, protected from light and stored in dry place.

Raubasine



$C_{21}H_{24}N_2O_3$ 352.43

Raubasine is (19a)-16,17-didehydro-19-methyl-Oxayhimban-16-carboxylic acid methyl ester. It contains not less than 98.5% of $C_{21}H_{24}N_2O_3$, calculated on the dried basis.

Description A white to slightly yellow powder; colourless; odourless.

Soluble in chloroform; slightly soluble in methanol, ethanol or acetone; practically insoluble in water.

Specific optical rotation -57° to -67° , in a solution of 2.5 mg per ml in chloroform (Appendix VI E).

Identification (1) Dissolve about 5 mg in 2 ml of dilute sulfuric acid TS, add 1 drop of bismuth potassium iodide TS, an orange red precipitate is produced immediately.

(2) The light absorption of a solution of 4 μ g per ml in ethanol exhibits a maxima at 227 nm (Appendix IV A).

(3) The infrared absorption spectrum (Appendix IV C) is concordant with the reference spectrum of Raubasine (Appendix X XIII).

Related substances Carry out the method for thin-layer chromatography (Appendix V B), using silica gel GF₂₅₄ as the coating substance and a mixture of chloroform-methanol (40 : 0.1) as mobile phase. Apply separately to the plate 10 μ l each of four solution in chloroform containing (1) 10 mg per ml, (2) 0.05 mg per ml, (3) 0.10 mg per ml, (4) 0.15 mg per ml of the substance being examined. After developing and removal of the plate, dry it in air and expose it to saturated iodine vapour until the spots appear, then examine immediately. The number of spots in the chromatogram other than the principal spot obtained with solution (1) is not more than 3. Any spot is compared with that of the principal spots obtained with solution (2), (3), (4), the total impurity is not more than 1.5%.

Chloroform Dissolve a quantity, accurately weighed, in dimethylformamide to produce a solution of 20 mg per ml. Carry out the test for the residual solvents (Appendix VIII P), complying with the requirements.

Loss on drying When dried to constant weight at 105°C, loses not more than 0.5% of its weight (Appendix VIII L).

Residue on ignition Not more than 0.1% (Appendix VIII N), using 1.0 g.

Heavy metals Carry out the limit test for heavy metals (Appendix VIII H, method 2), using the residue obtained in the test for residue on ignition; not more than 0.002%.

Assay Dissolve about 0.3 g, accurately weighed, in 20 ml of glacial acetic acid, add 1 drop of crystal violet IS, titrate with perchloric acid VS (0.1 mol/L) until the colour

changes to blue. Perform a blank determination and make any necessary correction. Each ml of perchloric acid VS (0.1 mol/L) is equivalent to 35.24 mg of $C_{21}H_{24}N_2O_3$.

Category Nootropic

Storage Preserve in tightly closed containers and cold place, protected from light.

Preparations Compound Almitrine Tablets

Recombinant Human Growth Hormone

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FPTIPLSRFL DNAMLRARHL HQLAFDTYQE
FEEAYIPKEQ KYSFLQNPQT SLCSSES IPT
PSNREETQQK SNLELLRISL LLIQSWLEPV
QFLRSVFANS LVYGASDSNV YDLLKDLEEG
IQTLMGRLED GSPRTGQIFK QTYSKFDYNS
HNDDALLKNY GLLYCFRKDM DKVETFLRIV
QCRSVEGSCG F
  
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Recombinant Human Growth Hormone is a protein having 191 amino acid residues or 192 amino acid residues with a methionine on N-terminal, mixed with suitable excipients or stabilizing agent. It contains not less than 90.0% and not more than 110.0% of the labelled amount of recombinant human Growth Hormone. Recombinant Human Growth Hormone is produced by a method based on recombinant DNA technology. It must be demonstrated that the manufacturing process produces a product having a biological activity of at least 2.5 Units per mg, using a suitable, validated vivo bioassay.

Host-cell and vector-derived DNA and host-cell derived proteins are potential specific impurities related to the manufacturing process and must be controlled strictly during the manufacturing process, the host cell derived proteins content of recombinant human somatotropin, determined by an appropriate and validated method, is not more than 10 ppm, the host cell or vector derived DNA content and limit of human insulin derived from a recombinant DNA process that utilizes prokaryotic or eukaryotic host cell are determined by a validated method.

Description A white lyophilized powder.

Identification (1) Dissolve a quantity in water to produce a solution of 2 mg per ml, to a quantity volume of the solution add the equal volume of sample buffer (measure 2.5 ml of concentrated gel buffer, 2.5 ml of 20% sodium dodecyl sulfate (SDS), 1.0 ml of 0.1% bromophenol blue solution and 3.5 ml of 87% glycerol solution, add water to 10 ml), add β -mercaptoethanol to make the final concentration of 5%, heat in a water bath for 3 minutes, cool as a test solution. Repeat the operation, using recombinant human somatotropin RS or formylate recombinant human somatotropin RS instead of the substance being examined as a reference

solution. Apply separately 10 μ l each of the reference solution and the test solution to the gel. Carry out the method for electrophoresis (Appendix V F, method 5, Coomassie staining method). the mobility of the principal component of the test solution is identical with that of the principal component of the reference solution.

(2) The retention time of principal peak of the substance being examined in the chromatogram obtained in the test for Related proteins is identical with that of the principal peak of recombinant human somatotropin RS or formylate recombinant human somatotropin RS in the chromatogram of the reference solution.

(3) Dissolve a quantity in water to produce a solution of 2 mg per ml, to 150 μ l of the solution add 150 μ l of trimetamol-acetic acid BS (dissolve 0.294 g calcium chloride and 12.11 g trimetamol in 400 ml of water, adjust pH value to 8.5 with 5 mol/L acetic acid solution, add water to 500 ml) and 10 μ l of trypsin solution (dissolve a quantity of trypsin previously treated with TPCK in 1 mol/L acetic acid-sodium acetate BS (pH 5.0) to produce a solution of 1 mg per ml), mix well, warm in a 37°C water bath for 4 hours, add 60 μ l of glacial acetic acid to stop the reaction, as a test solution. Repeat the operation using recombinant human somatotropin RS or formylate recombinant human somatotropin RS instead of the substance being examined, as a reference solution. Carry out the method for high performance liquid chromatography (Appendix V D), using a column packed with octasilane bonded silica gel (5~10 μ m), a 0.1% solution of trifluoroacetic acid in water as mobile phase A and a 0.1% solution of trifluoroacetic acid in 90% acetonitrile as mobile phase B and performing the gradient elution program. Flow rate is 1.0 ml per minutes, column temperature is 35°C and detection wavelength is 214 nm.

Time (minute)	mobile phase A	mobile phase B
0	100%	0%
20	80%	20%
45	75%	25%
70	50%	50%
75	20%	80%

Inject separately 100 μ l each of the reference solution and the test solution into the column, and record the chromatogram. The peptide map of the test solution is identical with that of the reference solution.

Related proteins Dissolve a quantity in 0.05 mol/L trimetamol-hydrochloric acid BS (pH 7.5) to produce a solution of 2 mg per ml as a test solution. Repeat the operation using recombinant human somatotropin RS or formylate recombinant human somatotropin RS as a reference solution. Carry out the method for high performance liquid chromatography (Appendix V D), using a column packed with butylsilyl silica gel (5~10 μ m) and a mixture of 0.05 mol/L trimetamol-hydrochloric acid BS (pH 7.5)-*n*-propanol (about 71:29) as the mobile phase, adjust the proportions of the *n*-propanol such that the retention time of the principal peak of human somatotropin is approximately 30-36 minutes. Flow rate is 0.5 ml per minute, column temperature is 45°C and detection wavelength is 220 nm. Inject 20 μ l of the system suitability test solution (Dissolve a quantity of recombinant human somatotropin RS or formylate recombinant human somatotropin RS in 0.05 mol/L trimetamol-hydrochloric acid BS (pH 7.5) to produce a solution of 2 mg per ml. The final processes are sterile filtration, and allow to stand at room temperature for 5 hours. into the column. The resolution factor between the peaks of recombinant human somatotropin and oxidation recombinant human somatotropin is not less than 1.0, the tailing factor is 0.9~1.8. Inject 20 μ l of the test solution into the column.

Calculate the content of total related proteins with respect to the peak areas obtained in the chromatograms by the area normalization method; not more than 10.0%.

High molecular weight proteins Carry out the method described under Assay, calculate the content of high molecular weight proteins with respect to the peak areas obtained in the chromatogram by the area normalization method; not more than 4.0%.

Sterility Complies with the test for sterility (Appendix XI H, membrane filtration method).

Water Not more than 10.0% (Appendix VIII M, method 1 A).

Bacterial endotoxin Carry out the test for bacterial endotoxin (Appendix XI E); less than 5 Eu per mg of recombinant human somatotropin.

Assay Carry out the method for size exclusion chromatography (Appendix V H), using a column packed with hydrophilic silica gel for chromatography suitable for separation of globular protein with 5000-60000 daltons and 2-propanol-0.06 mol/L phosphate buffer solution (Dissolve 5.18 g of anhydrous phosphate hydrate sodium and 3.65 g of phosphate dihydrate sodium in 950 ml of water, adjust the pH to 7.0 with 85% phosphoric acid, dilute to 1000 ml with water) (3 : 97) as the mobile phase. Flow rate is 0.6 ml per minute and detection wavelength is 214 nm. Inject 20 µl of solution for system suitability test (dissolve monomer-dimer human somatotropin CRS in 0.025 mol/L phosphate buffer solution pH (7.0) (0.063 mol/L phosphate buffer solution 1→2.5) to produce a solution of 1.0 mg per ml) into the column. The resolution between the peak of monomer of human somatotropin and dimer should comply with the requirement.

Procedure Dissolve a quantity in 0.025 mol/L phosphate buffer solution (pH 7.0) to produce a solution of 1.0 mg per ml, inject 20 µl into the column. Repeat the operation, using recombinant human somatotropin CRS instead of the substance being examined. Calculate the content of recombinant human somatotropin with respect to the peak area obtained in the chromatogram by the external standard method.

Category Growth hormone.

Storage Preserve in tightly closed containers, stored at a temperature of 2°C to 8°C.

Preparation Recombinant Human Growth Hormone for Injection.

Recombinant Human Growth Hormone for Injection

Recombinant Human Growth Hormone for Injection is a lyophilized preparation of recombinant human somatotropin. It contains not less than 90.0% and not more than 110.0% of the labelled amount of recombinant human growth hormone.

Description A white lyophilized powder.

Identification Complies with tests (1) and (2) for Identification described under recombinant human somatotropin.

Acidity or alkalinity To each container add 1 ml of water for Injection, pH 6.5-8.5 (Appendix VI H).

Clarity and colour of solution A solution of 1.6 mg per ml in

water is clear and colourless; any opalescence produced is not more pronounced than that of reference suspension 2 (Appendix IX B).

Water Not more than 3.0% (Appendix VIII M, method 1 A).

Related proteins Carry out the method for Related proteins described under Recombinant Human Somatotropin; not more than 13.0%.

High molecular weight protein Carry out the method for High molecular weight proteins described under Recombinant Human Somatotropin; not more than 6.0%.

Bacterial endotoxin and Sterility Complies with the test for Bacterial endotoxin and Sterility described under Recombinant Human Somatotropin.

Other requirements Complies with the general requirements for injections (Appendix I B).

Assay Carry out the Assay described under Recombinant Human Somatotropin.

Category As described under Recombinant Human Growth Hormone.

Strength (1) 1.6 mg (4IU) (2) 4.0 mg (10IU)
(3) 1.0 mg (2.5IU) (4) 1.2 mg (3IU)

Storage Preserve in well closed containers, stored at a temperature of 2°C to 8°C and protected from light.

Recombinant Human Growth Hormone Bulk Solution

Recombinant Human Growth Hormone Bulk Solution is a solution containing a protein having 191 amino acid residues or 192 amino acid residues with a methionine on N-terminal and suitable excipients or stabilizing agent. It contains not less than 90.0% and not more than 110.0% of the labelled amount of recombinant human growth hormone bulk.

Recombinant Human Growth Hormone Bulk solution is produced by a method based on recombinant DNA technology. It must be demonstrated that the manufacturing process produces a product having a biological activity of at least 2.5 Units per mg, using a suitable, validated vivo bioassay.

Host-cell and vector-derived DNA and host-cell derived proteins are potential specific impurities related to the manufacturing process and must be controlled strictly during the manufacturing process, the limit must meet the related requirements described under Recombinant Human Growth Hormone Bulk.

Description A colourless, clear or slightly opalescent liquid.

Identification Complies with test for Identification described under recombinant human growth hormone.

Related proteins, High molecular weight Protein, Bacterial endotoxin and sterility Complies with the tests described under Recombinant Human Growth Hormone.

Assay Dilute a quantity with 0.025 mol/L phosphate BS

which becomes brownish-yellow on the addition of a few drops of ammonia TS.

(2) Dissolve 0.1 g in 2 ml of sodium hydroxide TS, add 1 drop of chloroform, a deep red colour is produced on heating; add a slight excess of hydrochloric acid, the colour changes to pale yellow.

(3) The infrared absorption spectrum (Appendix IV C) is concordant with the reference spectrum of resorcinol (Appendix XVI).

Phenol Dissolve 0.25 g in 5 ml of water, heat gently, no odour of phenol is perceptible.

Catechol Dissolve 0.50 g in 10 ml of water, add 2 drops of dilute acetic acid and 0.5 ml of lead acetate TS, no turbidity is produced.

Loss on drying When dried over sulfuric acid to constant weight, loses not more than 1.0% of its weight (Appendix VII L).

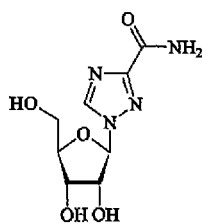
Residue on ignition Not more than 0.05% (Appendix VIII N).

Assay Dissolve about 0.15 g, accurately weighed, in water in a 100 ml volumetric flask, dilute with water to volume and mix well. Transfer 25 ml of the resulting solution to an iodine flask, add 30 ml of bromine (0.05 mol/L) VS, 50 ml of water and 5 ml of hydrochloric acid. Stopper the flask immediately, shake and allow to stand in the dark for 15 minutes. Add 5 ml of potassium iodide TS, immediately stopper the flask, shake thoroughly, allow to stand in the dark for 15 minutes. Titrate with sodium thiosulfate (0.1 mol/L) VS, add 1 ml of starch IS towards the end point, and continue the titration until the blue colour disappears. Perform a blank determination and make any necessary correction. Each ml of bromine (0.1 mol/L) VS is equivalent to 1.835 mg of $C_8H_{12}N_4O_5$.

Category Antiseptic Disinfectant.

Storage Preserve in tightly closed containers, protected from light.

Ribavirin



$C_8H_{12}N_4O_5$ 244.21

[36791-04-5]

Ribavirin is 1- β -D-ribofuranosyl-1*H*-1,2,4-triazole-3-carboxamide. It contains not less than 98.5% and not more than 101.5% of $C_8H_{12}N_4O_5$, calculated on the dried basis.

Description A white crystalline powder; odourless; tasteless. Freely soluble in water; slightly soluble in ethanol; insoluble in ether or chloroform.

Specific optical rotation -35.0° to -37.0° , in a solution of 40 mg per ml in water (Appendix VI E).

Identification (1) Dissolve about 0.1 g in 10 ml of water, add 5 ml of sodium hydroxide TS, heat to boiling, an odour characteristic of ammonia is perceptible, and the vapor produced turns the moistened red litmus paper to blue.

(2) The retention time of principal peak in the substance being examined in the chromatogram obtained in the Assay is identical with that of principal peak of ribavirin CRS in the chromatogram of the reference solution.

(3) The infrared absorption spectrum (Appendix IV C) is concordant with the reference spectrum of ribavirin (Appendix XVI).

Acidity Dissolve 0.5 g in 25 ml of water, pH 4.0-6.5 (Appendix VI H).

Light absorption The absorbance of a solution of 1.0 g in 25 ml of water at 430 nm (Appendix IV A) is not more than 0.02.

Related substances Carry out the method as described under Assay. Dissolve a quantity of the substance being examined in water to produce a test solution of 0.4 mg per ml. Accurately measure 1 ml into 100 ml of volumetric flask, dilute with the mobile phase to volume, mix well, as the reference solution. Inject 20 μ l of the reference solution into the column, adjust the attenuation so that the principal peak height in the chromatogram is 20%-25% of the full scale of the chart. Inject 20 μ l of the test solution into the column, and record the chromatogram for twice the retention time of the principal peak. The sum of the areas of all secondary peaks obtained with the test solution is not greater than the area of the principle peak in the chromatogram obtained with the reference solution (1.0%).

Loss on drying When dried to constant weight at 105°C , loses not more than 0.5% of its weight (Appendix VII L).

Residue on ignition Not more than 0.1% (Appendix VIII N), using 1.0 g.

Heavy metals Carry out the limit test for heavy metals (Appendix VIII H, method 2), using the residue obtained in the test for Residue on ignition; not more than 0.001%.

Assay Carry out the method for high performance liquid chromatography (Appendix V D), using a column packed with hydrogen cation-exchange resin consisting of sulfonated cross-linked styrene-divinylbenzene copolymer in the hydrogen form and water adjusted pH to 2.5 ± 0.1 , using dilute sulfate acid as the mobile phase. Detection wavelength is 207 nm and the number of the theoretical plates of the column is not less than 3000, calculated with reference to the peak of ribavirin.

Procedure Dissolve an accurately weighed quantity in water to produce a solution of 50 μ g per ml. Inject 20 μ l into the column. Repeat the operation, using ribavirin CRS instead of the substance being examined. Calculate the content of $C_8H_{12}N_4O_5$ with respect to the peak area obtained in the chromatogram by the external standard method.

Category Antiviral.

Storage Preserved in tightly closed containers, protected from light.

Preparation

- (1) Ribavirin and Glucose Injection
- (2) Ribavirin and Sodium Chloride Injection
- (3) Ribavirin Bawal Tablets
- (4) Ribavirin Capsules
- (5) Ribavirin Eye Drops
- (6) Ribavirin for Injection
- (7) Ribavirin Granules
- (8) Ribavirin Injection
- (9) Ribavirin Nasal Drops
- (10) Ribavirin Oral Solution
- (11) Ribavirin Tablets

Ribavirin Buccal Tablets

Ribavirin Buccal Tablets contain not less than 90.0% and not more than 110.0% of the labelled amount of ribavirin ($C_8H_{12}N_4O_5$).

Description Pale yellow buccal tablets; odour, flavor; taste, sweet.

Identification To a quantity of the powdered tablets equivalent to about 0.1 g of ribavirin, add 20 ml of water, triturate and filter. The successive filtrate complies with tests (1) and (2) for Identification described under Ribavirin.

Other requirements Comply with the general requirements for tablets (Appendix I A), other than Disintegration.

Assay Weigh accurately and powder 20 tablets. Dissolve an accurately weighed quantity of the powder in mobile phase to produce a solution of 50 µg of ribavirin per ml, shake thoroughly and filter. Carry the Assay as described under Ribavirin, using the successive filtrate.

Category As described under Ribavirin.

Strength (1) 20 mg (2) 50 mg (3) 100 mg

Storage Preserve in tightly closed containers.

Ribavirin Capsules

Ribavirin capsules contain not less than 90.0% and not more than 110.0% of the labelled amount of ribavirin ($C_8H_{12}N_4O_5$).

Description Capsules containing white or almost white granule or powder.

Identification A quantity of the contents of the capsules, equivalent to about 0.1 g of ribavirin, comply with the tests (1) and (2) for Identification described under Ribavirin.

Other requirements Comply with the general requirements for capsules (Appendix I E).

Assay Weigh accurately a quantity of the mixed contents obtained in the test for Weight variation, dissolve and dilute it with mobile phase to produce a solution of 50 µg of ribavirin per ml and filter. Carry out the Assay as described under Ribavirin, using the successive filtrate.

Category As described under Ribavirin.

Strength 0.15 g

Storage Preserve in tightly closed containers.

Ribavirin Eye Drops

Ribavirin Eye Drops contain not less than 90.0% and not more than 110.0% of the labelled amount of ribavirin ($C_8H_{12}N_4O_5$). It contains benzalkonium bromide as preservative.

Description A clear, colourless solution.

Identification Comply with tests (1) and (2) for Identification described under Ribavirin.

Acidity 5.0-7.0 (Appendix VI H).

Other requirements Comply with the general requirements for eye preparations (Appendix I G).

Assay Carry out the Assay as described under Ribavirin, using an accurately measured quantity. The resolution factor between the peaks of ribavirin and the preservative complies with the related requirements.

Category As described under Ribavirin.

Strength (1) 8 ml : 8 mg (2) 10 ml : 10 mg
(3) 10 ml : 50 mg

Storage Preserve in tightly closed containers, stored in a cool place.

Ribavirin for Injection

Ribavirin for Injection is a sterile Lyophilized powder of ribavirin and suitable excipient. It contains not less than 90.0% and not more than 110.0% of the labelled amount of ribavirin ($C_8H_{12}N_4O_5$).

Description A white or almost white lyophilized powder.

Identification Complies with tests (1) and (2) for identification described under Ribavirin.

Acidity An aqueous solution of 25 mg of ribavirin per ml, pH 4.0-7.0 (Appendix VI H).

Clarity and colour of solution An aqueous solution of 50 mg of ribavirin per ml is clear and colourless; any colour produced is not more intense than that of reference solution Y₁ or YG₁ (Appendix IX A).

Related substances Carry out the test for Related substances as described under Ribavirin; not more than 1.0%.

Loss on drying When dried to constant weight at 105°C, loses not more than 5.0% of its weight (Appendix VII L).

Bacterial endotoxin Carry out the test for Bacterial endotoxin (Appendix XI E); less than 0.15 EU per mg of ribavirin.

Other requirements Complies with the general requirements for injections (Appendix I B).

Assay Weigh accurately a quantity of the mixed contents obtained in the test for Weight variation, Dissolve and dilute to produce a solution of 50 µg of ribavirin per ml and filter. Carry out the Assay as described under Ribavirin, using the successive filtrate.

Category As described under ribavirin.

Strength 0.25g

Storage Preserve in well closed containers, stored in a cool place.

Ribavirin Granules

Ribavirin granules contain not less than 90.0% and not more than 110.0% of the labelled amount of Ribavirin ($C_8H_{12}N_4O_5$).

Description White or almost white soluble granules.

Identification To a quantity of granules, equivalent to about 0.1 g of ribavirin, add 20 ml of water, triturate and filter. The successive filtrate complies with tests (1) and (2) for Identification described under Ribavirin.

Loss on drying When dried to constant weight at 105°C, loses not more than 2.0% of its weight (Appendix VIII L).

Other requirements Comply with the general requirements for granules (Appendix I N).

Assay Weigh accurately a quantity of the mixed contents obtained in the test for Weight variation, triturate it with mobile phase to dissolve ribavirin, and dilute it with mobile phase to produce a solution of 50 µg per ml and filter. Carry out the Assay as described under Ribavirin, using the successive filtrate.

Category As described under Ribavirin.

Strength 50 mg

Storage Preserve in tightly closed containers, stored in a dry place.

Ribavirin Injection

Ribavirin Injection is a sterile solution of Ribavirin in Water for Injection. It contains not less than 90.0% and not more than 110.0% of the labelled amount of ribavirin ($C_8H_{12}N_4O_5$).

Description A clear, colourless liquid.

Identification Complies with tests (1) and (2) for Identification described under Ribavirin.

pH value 4.0-6.0 (Appendix VI H).

Related substances Carry out the test for Related Substances described under Ribavirin; not more than 1.0%.

Bacterial endotoxin Comply with the test for bacterial endotoxin (Appendix XI E): Less than 0.15 EU per mg.

Other requirements Complies with the general requirements for injections (Appendix I B).

Assay Carry out the Assay as described under Ribavirin, using an accurately measured quantity.

Category As described under Ribavirin.

Strength (1) 1 ml : 100 mg (2) 2 ml : 250 mg
(3) 2 ml : 100 mg (4) 2 ml : 200 mg
(5) 5 ml : 250 mg

Storage Preserve in well closed containers.

Ribavirin Nasal Drops

Ribavirin Nasal Drops contain not less than 90.0% and not more than 110.0% of the labelled amount of ribavirin ($C_8H_{12}N_4O_5$). It may contain suitable preservative.

Description A clear, colourless liquid.

Identification Comply with tests (1) and (2) for Identification described under Ribavirin.

pH value 4.5-6.5 (Appendix VI H).

Other requirements Comply with the general requirements for nasal preparations (Appendix I R).

Assay Carry out the Assay described under Ribavirin, using an accurately measured quantity. The resolution factor

between the peaks of ribavirin and the preservative complies with the related requirements.

Category As described under Ribavirin.

Strength 10 ml : 50 mg

Storage Preserved in tightly closed containers, stored in a cool place.

Ribavirin Oral Solution

Ribavirin Oral Solution contains not less than 90.0% and not more than 110.0% of the labelled amount of Ribavirin ($C_8H_{12}N_4O_5$).

Description A colourless or pale yellow liquid; taste, sweet.

Identification Complies with tests (1) and (2) for Identification described under ribavirin.

Colour Not more intense than the colour of reference solution Y₄ (Appendix IX A, method 1).

pH value 4.0-6.0 (Appendix VI H).

Other requirements Complies with the general requirements for oral solution (Appendix I O).

Assay Carry out the method for high performance liquid chromatography (Appendix V D), using a column packed with octadecylsilane bonded silica gel and water as the mobile phase. Detection wavelength is 207 nm and the number of the theoretical plates of the column is not less than 2500, calculated with reference to the peak of ribavirin.

Procedure Measure accurately a quantity of the oral solution being examined, equivalent to about 150 mg of ribavirin, dilute with water to produce a solution of 30 µg per ml. Inject 20 µl into the column. Repeat the operation, using ribavirin CRS instead of the substance being examined. Calculate the content of $C_8H_{12}N_4O_5$ with respect to the peak area obtained in the chromatogram by the external standard method.

Category As described under Ribavirin.

Strength (1) 10 ml : 0.3 g (2) 5 ml : 0.15 g

Storage Preserve in tightly closed containers.

Ribavirin Tablets

Ribavirin Tablets contain not less than 90.0% and not more than 110.0% of the labelled amount of ribavirin ($C_8H_{12}N_4O_5$).

Description White tablets.

Identification To a quantity of the powdered tablets equivalent to about 0.1 g of ribavirin add 20 ml of water, triturate and filter. The filtrate complies with tests (1) and (2) for Identification described under Ribavirin.

Other requirements Comply with the general requirements for tablets (Appendix I A).

Assay Weigh accurately and powder finely 20 tablets. Dissolve an accurately weighed quantity of the powder in water to produce a solution containing 50 µg ribavirin per ml. Filter, and carry out the Assay described under Ribavirin, using the successive filtrate.

Category As described under Ribavirin.

Strength (1) 20 mg (2) 50 mg (3) 100 mg
(4) 200 mg

Storage Preserve in tightly closed containers.

Ribavirin and Glucose Injection

Ribavirin and Glucose Injection is a sterile solution of Ribavirin and Glucose in Water for Injection. It contains not less than 90.0% and not more than 110.0% of the labelled amount of ribavirin ($C_8H_{12}N_4O_5$); not less than 95.0% and not more than 105.0% of the labelled amount of glucose ($C_6H_{12}O_6 \cdot H_2O$).

Description A clear, colourless liquid.

Identification (1) Complies with tests (1) and (2) for Identification described under Ribavirin.

(2) Add dropwise slowly warm alkaline cupric tartrate TS, a red precipitate of cuprous oxide is produced.

pH Value 4.0-6.0 (Appendix VI H).

5-hydroxymethylfurfural Transfer an accurately measured quantity of the injection, equivalent to about 0.1 g of glucose, in a 50 ml volumetric flask, dilute with water to volume and mix well. Measure the absorbance of the resulting solution at 284 nm (Appendix IV A), the absorbance is not greater than 0.25.

Related substances Carry out the test for Related substances described under Ribavirin; not more than 1.0%.

Heavy metals Evaporate a quantity of injection, equivalent to about 3 g of glucose, to about 20 ml if necessary, cool, add 2 ml of acetate BS (pH 3.5) and sufficient water to produce 25 ml. Carry out the limit test for heavy metals (Appendix VIII H, method 1); not more than 0.0005%.

Bacterial endotoxin Carry out the test for Bacterial endotoxin (Appendix XI E); less than 0.5 EU per ml.

Other requirements Complies with the general requirements for injections (Appendix I B).

Assay Ribavirin Carry out the Assay as described under Ribavirin. Measure accurately a quantity of the injection, add mobile phase to produce a solution of 50 µg of ribavirin per ml as test solution.

Glucose Measure accurately 2 ml of the injection, equivalent to about 0.1 g of glucose, to a conical flask with stopper, add accurately 25 ml of iodine (0.05 mol/L) VS, add 40 ml of sodium hydroxide (0.1 mol/L) VS dropwise with shaking, allow to stand 30 minutes in dark place, add 4 ml of dilute sulfuric acid. Titrate with sodium thiosulfate (0.1 mol/L) VS, add 2 ml of starch IS when the end point is nearly approached, continue the titration until blue colour disappears. Perform a blank determination and necessary correction. Each ml of iodine (0.05 mol/L) VS is equivalent to 9.909 mg of glucose ($C_6H_{12}O_6 \cdot H_2O$).

Category As described under ribavirin.

Strength (1) 100 ml : ribavirin 0.1 g and glucose 5 g
(2) 100 ml : ribavirin 0.2 g and glucose 5 g
(3) 250 ml : ribavirin 0.25 g and glucose 12.5 g
(4) 250 ml : ribavirin 0.5 g and glucose 12.5 g
(5) 500 ml : ribavirin 0.5 g and glucose 25 g

Storage Preserve in well closed containers, stored in cool place and protected from light.

Ribavirin and Sodium Chloride Injection

Ribavirin and Sodium Chloride Injection is a sterile solution of Ribavirin and Sodium Chloride in Water for Injection. It contains not less than 90.0% and not more than 110.0% of the labelled amount of ribavirin ($C_8H_{12}N_4O_5$); not less than 95.0% and not more than 105.0% of the labelled amount of sodium chloride (NaCl).

Description A clear, colourless liquid.

Identification (1) To 5 ml of the injection add 5 ml of sodium hydroxide TS, boil gently, the vapour produced turns moistened red litmus paper to blue.

(2) The retention time of the principal peak in the chromatogram obtained with the test solution in the Assay is identical with that of the principal peak in the chromatogram of the reference solution.

(3) Yields the reaction characteristic of sodium salts and the reactions characteristic of chlorides (Appendix III).

pH Value 4.0-6.0 (Appendix VI H).

Related substances Carry out the test for Related substances as described under ribavirin; not more than 1.0%.

Heavy metals Evaporate 50 ml of the injection to about 20 ml, cool, add 2 ml of acetate BS (pH 3.5) and sufficient water to 25 ml. Carry out the limit test for heavy metals (Appendix VIII H, method 1); not more than 0.00003%.

Bacterial endotoxin Carry out the test for Bacterial endotoxin (Appendix XI E); less than 0.5 EU per ml.

Other requirements Complies with the general requirements for injection (Appendix I B).

Assay Ribavirin Measure accurately a quantity of the injection, dilute with mobile phase to produce a solution of 50 µg of ribavirin per ml as test solution. Carry out the test for the Assay as described under Ribavirin.

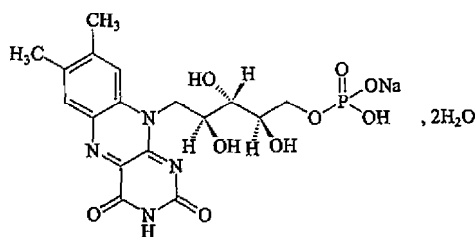
Sodium Chloride Measure accurately 10 ml of the injection, add 40 ml of water, 5 ml of dextrin solution (1→50), 0.1 g of calcium carbonate and 8 drops of fluorescein IS. Titrate with silver nitrate (0.1 mol/L) VS. Each ml of silver nitrate (0.1 mol/L) VS is equivalent to 5.844 mg of NaCl.

Category As described under Ribavirin.

Strength (1) 100 ml : ribavirin 0.2 g and sodium chloride 0.9 g
(2) 250 ml : ribavirin 0.5 g and sodium chloride 2.25 g
(3) 250 ml : ribavirin 0.5 g and sodium chloride 2.125 g
(4) 100 ml : ribavirin 0.5 g and sodium chloride 0.9 g
(5) 250 ml : ribavirin 0.5 g and sodium chloride 1.95 g

Storage Preserve in tightly closed containers, stored in a cool place and protected from light.

Riboflavin Sodium Phosphate



$C_{17}H_{20}N_4NaO_6P \cdot 2H_2O$ 514.36

Riboflavin Sodium Phosphate is riboflavin 5'-(sodium hydrogen phosphate) dihydrate. It contains not less than 74.0% and not more than 79.0% of $C_{17}H_{20}N_4O_6$, calculated on the dried basis.

Description An orange yellow crystalline powder; almost odourless; taste, slightly bitter; hygroscopic. Soluble in water; practically insoluble in ethanol, chloroform or ether.

Specific optical rotation Protect from light throughout the procedure, $+38.0^\circ$ to $+42.0^\circ$, in a solution of about 15 mg per ml in hydrochloric acid solution (45→100) (Appendix VI E).

Identification (1) Dissolve about 1 mg in 100 ml of water. The solution is pale yellow by transmitted light, and has an intense yellowish green fluorescence which disappears on the addition of mineral acids or alkalis.

(2) The light absorption of a solution of 10 μ g per ml in phosphate BS (pH 7.0) exhibits three maxima at 267 nm, 372 nm and 444 nm, and a minimum at 240 nm (Appendix IV A).

(3) The infrared absorption spectrum (Appendix IV C) is concordant with the reference spectrum of riboflavin sodium phosphate (Appendix XVI).

(4) To 0.5 g add 10 ml of nitric acid, evaporate the mixture to dryness on a water bath, ignite the residue until the carbon is removed. Dissolve the residue in 5 ml of water, filter if necessary. The filtrate yields the reactions characteristic of sodium salts (Appendix III).

Clarity of the solution A solution of 0.20 g in 10 ml of water is clear (Appendix IX B).

Acidity Dissolve 0.4 g in 20 ml of water, pH 4.0-6.5 (Appendix VI H).

Lumiflavin Shake 35 mg with 10 ml of ethanol-free chloroform for 5 minutes and filter, the light absorbance of the filtrate at 440 nm is not greater than 0.025 (Appendix IV A).

Loss on drying When dried to constant weight at 130°C , loses not more than 10% of its weight (Appendix VIII L), using 0.3 g.

Free phosphoric acid Place 0.2 g, accurately weighed and calculated on the dried basis, in a 100 ml volumetric flask. Add 10 ml of a standard phosphate solution [place 0.42 g of potassium dihydrogen phosphate, previously dried at 105°C for 2 hours and accurately weighed, in a 1000 ml volumetric flask, dissolve it in water, add 10 ml of sulfuric acid solution (3→10) and dilute with water to volume, mix well, dilute with water to produce a solution of 1/10 of its original concentration immediately before use] in another 25 ml volumetric flask. To each flask add 5 ml of water, 2.5 ml of ammonium molybdate in sulfuric acid TS and 1 ml of 1-

amino-2-naphthol-4-sulfuric acid solution (mix 5 g of anhydrous sodium sulfite, 94.3 g of sodium bisulfite with 0.7 g of 1-amino-2-naphthol-4-sulfuric acid, dissolve 1.5 g of above the mixture in 10 ml of water before use, filter if necessary), dilute with water to volume, mix well and allow to stand at 20°C for 30 minutes. The absorbance of the solution containing the substance being examined, measured at 740 nm (Appendix IV A), is not greater than that of the standard solution under same condition.

Assay Protect from light throughout the procedure. Dissolve about 0.1 g, accurately weighed, in 1 ml of glacial acetic acid and 75 ml of water in a 500 ml volumetric flask, dilute with water to volume and mix well. Transfer 10 ml of the solution, accurately measured, to a 100 ml volumetric flask, add 7 ml of 1.4% sodium acetate solution, dilute with water to volume and mix well, measure the absorbance of the resulting solution at 444 nm (Appendix IV A). Calculate the content of $C_{17}H_{20}N_4O_6$, taking 323 as the value of A (1%, 1 cm).

Category Vitamin.

Storage Preserve in tightly closed containers, protected from light.

Preparation Riboflavin Sodium Phosphate Injection

Riboflavin Sodium Phosphate Injection

Riboflavin Sodium Phosphate Injection is a sterile solution of Riboflavin Sodium Phosphate in Water for Injection. It contains not less than 90.0% and not more than 115.0% of the labelled amount of riboflavin ($C_{17}H_{20}N_4O_6$).

Description A clear, yellow to orange yellow liquid, deteriorates easily on exposure to light.

Identification (1) Dilute a quantity of the injection equivalent to about 1 mg of riboflavin with water to 100 ml, the solution is pale yellow by transmitted light and has an intense yellowish green fluorescence which disappears upon the addition of mineral acids or alkalis.

(2) Evaporate a quantity of the injection equivalent to about 0.1 g of riboflavin sodium phosphate to dryness on a water bath. Add 10 ml of nitric acid and evaporate it to dryness on a water bath. Ignite the residue until the carbon is removed, dissolve the residue in 5 ml of water, filter if necessary. The filtrate yields the reactions characteristic of sodium salts and phosphates (Appendix III).

pH value 5.6-6.5 (Appendix VI H).

Other requirements Complies with the general requirements of injections (Appendix I B).

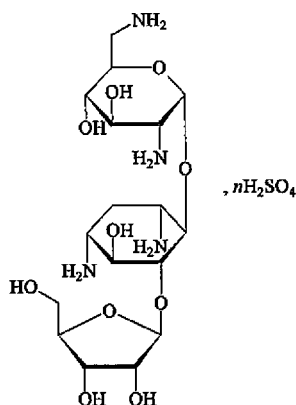
Assay Protect from light throughout the procedure. Transfer a quantity of the injection equivalent to about 10 mg of riboflavin, accurately measured, to a 1000 ml volumetric flask, add 2 ml of 10% acetic acid solution and 7 ml of 14% sodium acetate solution, dilute with water to volume and mix well. Measure the absorbance of the resulting solution at 444 nm (Appendix IV A). Calculate the content of $C_{17}H_{20}N_4O_6$, taking 323 as the value of A (1%, 1 cm).

Category As described under Riboflavin Sodium Phosphate.

Strength (1) 2 ml : 5 mg (2) 2 ml : 10 mg
(calculated on $C_{17}H_{20}N_4O_6$)

Storage Preserve in well closed containers, protected from light.

Ribostamycin Sulfate



$C_{17}H_{34}N_4O_{10} \cdot nH_2SO_4$ ($n < 2$)

[25546-65-0]

Ribostamycin Sulfate is *O*-3-*D*-ribofuranosyl-(1→5)-*O*-[α-2,6,diamino-2,6-dideoxy-*D*-glucopyranosyl (1→4)]-α-deoxy-streptamine, sulfuric acid salt. It has a potency of not less than 680 Ribostamycin Units per mg calculated on the dried basis.

Description A white or almost white powder; odourless or almost odourless; taste slightly bitter; hygroscopic. Freely soluble in water; practically insoluble in methanol, ethanol, acetone, chloroform or ether.

Identification (1) Dissolve 10 mg in 2 ml of water, add 3 ml of a 0.1% solution of anthrone in sulfuric acid; a blue to bluish-green colour is produced.

(2) Dissolve 20 mg in 2 ml of water, add 1 ml of a 0.1% solution of ninhydrine in *n*-butanol saturated with water, heat in a water bath, a violet colour is produced.

(3) The aqueous solution yields the reactions characteristic of sulfates (Appendix III).

Acidity or alkalinity An aqueous solution of 50 mg per ml, pH 6.0-8.0 (Appendix VI H).

Clarity and colour of solution Dissolve separately each 1.5 g of the 5 portions in 5 ml of water, the solutions are clear and colourless; any opalescence produced is not more pronounced than that of reference suspension I (Appendix IX B); any colour produced is not more intense than that of reference solution Y₄ or YG₄ (Appendix IX A, method 1).

Loss on drying When dried in vacuum over phosphorous pentoxide to constant weight at 60°C, loses not more than 4.7% of its weight (Appendix VII L).

Bacterial endotoxin Carry out the test for bacterial endotoxin (Appendix XI E), less than 2.5 EU per 1000 Ribostamycin Units.

Sterility Complies with the test for sterility (Appendix XI H, membrane filtration method), dissolving each portion and transfer to at least 500 ml of 0.9% sterile sodium chloride solution respectively.

Assay Dissolve an accurately weighed quantity in sterile water to produce a solution of about 1000 Units per ml. Carry out the Microbiological Assay of Antibiotics (Appendix XI A). 1000 Ribostamycin Units are equivalent to 1 mg of $C_{17}H_{34}N_4O_{10}$.

Category Aminoglycoside Antibiotic.

Storage Preserve in hermetically sealed containers, stored

in a dry place.

Preparation Ribostamycin Sulfate for Injection

Ribostamycin Sulfate for Injection

Ribostamycin Sulfate for Injection is a sterile powder of Ribostamycin Sulfate. It has a potency of not less than 680 Ribostamycin Units per mg, calculated on the dried basis; it contains not less than 93.0% and not more than 107.0% of the labelled amount of ribostamycin ($C_{17}H_{34}N_4O_{10}$), calculated on the basis of the average weight of contents.

Description A white or almost white powder.

Identification Complies with the tests for Identification described under Ribostamycin Sulfate.

Clarity and colour of solution To each of 5 containers add water to produce solutions containing 200000 Units per ml. The solutions are clear and colourless; any opalescence produced is not more pronounced than that of reference suspension I (Appendix IX B); any colour produced is not more intense than that of reference solution Y₄ or YG₄ (Appendix IX A, method 1).

Loss on drying When dried in vacuum over phosphorous pentoxide to constant weight at 60°C, loses not more than 5.0% of its weight (Appendix VII L).

Acidity or alkalinity, Bacterial endotoxin, sterility Complies with the corresponding requirements described under Ribostamycin Sulfate.

Other requirements Complies with the general requirements for injections (Appendix I B).

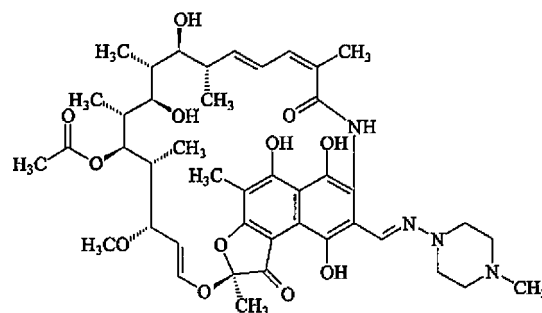
Assay Carry out the Assay described under Ribostamycin Sulfate, using the mixed contents obtained in the test for weight variation of contents.

Category As described under Ribostamycin Sulfate.

Strength 1 g (1000000 Units)

Storage Preserve in well closed containers, stored in a dry place.

Rifampicin



$C_{43}H_{58}N_4O_{12}$ 822.95

[13292-46-1]

Rifampicin is 3-[(4-methyl-1-piperazinyl)-iminomethyl]-rifamycin. It contains not less than 93.0% of $C_{43}H_{58}N_4O_{12}$, calculated on the dried

basis.

Description A bright red or dark red crystalline powder; odourless; tasteless.

Freely soluble in chloroform; soluble in methanol; practically insoluble in water.

Identification (1) Dissolve about 5 mg in 2 ml of 0.1 mol/L hydrochloric acid solution. add 2 drops of 0.1 mol/L sodium nitrite solution; the colour changes from orange to dark red. (2) The retention time of principal peak of the substance being examined in the chromatogram obtained in the Assay are identical with that of the reference solution. (3) The infrared absorption spectrum (Appendix IV C) is concordant with the reference spectrum of rifampicin (Appendix XVI).

Crystallinity complies with the test for crystallinity (Appendix IX D).

Acidity A suspension of 10 mg per ml in water, pH 4.0-6.5 (Appendix VI H).

Relate substances Dissolve a quantity of the substance being examined, accurately weighed, in acetonitrile to produce the test solution of 1 mg per ml; Dissolve an accurately weighed amount of rifampicin CRS in acetonitrile to produce the reference solution of 10 µg per ml. Carry out the method as described under Assay. Inject 10 µl of the reference solution into the column and adjust the attenuation so that principal peak height in the chromatogram is 25% of the full scale of the chart. Inject accurately 10 µl of the test solution and the reference solution into the column, separately, and record the chromatogram for four times the retention time of principal peak. Calculate separately the contents of secondary peaks on the chromatogram obtained with the test solution according to the corrected peak area of the principal peak obtained with reference solution (the corrected factor to Rifampicin, Rifampicinquinone, N-oxid Rifampicin, 3-Formylrifamycin SV are 1.0, 1.4, 1.67 and 1.08 respectively). The contents of Rifampicinquinone, N-oxid Rifampicin, 3-Formylrifamycin SV are not more than 1.5% (1.5 times), 0.5% (0.5 times) and 0.5% (0.5 times) of the area of the principal peak obtained with reference solution; the total contents of other secondary peaks (the corrected factor is 1.0) are not more than 3.0% (3 times).

Loss on drying When dried to constant weight at 105°C, loses not more than 1.0% of its weight (Appendix VIII L).

Residue on ignition Not more than 0.1% (Appendix VIII N); use 1 g.

Heavy metals Carry out the limit test for heavy metals (Appendix VIII H, method 2), using the residue obtained in the test for Residue on ignition; not more than 0.002%.

Assay Carry out the method for high performance liquid chromatography (Appendix V D), using a column packed with octylsilicane bonded silica gel and a mixture of methanol-acetonitrile-0.075 mol/L potassium dihydrogen phosphate-1.0 mol/L citric acid (30 : 30 : 26 : 4) as the mobile phase. Detection wavelength is 254 nm. Dissolve Rifampicin CRS, Rifampicinquinone CRS N-oxid Rifampicin CRS, 3-Formylrifamycin SV CRS and Rifamycin SV CRS in acetonitrile to produce a solution of 0.04 mg per ml respectively. Inject 10 µl into column. The retention time of the substance in mixture solution are Rifampicinquinone, Rifampicin, Rifamycin SV, N-oxid Rifampicin and 3-Formylrifamycin in turn; the resolution factor among these peaks complies with related requirements. The number of theoretical plates of the column is not less than 1500, calculated with reference to the peak of rifampicin.

Produce Dissolve a quantity in acetonitrile to produce a

solution of 0.08 mg per ml. Inject 10 µl into volume, Repeat the operations, using Rifampicin CRS instead of the substance being examined. Calculate the content of $C_{43}H_{58}N_4O_{12}$.

Category Tuberculostatics.

Storage Preserve in tightly closed containers, protected from light, stored in a cool and dry place.

Preparation (1) Rifampicin Capsules
(2) Rifampicin for Eye Use
(3) Rifampicin Tablets

Rifampicin Capsules

Rifampicin Capsules contain not less than 90.0% and not more than 110.0% of the labelled amount of rifampicin ($C_{43}H_{58}N_4O_{12}$).

Identification Complies with the tests (1) and (2) for Identification described under Rifampicin, using the contents of capsules.

Relate substances Dissolve a accurately weighed quantity (equivalent to 125 mg Rifampicin) of mixed contents obtained in the test for weight variation of contents add acetonitrile to produce a solution of 5 mg per ml. Filter this solution with 0.45 µm membrane, measure accurately a quantity of the successive filtrate in acetonitrile to produce the test solution of 1 mg per ml. Carry out the method as described under Rifampicin. Calculate separately the contents of secondary peaks on the chromatogram obtained with the test solution according to the corrected peak area of the principal peak obtained with reference solution (the corrected factor to Rifampicin, Rifampicinquinone, N-oxid Rifampicin, 3-Formylrifamycin SV are 1.0, 1.4, 1.67 and 1.08 respectively). The contents of Rifampicinquinone, N-oxid Rifampicin, 3-Formylrifamycin SV are not more than 2.0% (2.0 times), 1.0% (1 times) and 0.5% (0.5 times) of the area of the principal peak obtained with reference solution; the total contents of other secondary peaks (the corrected factor is 1.0) are not more than 3.5% (3.5 times).

Dissolution Carry out the dissolution test (Appendix X C method 1), using 900 ml of hydrochloric acid solution (9→1000) as the dissolution medium, adjust the rotational speed of the basket to 50 rpm. Withdraw the solution after exactly 45 minute and filter, measure accurately a quantity of the successive filtrate and dilute with phosphate buffer solution (dissolve 3.02 g of potassium dihydrogen phosphate and 6.2 g of dipotassium hydrogen phosphate in 1000 ml of water, adjust pH to 7.0) to produce a solution of 20 µg per ml. Measure the absorbance of the resulting solution at 474 nm (Appendix IV A). Calculate the dissolution of $C_{43}H_{58}N_4O_{12}$ from each capsule, taking 187 as the value of A (1%, 1 cm). Not less than 75% of the labelled amount is dissolved.

Loss on drying When dried to constant weight at 105°C, loses not more than 2.0% of its weight (Appendix VIII L), using the mixed contents of the capsules.

Other requirements Comply with the general requirements for capsules (Appendix I E).

Assay To accurately weighed quantity of mixed contents obtained in the test for weight variation of contents equivalent to 80 mg rifampicin add acetonitrile to produce a solution of 0.8 mg per ml. Filter this solution with 0.45 µm membrane, measure accurately a quantity of the successive

filtrate in acetonitrile to produce a solution of 0.08 mg per ml. Carry out the Assay described under Rifampicin.

Category As described under Rifampicin.

Strength (1) 0.15 g (2) 0.3 g

Storage Preserve in tightly closed containers, protected from light, stored in a cool and dry place.

Rifampicin for Eye Use

Rifampicin for eye use is a mixed preparation of rifampin tablets/pills/granules and buffer solution, dissolving rifampin with the buffer solution before using. It contains not less than 90.0% and not more than 110.0% of the labeled content of rifampicin ($C_{43}H_{58}N_4O_{12}$).

Description A orange or dark red tablets/pills/granules, and a clear, colourless buffer solution.

Identification Complies with the tests (1) and (2) for Identification described under Rifampicin, using a quantity of powdered tablets/pills/granules.

Acidity or Alkalinity Dissolve 1 tablet/pill/granule in buffer solution, pH 6.0~8.0 (Appendix VI H).

Weight variation Complies with the requirements for weight variation test (Appendix I G).

Volume of buffer solution Complies with the requirements for the volume test of buffer solution (Appendix I G).

Dispersion limit Complies with the requirements for pills (Appendix I H).

Visible impurities Complies with the requirements for the buffer solution (Appendix XI H).

Microbial limit Dissolve 2 tablets/pills/granules in the buffer solution. Use 10 ml of the solution above as liquid sample to prepare the test solution. Complies with the requirements for microbial limit test (Appendix XI J membrane filtration method).

Assay Carry out the method for high performance liquid chromatography (Appendix V D), using a column packed with octylsilicane bonded silica gel and a mixture of methanol-acetonitrile-0.0075 mol/L potassium dihydrogen phosphate-1.0 mol/L citric acid (30 : 30 : 36 : 4) as the mobile phase. Detection wavelength is 254 nm. Dissolve rifampicin CRS and rifampicinquinone CRS in acetonitrile to produce a mixture solution of 0.08 mg per ml. Inject 10 μ l in to column. The resolution factor between the peaks of rifampicinquinone and rifampicin is not less than 4.0.

Procedure Transfer 5 tablets/pills/granules in a 50 ml volumetric flask, dilute with the buffer solution to volume, mix well and filter. Measure an accurately quantity of the successive filtrate in acetonitrile to produce test solution of 0.08 mg per ml. Inject 10 μ l in to column and record the chromatogram. Repeat the operations, using Rifampin CRS instead of the substance being examined. Calculate the contents of $C_{43}H_{58}N_4O_{12}$ with respect to the peak area obtained in the chromatogram by the external standard method.

Category As described under Rifampicin.

Strength (1) Tablets (10 mg of $C_{43}H_{58}N_4O_{12}$ and 10 ml of the buffer solution; 5 mg of $C_{43}H_{58}N_4O_{12}$ and 10 ml of the buffer solution) (2) Pills (10 mg of $C_{43}H_{58}N_4O_{12}$ and 10 ml of the buffer solution) (3) Granules (10 mg of

$C_{43}H_{58}N_4O_{12}$ and 10 ml of the buffer solution; 5 mg of $C_{43}H_{58}N_4O_{12}$ and 10 ml of the buffer solution)

Storage Preserve in tightly closed containers, protected from light and stored in a dry place.

Rifampicin Tablets

Rifampicin Tablets contain not less than 90.0% and not more than 110.0% of the labelled amount of rifampicin ($C_{43}H_{58}N_4O_{12}$).

Description Sugar coated tablets with orange or dark red core.

Identification Comply with the tests (1) and (2) for Identification described under Rifampicin, using a quantity of powdered tablets.

Related substances Dissolve a accurately weighed quantity (equivalent to 125 mg Rifampicin) of powdered tablets obtained in the test for Assay add acetonitrile to produce a solution of 5 mg per ml. Filter this solution with 0.45 μ m membrane, measure accurately a quantity of the successive filtrate in acetonitrile to produce the test solution of 1 mg per ml. Carry out the method as described under Rifampicin. Calculate separately the contents of secondary peaks on the chromatogram obtained with the test solution according to the corrected peak area of the principal peak obtained with reference solution (the corrected factor to Rifampicin, Rifampicinquinone, N-oxid Rifampicin, 3-Formylrifamycin SV are 1.0, 1.4, 1.67 and 1.08 respectively). The contents of Rifampicinquinone, N-oxid Rifampicin, 3-Formylrifamycin SV are not more than 3.0% (3.0 times), 1.0% (1 times) and 0.5% (0.5 times) of the area of the principal peak obtained with reference solution; the total contents of other secondary peaks (the corrected factor is 1.0) are not more than 3.5% (3.5 times).

Dissolution Carry out the dissolution test (Appendix X C, method 1), using 900 ml of hydrochloric acid solution (9→1000) as the dissolution medium, adjust the rotational speed of the basket to 50 rpm. Withdraw the solution after exactly 45 minutes and filter, measure accurately a quantity of the successive filtrate and dilute with phosphate buffer solution, prepared by dissolving 3.02 g of potassium dihydrogen phosphate and 6.2 g of dipotassium hydrogen phosphate in 1000 ml of water, adjusted to pH 7.0 to produce a solution of 20 μ g per ml. Measure the absorbance of the resulting solution at 474 nm (Appendix IV A). Calculate the dissolution of $C_{43}H_{58}N_4O_{12}$ from each tablet, taking 187 as the value of A (1%, 1 cm). Not less than 70% of the labelled amount is dissolved.

Other requirements Comply with the general requirements for tablets (Appendix I A).

Assay Weigh accurately and powder 10 tablets. Triturate an accurately weighed quantity of the powder equivalent to 80 mg of rifampicin in acetonitrile to produce a solution of 0.8 mg per ml. Withdraw the solution and filter with 0.45 μ m membrane, measure accurately a quantity of the successive filtrate in acetonitrile to produce a solution of 0.08 mg per ml. Carry out the Assay described under rifampicin.

Category As described under Rifampicin.

Strength 0.15 g

Storage Preserve in tightly closed containers, protected from light and stored in a cool and dry place.

Rifampin and Isoniazid Capsules

Rifampin and Isoniazid capsule is a mixed preparation of rifampin and isoniazid. It contains not less than 90.0% and not more than 110.0% of the labeled content of rifampin ($C_{43}H_{58}N_4O_{12}$) and isoniazid ($C_6H_7N_3O$).

Description The contents of capsules is orange red or dark red powder.

Identification (1) Dissolve about weighed quantity of the content of capsules, equivalent to 5 mg of Rifampin, in 2 ml of 0.1 mol/L hydrochloric acid solution, add 2 drops of 0.1 mol/L sodium nitrite solution; the colour changes from orange red to dark red.

(2) Dissolve about weighed quantity of the content of capsules (equivalent to 0.1 g of Isoniazid) in 10 ml of water in a test tube, shake and filter. Use the filtrate, add 1 ml of ammoniated silver nitrate TS, bubbles and a black turbidity are produced immediately, and a silver mirror is formed on the wall of the tube.

(3) The retention time of principal peaks of rifampin and isoniazid in the chromatogram obtained in the Assay are identical with that of principal peaks of Rifampin CRS and Isoniazid CRS in the chromatogram of the reference solution correspondingly.

Dissolution Carry out the dissolution test (Appendix X C, method 2), using 900 ml of hydrochloric acid solution (9→1000) as the dissolution medium, adjust the rotational speed of the paddle to 50 rpm. Withdraw the solution after exactly 30 minutes and filter, measure accurately a quantity of the successive filtrate and dilute with phosphate buffer solution (dissolve 3.02 g of potassium dihydrogen phosphate and 6.2 g of dipotassium hydrogen phosphate in 1000 ml of water, adjusted to pH 7.0), to produce a solution of 30 µg of rifampicin per ml. Dissolve an accurately weighed quantity of Rifampicin CRS in phosphate buffer solution to produce a solution of 30 µg of rifampicin per ml. Measure the absorbance of the resulting solution at 474 nm (Appendix IV A). Calculate the dissolution of $C_{43}H_{58}N_4O_{12}$ from each capsule. Not less than 75% of the labeled amount is dissolved.

Loss on drying When dried in a vacuum over phosphorous pentoxide to constant weight at 60°C, loses not more than 3.0% of its weight (Appendix VIII L).

Other requirements Comply the general requirements for capsules (Appendix I E).

Assay Carry out the method for high performance liquid chromatography (Appendix V D), using a column packed with nitrile groups chemically bonded to porous silica particles and a mixture of 0.01 mol/L sodium heptanesulfonate solution (adjust to pH 2.2 with dilute phosphoric acid)-acetonitrile (44 : 56) as the mobile phase. Detection wavelength is 254 nm. Dissolve Rifampicin CRS, Rifampicinquinone CRS and Isoniazid CRS in mobile phase to produce a mixture solution, contains 60 µg of Rifampicin, 60 µg of Rifampicinquinone and 30 µg of Isoniazid per ml. Inject 20 µl in to column and record the chromatogram. The retention time of the substance in mixture solution are Isoniazid, Rifampicinquinone and Rifampicin in turn; and the resolution factor among these peaks complies with related requirements.

Procedure Triturate the mixed contents obtained in the test for weight variation of contents. Weigh accurately a quantity (equivalent to 60 mg of Rifampicin) in a 100 ml volumetric flask, dilute with mobile phase to volume, mix well and

filter. Measure accurately 5 ml of the successive filtrate in 50 ml volumetric flask, dilute with mobile phase to volume, and mix well. Inject 20 µl in to column and record the chromatogram. Repeat the operations, using Rifampicin CRS and Isoniazid CRS instead of the substance being examined. Calculate the contents of $C_{43}H_{58}N_4O_{12}$ and $C_6H_7N_3O$ with respect to the peak area obtained in the chromatogram by the external standard method.

Category Antibiotics for tuberculosis.

Strength (1) 0.25 g (0.15 g of $C_{43}H_{58}N_4O_{12}$ and 0.1 g of $C_6H_7N_3O$)
(2) 0.225 g (0.15 g of $C_{43}H_{58}N_4O_{12}$ and 0.075 g of $C_6H_7N_3O$)

Storage Preserve in tightly closed containers, protected from light and stored in a dry place.

Rifampin and Isoniazid Tablets

Rifampin and Isoniazid tablet is a mixed preparation of rifampin and isoniazid. It contains not less than 90.0% and not more than 110.0% of the labeled content of rifampin ($C_{43}H_{58}N_4O_{12}$) and isoniazid ($C_6H_7N_3O$).

Description Film coated tablets with orange red or dark red core.

Identification

(1) Dissolve about weighted quantity of the powdered tablets, equivalent to 5 mg of Rifampin, in 2 ml of 0.1 mol/L hydrochloric acid solution, add 2 drops of 0.1 mol/L sodium nitrite solution; the colour changes from orange red to dark red.

(2) Dissolve about weighed quantity of the content of capsules (equivalent to 0.1 g of Isoniazid) in 10 ml of water in a test tube, shake and filter. Use the filtrate, add 1 ml of ammoniated silver nitrate TS, bubbles and a black turbidity are produced immediately, and a silver mirror is formed on the wall of the tube.

(3) The retention time of principal peaks of rifampin and isoniazid in the chromatogram obtained in the Assay are identical with that of principal peaks of Rifampin CRS and Isoniazid CRS in the chromatogram of the reference solution correspondingly.

Dissolution Carry out the dissolution test (Appendix X C, method 1), using 900 ml of hydrochloric acid solution (9→1000) as the dissolution medium, adjust the rotational speed of the basket to 100 rpm. Withdraw the solution after exactly 30 minutes and filter, measure accurately a quantity of the successive filtrate and dilute with phosphate buffer solution, prepared by dissolving 3.02 g of potassium dihydrogen phosphate and 6.2 g of dipotassium hydrogen phosphate in 1000 ml of water, adjusted to pH 7.0, to produce a solution of 30 µg of rifampicin per ml. Dissolve an accurately weighed quantity of Rifampicin CRS in Measure the absorbance of the resulting solution at 474 nm (Appendix IV A). Calculate the dissolution of $C_{43}H_{58}N_4O_{12}$ from each tablet. Not less than 75% of the labeled amount is dissolved.

Other requirements Comply the general requirements for tablets (Appendix I A).

Assay Carry out the method for high performance liquid chromatography (Appendix V D), using a column packed with nitrile groups chemically bonded to porous silica particles and a mixture of 0.01 mol/L sodium heptanesulfonate solution (adjust to pH 2.2 with dilute phosphoric acid)-acetonitrile (44 : 56) as the mobile phase.

Detection wavelength is 254 nm. Dissolve Rifampicin CRS, Rifampicinquinone CRS and Isoniazid CRS in mobile phase to produce a mixture solution, contains 60 µg of Rifampicin, 60 µg of Rifampicinquinone and 30 µg of Isoniazid per ml. Inject 20 µl in to column and record the chromatogram. The retention time of the substance in mixture solution are Isoniazid, Rifampicinquinone and Rifampicin in turn; and the resolution factor among these peaks complies with related requirements.

Procedure Triturate 10 tablets with the coating removed. Weigh accurately a quantity (equivalent to 60 mg of Rifampicin) in a 100 ml volumetric flask, dilute with mobile phase to volume, mix well and filter. Measure accurately 5 ml of the successive filtrate in 50 ml volumetric flask, dilute with mobile phase to volume, and mix well. Inject 20 µl in to column and record the chromatogram. Repeat the operations, using Rifampin CRS and Isoniazid CRS instead of the substance being examined. Calculate the contents of $C_{43}H_{58}N_4O_{12}$ and $C_6H_7N_3O$ with respect to the peak area obtained in the chromatogram by the external standard method.

Category Antibiotics for tuberculosis.

Strength 0.45 g ($C_{43}H_{58}N_4O_{12}$ 0.3 g and $C_6H_7N_3O$ 0.15 g)

Storage Preserve in tightly closed containers, protected from light and stored in a dry place.

Rifampin Isoniazid and Pyrazinamide Capsules

Rifampin Isoniazid and Pyrazinamide tablet is a mixed preparation of rifampin, isoniazid and pyrazinamide. It contains not less than 90.0% and not more than 110.0% of the labeled content of rifampin ($C_{43}H_{58}N_4O_{12}$), isoniazid ($C_6H_7N_3O$) and pyrazinamide ($C_5H_5N_3O$).

Description The contents of capsules orange or red powder.

Identification

(1) Dissolve about weighed quantity of the content of capsules, equivalent to 5 mg of rifampin, in 2 ml of 0.1 mol/L hydrochloric acid solution, add 2 drops of 0.1 mol/L sodium nitrite solution; the colour changes from orange red to dark red.

(2) Dissolve about weighed quantity of the content of capsules (equivalent to 0.1 g of Isoniazid) in 10 ml of water in a test tube, shake and filter. Use the filtrate, add 1 ml of ammoniated silver nitrate TS, bubbles and a black turbidity are produced immediately, and a silver mirror is formed on the wall of the tube.

(3) Heat a quantity of the content of capsules (equivalent to 0.2 g of Pyrazinamide) with 5 ml of sodium hydroxide TS, the characteristic odour of ammonia is perceived, the vapour turns moistened red litmus paper to blue.

(4) The retention time of principal peaks of rifampin, isoniazid and pyrazinamide in the chromatogram obtained in the Assay are identical with that of principal peaks of Rifampin CRS, Isoniazid CRS and Pyrazinamide CRS in the chromatogram of the reference solution correspondingly.

Loss on drying When dried in a vacuum over phosphorous pentoxide to constant weight at 60°C for 3 hours, loses not more than 3.0% of its weight (Appendix VIII L).

Dissolution Carry out the dissolution test (Appendix X C,

method 2), using 900 ml of hydrochloric acid solution (9→1000) as the dissolution medium, adjust the rotational speed of the paddle to 50 rpm. Withdraw a quantity of the solution after exactly 30 minutes and filter, measure accurately a quantity of the successive filtrate and dilute with phosphate buffer solution (dissolve 3.02 g of potassium dihydrogen phosphate and 6.2 g of dipotassium hydrogen phosphate in 1000 ml of water, adjusted to pH 7.0), to produce a solution of 30 µg of rifampicin per ml. Dissolve an accurately weighed quantity of rifampicin CRS in phosphate buffer solution to produce a solution of 30 µg of rifampicin per ml. Measure the absorbance of the resulting solution at 474 nm (Appendix IV A). Calculate the dissolution of $C_{43}H_{58}N_4O_{12}$ from each capsule. Not less than 75% of the labeled amount is dissolved.

Other requirements Comply the general requirements for capsules (Appendix I E).

Assay Carry out the method for high performance liquid chromatography (Appendix V D), using a column packed with nitrile groups chemically bonded to porous silica particles and a mixture of 0.01 mol/L sodium heptanesulfonate solution (adjust to pH 2.2 with diluted phosphoric acid solution)-acetonitrile (44 : 56) as the mobile phase. Detection wavelength is 254 nm. Dissolve Rifampicin CRS, Rifampicinquinone CRS, Isoniazid CRS, and Pyrazinamide CRS in mobile phase to produce a mixture solution, contains 60 µg of Rifampicin, 60 µg of Rifampicinquinone 30 µg of Isoniazid and 125 µg of pyrazinamide per ml. Inject 20 µl in to column and record the chromatogram. The retention time of the substance in mixture solution are Pyrazinamide, Isoniazid, Rifampicinquinone and Rifampicin in turn; and the resolution factor among these peaks complies with related requirements. The number of theoretical plates of the column is not less than 1500, calculated with reference to the peak of Pyrazinamide.

Procedure Triturate the mixed contents obtained in the test for weight variation of contents. Weigh accurately a quantity (equivalent to 60 mg of rifampicin) in a 100 ml volumetric flask, dilute with mobile phase to volume, mix well and filter. Measure accurately 5 ml of the successive filtrate in 50 ml volumetric flask, dilute with mobile phase to volume, and mix well. Inject 20 µl in to column and record the chromatogram. Repeat the operations, using Rifampin CRS, Isoniazid CRS and Pyrazinamide CRS instead of the substance being examined. Calculate the contents of $C_{43}H_{58}N_4O_{12}$, $C_6H_7N_3O$ and $C_5H_5N_3O$ with respect to the peak area obtained in the chromatogram by the external standard method.

Category Antibiotics for tuberculosis.

Strength (1) 0.225 g (0.06 g of $C_{43}H_{58}N_4O_{12}$, 0.04 g of $C_6H_7N_3O$ and 0.125 g of $C_5H_5N_3O$)
(2) 0.45 g (0.12 g of $C_{43}H_{58}N_4O_{12}$, 0.08 g of $C_6H_7N_3O$ and 0.25 g of $C_5H_5N_3O$)

Storage Preserve in tightly closed containers, protected from light and stored in a dry place.

Rifampin Isoniazid and Pyrazinamide Tablets

Rifampin Isoniazid and Pyrazinamide tablet is a mixed preparation of rifampin, isoniazid and pyrazinamide. It contains not less than 90.0% and not more than 110.0% of the labeled content of rifampin ($C_{43}H_{58}N_4O_{12}$), isoniazid ($C_6H_7N_3O$)

and pyrazinamide ($C_5H_5N_3O$).

Description Film coated tablets with orange red or dark red core.

Identification

(1) Dissolve about weighed quantity of the powdered tablets, equivalent to 5 mg of rifampin, in 2 ml of 0.1 mol/L hydrochloric acid solution, add 2 drops of 0.1 mol/L sodium nitrite solution; the colour changes from orange red to dark red.

(2) Dissolve about weighed quantity of the powdered tablets (equivalent to 0.1 g of Isoniazid) in 10 ml of water in a test tube, shake and filter. Use the filtrate, add 1 ml of ammoniated silver nitrate TS, bubbles and a black turbidity are produced immediately, and a silver mirror is formed on the wall of the tube.

(3) Heat a quantity of the powdered tablets (equivalent to . g P. z d with 5 ml of sodium hydroxide TS, the characteristic odour of ammonia is perceived, the vapour turns moistened red litmus paper to blue.

(4) The retention time of principal peaks of rifampin, isoniazid and pyrazinamide in the chromatogram obtained in the Assay are identical with that of principal peaks of Rifampin CRS, Isoniazid CRS and Pyrazinamide CRS in the chromatogram of the reference solution correspondingly.

Dissolution Carry out the dissolution test (Appendix X C, method 1), using 900 ml of hydrochloric acid solution (9→1000) as the dissolution medium, adjust the rotational speed of the basket to 100 rpm. Withdraw a quantity of the solution at 30 minutes and filter, measure accurately a quantity of the successive filtrate and dilute with phosphate buffer solution (dissolve 3.02 g of potassium dihydrogen phosphate and 6.2 g of dipotassium hydrogen phosphate in 1000 ml of water, adjusted to pH 7.0), to produce a solution of 30 µg of rifampicin per ml. Dissolve an accurately weighed quantity of rifampicin CRS in phosphate buffer solution to produce a solution of 30 µg of rifampicin per ml. Measure the absorbance of the resulting solution at 474 nm (Appendix IV A). Calculate the dissolution of $C_{43}H_{58}N_4O_{12}$ from each tablet. Not less than 75% of the labeled amount is dissolved.

Other requirements Comply the general requirements for tablets (Appendix I A).

Assay Carry out the method for high performance liquid chromatography (Appendix V D), using a column packed with nitrile groups chemically bonded to porous silica particles and a mixture of 0.01 mol/L sodium heptanesulfonate solution (adjust to pH 2.2 with dilute phosphoric acid)-acetonitrile (44 : 56) as the mobile phase. Detection wavelength is 254 nm. Dissolve Rifampicin CRS, Rifampicinquinone CRS, Isoniazid CRS, and Pyrazinamide CRS in mobile phase to produce a mixture solution, contains 60 µg of Rifampicin, 60 µg of Rifampicinquinone 20 µg of Isoniazid and 62.5 µg of pyrazinamide per ml. Inject 20 µl in to column and record the chromatogram. The retention time of the substance in mixture solution are Pyrazinamide, Isoniazid, Rifampicinquinone and Rifampicin in turn; and the resolution factor among these peaks complies with related requirements. The number of theoretical plates of the column is not less than 1500, calculated with reference to the peak of Pyrazinamide.

Procedure Weigh accurately and powder 10 tablets with coating removed. Triturate an accurately weighed quantity of the powder (equivalent to 60 mg of Rifampicin) in a 100 ml volumetric flask, dilute with mobile phase to volume, mix well and filter. Measure accurately 5 ml of the successive filtrate in 50 ml volumetric flask, dilute with mobile phase to volume, mix well and filter. Inject 20 µl in to column

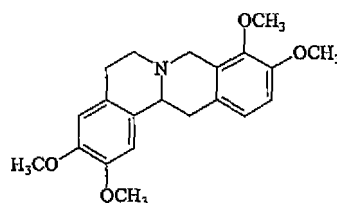
and record the chromatogram. Repeat the operations, using Rifampin CRS, Isoniazid CRS and Pyrazinamide CRS instead of the substance being examined. Calculate the contents of $C_{43}H_{58}N_4O_{12}$, $C_6H_7N_3O$ and $C_5H_5N_3O$ with respect to the peak area obtained in the chromatogram by the external standard method.

Category Antibiotics for tuberculosis.

Strength 0.45 g (0.12 g of $C_{43}H_{58}N_4O_{12}$, 0.08 g of $C_6H_7N_3O$ and 0.25 g of $C_5H_5N_3O$)

Storage Preserve in tightly closed containers, protected from light and stored in a dry place.

Rotundine



$C_{21}H_{25}NO_4$ 355.43

Rotundine is 5,8,13,13α-tetrahydro-2,3,9,10-tetramethoxy-6H-dibenzo [a, g] quinolizine. It contains not less than 98.0% of $C_{21}H_{25}NO_4$, calculated on the dried basis.

Description White to slightly yellow crystals; odourless; tasteless. It turns to yellow on exposure to light or heat. Soluble in chloroform; sparingly soluble in ethanol or ether; insoluble in water; freely soluble in dilute sulfuric acid.

Melting point 141-144°C (Appendix VI C).

Specific optical rotation -290° to -300°, measured at 25°C in a solution of 8 mg per ml in ethanol (Appendix VI E).

Specific absorbance Measure the absorbance of a 30 µg per ml solution in 0.5% sulfuric acid solution at 281 nm (Appendix IV A), the value of A (1%, 1 cm) is 150-160.

Identification (1) Carry out the following tests using a solution of 0.1 g in a mixture of 10 ml of water and 1 ml of dilute sulfuric acid.

To 2 ml of the solution add 1 drop of potassium dichromate TS, a yellow precipitate is produced; To 2 ml of the solution add 1 drop of saturated sodium chloride solution, a white precipitate is produced; To 2 ml of the solution add dilute potassium ferricyanide TS; A yellow precipitate is produced, which gradually turns to green and finally changes to blue on gentle heating.

(2) The infrared absorption spectrum (Appendix IV C) is concordant with the reference spectrum of rotundine (Appendix XVI).

Clarity and colour of acidity solution Dissolve 0.15 g in 5 ml of 5% sulfuric acid solution, the solution is clear; any colour produced is not more intense than reference solution YG₄ (Appendix IX A, method 1).

Other alkaloids Carry out the method for thin-layer chromatography (Appendix V B), using silica gel G as the coating substance and a mixture of chloroform-dehydrated ethanol-concentrated ammonia solution (98 : 2 : 0.5) as the mobile phase. Apply separately to the plate 20 µl of each of

two solutions in dehydrated ethanol containing (1) 10 mg, (2) 50 μg of the substance being examined per ml. After developing and removal of the plate, allow it to dry in air and visualize with iodine vapour. Any spot, other than the principal spot in the chromatogram obtained with solution (1) is not more intense than the principal spot obtained with solution (2).

Loss on drying When dried to constant weight at 105°C, loses not more than 5.0% of its weight (Appendix VIII L).

Residue on ignition Not more than 0.1% (Appendix VII N).

Assay Dissolve about 0.3 g, accurately weighed, in 2 ml of acetic acid and 15 ml of water in a 50 ml volumetric flask with heating, mix well. Add 25 ml of 1.7% potassium iodide solution, accurately measured dilute with water to volume and mix well. Filter through dry filter. Measure accurately 25 ml of the successive filtrate, add 3-5 drops of eosin sodium IS, titrate with silver nitrate (0.05 mol/L) VS until the pink precipitate coagulates. Perform a blank determination and make any necessary corrections. Each ml of silver nitrate (0.05 mol/L) VS is equivalent to 17.77 mg of $\text{C}_{21}\text{H}_{25}\text{NO}_4$.

Category Analgesic.

Storage Preserve in tightly closed containers, protected from light.

Preparation (1) Rotundine Sulfate Injection
(2) Rotundine Tablets

Rotundine Tablets

Rotundine Tablets contain not less than 93.0% and not more than 107% of the labelled amount of rotundine ($\text{C}_{21}\text{H}_{25}\text{NO}_4$).

Description White to slightly yellow tablets.

Identification (1) To a quantity of the powdered tablets equivalent to about 0.1 g of rotundine add 10 ml of water and 1 ml of dilute sulfuric acid, shake to dissolve rotundine and filter. The filtrate complies with test (1) for Identification described under Rotundine.

(2) To a quantity of powdered tablets add ethanol to produce a suspension containing 8 mg of rotundine per ml and filter. The specific optical rotation of the filtrate (Appendix VI E) is not less than -270° , calculated on the basis of the labelled amount (distinction from tetrahydropalmatine sulfate).

Dissolution Carry out the dissolution test (Appendix X C, method 1), using 900 ml of hydrochloric acid solution (9 \rightarrow 1000) as the dissolution medium, adjust the rotational speed of the basket to 100 rpm. Withdraw the solution after exactly 45 minutes and filter. Transfer 5 ml (for strength 60 mg) of successive filtrate in a 10 ml volumetric flask and dilute with dissolution medium to the volume. Measure the absorbance at 281 nm (Appendix IV A), calculate the dissolution of $\text{C}_{21}\text{H}_{25}\text{NO}_4$ of each tablet, taking 155 as the value of A (1%, 1 cm), not less than 70% of the labelled amounts dissolved.

Other requirements Comply with the general requirements for tablets (Appendix I A).

Assay Weigh accurately and powder finely 20 tablets. Weigh accurately a quantity equivalent to about 60 mg of rotundine to a 100 ml volumetric flask, add 0.5% sulfuric

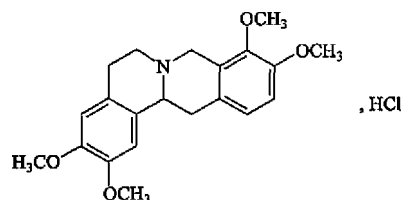
acid solution, shake to dissolve rotundine, dilute with the same solvent to volume, mix well and filter. Measure accurately 5 ml of the successive filtrate to a 100 ml volumetric flask, dilute with 0.5% sulfuric acid solution to volume and mix well. Measure the absorbance of the resulting solution at 281 nm (Appendix IV A), calculate the content of $\text{C}_{21}\text{H}_{25}\text{NO}_4$, taking 155 as the value of A (1%, 1 cm).

Category As described under Rotundine.

Strength (1) 30 mg (2) 60 mg

Storage Preserve in tightly closed containers, protected from light.

Rotundine Hydrochloride



$\text{C}_{21}\text{H}_{25}\text{NO}_4 \cdot \text{HCl}$ 391.89

Rotundine Hydrochloride is 2,3,9,10-tetramethoxy-5,8,13,13 α -tetrahydro-6H-dibenzo (a, g) quinolizine. It contains not less than 98.5% of $\text{C}_{21}\text{H}_{25}\text{NO}_4 \cdot \text{HCl}$, calculated on the dried basis.

Description White to slightly yellow crystals; odourless; taste bitter; readily turns to yellow on exposure to light on heating.

Soluble in chloroform, methanol or boiled water; sparingly soluble in water; slightly soluble in dehydrated ethanol; practically insoluble in ether or acetone.

Specific optical rotation Above -232°C , measured at 25°C in a solution of 10 mg per ml in water (Appendix VI E).

Specific absorbance Measure the absorbance of a solution of about 30 μg per ml in 0.01 mol/L hydrochloric acid solution at 281 nm (Appendix IV A), the value of A (1%, 1 cm) is 135 to 146.

Identification (1) Dissolve 10 mg in 2 ml of water, add 1 drop of potassium dichromate TS, a yellow precipitate is produced.

(2) Dissolve 10 mg in 2 ml of water, add 1 drop of potassium dichromate TS, a yellow precipitate is produced, which gradually turns to green, and then to blue on heating slowly.

(3) The infrared absorption spectrum (Appendix IV C) is concordant with the spectrum of rotundine hydrochloride (Appendix XIV).

Acidity Dissolve a quantity in water to produce a solution of 2 mg per ml, pH 4.0-4.7 (Appendix VI H).

Other alkaloids Carry out the method for thin-layer chromatography (Appendix V B), using silica gel G as the coating substance and a mixture of chloroform-dehydrated ethanol (98 : 2) as the mobile phase. Apply separately to the plate 10 μl of each of two solutions in a mixture of dehydrated ethanol-concentrate ammonia solution (9 : 1) containing (1) 10 mg per ml, (2) 0.1 mg per ml of the substance being examined. After developing and removal of the plate, dry it in air and expose to iodine vapour. Any spot in the chromatogram other than the principal spot obtained with solution (1) is not more intense than the principal spot

obtained with solution (2).

Loss on drying When dried to constant weight at 105°C, loses not more than 6.0% of its weight (Appendix VIII L).

Residue on ignition Not more than 0.1% (Appendix VIII N).

Assay Weigh accurately 0.35 g, add 25 ml of glacial acetic acid, 2 ml of acetic anhydride and 5 ml of mercuric acetate TS, shake to dissolve, add 1 drop of crystal violet IS, titrate with perchloric acid (0.1 mol/L) VS until the solution turns to blue. Perform a blank determination and make any necessary correction. Each ml of perchloric acid (0.1 mol/L) VS is equivalent to 39.19 mg of $C_{21}H_{25}NO_4 \cdot HCl$.

Category Analgesic.

Storage Preserve in tightly closed containers, protected from light.

Preparation Rotundine Hydrochloride Tablets

Rotundine Hydrochloride Tablets

Rotundine Hydrochloride Tablets contain not less than 93.0% and not more than 107.0% of the labelled amount of rotundine hydrochloride ($C_{21}H_{25}NO_4 \cdot HCl$).

Description White to pale yellow tablets.

Identification To a quantity of powdered tablets equivalent to about 0.1 g of rotundine hydrochloride add 20 ml of water, shake to dissolve rotundine hydrochloride, filter, the filtrate complies with tests (1) and (2) for Identification described under Rotundine Hydrochloride.

Other requirements Comply with the general requirements for tablets (Appendix I A).

Assay Weigh accurately and triturate 20 tablets, dissolve an accurately weighed quantity equivalent to about 30 mg of rotundine hydrochloride in 0.01 mol/L hydrochloric acid in a 100 ml volumetric flask and dilute to volume, mix well, filter. Measure accurately 5 ml of the successive filtrate to a 50 ml volumetric flask, dilute with 0.01 mol/L hydrochloric acid solution to volume, mix well. Measure the absorbance at 281 nm (Appendix IV A), calculate the content of $C_{21}H_{25}NO_4 \cdot HCl$, taking 140.4 as the value of A (1%, 1 cm).

Category As described under Rotundine Hydrochloride.

Strength 30 mg

Storage Preserve in tightly closed containers, protected from light.

Rotundine Sulfate Injection

Rotundine Sulfate Injection is a sterile solution of Rotundine in Water for Injection containing a quantity of dilute sulfuric acid. It contains not less than 93.0% and not more than 107.0% of the labelled amount of rotundine sulfate [$(C_{21}H_{25}NO_4)_2 \cdot H_2SO_4$].

Description A clear, pale yellow to yellow liquid; the colour deepens on exposure to light or heat.

Identification (1) Complies with test (1) for Identification described under Rotundine.

(2) Mix 5 ml, measured accurately, with 10 ml of water, the specific optical rotation of the resulting solution (Appendix VI E) is not less than -237° (distinction from tetrahydropalmatine sulfate).

pH value 2.5-4.0 (Appendix VI H).

Colour Not more intense than that of reference solution YG₉ (Appendix IX A, method 1); use 5 ml.

Other requirements Complies with the general requirements for injections (Appendix I B).

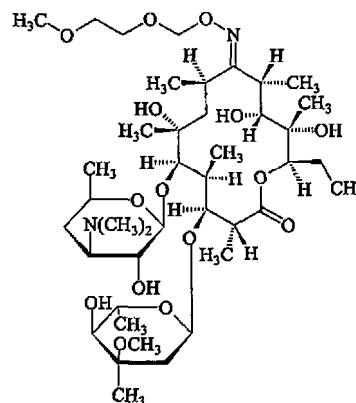
Assay Measure accurately a quantity of rotundine sulfate, dilute with 0.5% sulfuric acid solution to produce a solution of 30 µg per ml. Measure the absorbance of the resulting solution at 281 nm (Appendix IV A), calculate the content of $(C_{21}H_{25}NO_4)_2 \cdot H_2SO_4$, taking 136 as the value of A (1%, 1 cm).

Category As described under Rotundine.

Strength 2 ml : 60 mg

Storage Preserve in well closed containers, protected from light.

Roxithromycin



$C_{41}H_{76}N_2O_{15}$ 837.03

[80214-83-1]

Roxithromycin is (3R,4S,5S,6R,7R,9R,11S,12R,13S,14R)-4-[(2,6-dideoxy-3-C,3-O-dimethyl-α-L-ribo-hexopyranosyl)oxy]-14-ethyl-7,12,13-trihydroxy-10-[(E)-[(2-methoxyethoxy)-methoxy]imino]-3,5,7,9,11,13-hexamethyl-6-[3,4,6-trideoxy-3-dimethylamino-β-D-xylo-hexopyranosyl]oxy oxacyclotetradecan-2-one. It contains not less than 94.0% of $C_{41}H_{76}N_2O_{15}$, calculated on the anhydrous basis.

Description A white or almost white crystalline powder; odourless; taste, bitter; slightly hygroscopic.

Freely soluble in ethanol or acetone; soluble in methanol or ether; sparingly soluble in acetonitrile, practically insoluble in water.

Specific optical rotation -82° to -87° , in a solution of 20 mg per ml in dehydrated ethanol (Appendix VI E).

Identification (1) The retention time of principal peak of the solution being examined in the chromatogram obtained in the Assay is identical with that the principal peak of the reference solution correspondingly.

(2) The infrared absorption spectrum (Appendix IV C) is concordant with the reference spectrum of roxithromycin (Appendix XIV). If any disagreement is found, dissolve a quantity in acetone, dry it in air first in vacuum at 60°C and then perform the determination.

Alkalinity To 0.1 g add 150 ml of water, shake thoroughly, pH 8.0-10.0 (Appendix VI H).

Related substances Dissolve a quantity in mobile phase to produce a solution of 2 mg per ml, using it as test solution. Measure accurately 1 ml to a 100 ml volumetric flask, dilute with mobile phase to volume, mix well as reference solution. Carry out the method as described under Assay. Inject 20 μ l of reference solution into the column. Adjust the attenuation so that the principal peak height in the chromatogram is about 20% of full scale of the chart. Inject accurately 20 μ l of the two solutions respectively into the column and record the chromatograms for four times the retention time of the principal peak. The area of each impurity peak in the chromatogram obtained with test solution is not greater than 1.5 times of the area of the principal peak in the chromatogram obtained with reference solution (1.5%); the sum of the area of all impurity peak in the chromatogram obtained with test solution is not greater than 4.5 times of the area of the principal peak in the chromatogram obtained with reference solution (4.5%).

Water Dissolve a quantity in pyridine, carry out the method for determination of water (Appendix VIII M, method 1 A); not more than 3.0%.

Residue on ignition Not more than 0.1% (Appendix VIII N), using 1.0 g.

Heavy metals Carry out the limit test for heavy metals (Appendix VIII H, method 2), using the residue obtained in the test for Residue on ignition; not more than 0.001%.

Assay Carry out the method for high performance liquid chromatography (Appendix V D), using a column packed with octadecylsilane bonded silica gel and a mixture of ammonium dihydrogen phosphate (adjust to pH 6.5 with triethylamine)-acetonitrile (65 : 35) as mobile phase. The detection wavelength is 210 nm; The retention time of roxithromycin is not less than 9 minutes. The resolution factor between peaks of roxithromycin and the front impurity peak is not less than 1.0, the resolution factor between peaks of roxithromycin and the back impurity peak is not less than 2.0; The number of theoretical plates of the column is not less than 2500, calculated with reference to the peak of roxithromycin.

Procedure Dissolve a quantity, accurately weighed, in mobile phase to produce a solution of 1 mg per 1 ml, inject 20 μ l into the column and record the chromatogram. Repeat the operation, using the roxithromycin CRS instead of the substance being examined, calculate the content of $C_{41}H_{76}N_2O_{15}$ with respect to the peak area obtained in the chromatogram by the external standard method.

Category Macrolide antibiotic.

Storage Preserve in tightly closed containers, stored in a dry place.

Preparation (1) Roxithromycin Capsules
(2) Roxithromycin Dispersible Tablets
(3) Roxithromycin for Suspension
(4) Roxithromycin Granules
(5) Roxithromycin Tablets

Roxithromycin Capsules

Roxithromycin Capsules contain not less than 90.0% and not more than 110.0% of the labelled amount of roxithromycin ($C_{41}H_{76}N_2O_{15}$).

Description White or almost white crystalline powder and granules.

Identification The retention time of the principal peak of the solution being examined in the chromatogram obtained in the Assay is identical with that the principal peak of the reference solution correspondingly.

Dissolution Carry out the dissolution test (Appendix X C, method 1), using hydrochloric acid solution (1 \rightarrow 1000) 900 ml as the dissolution medium (600 ml for 50 mg), adjust the rotational speed of the basket to 100 rpm. Withdraw the solution after exactly 45 minutes and filter, dilute an accurately measured quantity of the successive filtrate with the dissolution medium to produce a solution of 80 μ g of roxithromycin per ml. Dissolve an accurately weighed quantity of the mixed contents obtained in the test for weight variation of contents equivalent to about the average weight of one capsule in ethanol (using 1 ml ethanol for 5 mg of roxithromycin), and dilute with the dissolution medium and filter, dilute an accurately measured quantity of the successive filtrate with the dissolution medium to produce a solution of 80 μ g of roxithromycin per ml according to the labelled amount. Measure accurately 5 ml each of the two solutions separately, add 5 ml of sulfuric acid solution (75 \rightarrow 100) respectively, mix well, allow to stand for 30 minutes, cool. Measure the absorbances of the resulting solutions at 482 nm (Appendix IV A), calculate the dissolution of $C_{41}H_{76}N_2O_{15}$ from each capsule. Not less than 75% of the labeled amount is dissolved. The disintegration of shell by swelling reduce not to be complied, using hydrochloric acid solution (1 \rightarrow 1000) containing 1% pepsin (1 : 1200-1 : 3000) as the solvent, repeat the test.

Related substances Dissolve an accurately weighed quantity of the mixed contents obtained in the test for weight variation of contents in mobile phase to produce a solution of 2 mg per ml, filter and use the successive filtrate as the test solution. Measure accurately 1 ml to a 100 ml volumetric flask, dilute with mobile phase to volume, mix well as the reference solution. Carry out the test for Related substances described under Roxithromycin. The area of each impurity peak in the chromatogram obtained with test solution is not greater than 2.5 times of the area of the principal peak in the chromatogram obtained with reference solution (2.5%).

Other requirements Comply with the general requirements for capsules (Appendix I E).

Assay Weigh accurately and powder a quantity of the mixed contents in the test for weight variation of contents, equivalent to about 50 mg of roxithromycin, add quantity mobile phase, sonicate for 20 minutes, dilute with mobile phase to produce a solution of 1 mg of roxithromycin per ml, filter, take the successive filtrate as the test solution and carry out the test of the Assay as described under Roxithromycin.

Category As described under Roxithromycin.

Strength (1) 50 mg (2) 75 mg (3) 150 mg

Storage Preserve in tightly closed containers, stored in a dry place and protected from light.

Roxithromycin Dispersible Tablets

Roxithromycin Dispersible Tablets contain not less than 90.0% and not more than 110.0% of the labelled amount of roxithromycin ($C_{41}H_{76}N_2O_{15}$).

Description White or almost white tablets.

Identification The retention time of the principal peak of the substance being examined in the chromatogram obtained in the Assay is identical with that the principal peak of the reference solution.

Related substances Dissolve a quantity of the powdered tablets in mobile phase to produce a solution of 2 mg per ml, filter and use the successive filtrate as the test solution. Measure accurately 1 ml to a 100 ml volumetric flask, dilute with mobile phase to volume, mix well as reference solution. Carry out the test for Related substances described under Roxithromycin. The area of each impurity peak in the chromatogram obtained with test solution is not greater than 2.5 times of the area of the principal peak in the chromatogram obtained with reference solution (2.5%).

Dissolution Carry out the dissolution test (Appendix X C, method 1), using hydrochloric acid solution (1→1000) 900 ml as the dissolution medium (600 ml for strength 50 mg), adjust the rotational speed of the basket to 100 rpm. Withdraw the solution after exactly 45 minutes and filter, dilute an accurately measured quantity of the successive filtrate with the dissolution medium to produce a solution of 80 µg of roxithromycin per ml. Dissolve a quantity of 10 powdered tablets, equivalent to about the average weight of one tablet, in ethanol (1 ml of ethanol per 5 mg of roxithromycin), dilute with the dissolution medium and filter, dilute an accurately measured quantity of the successive filtrate with the dissolution medium to produce a solution of 80 µg of roxithromycin per ml according to the labelled amount. Measure accurately 5 ml each of the two solutions separately, add 5 ml of sulfuric acid solution (75→100), mix well, allow it to stand for 30 minutes, cool to room temperature. Measure the absorbances of the resulting solutions at 482 nm (Appendix VI A), calculate the dissolution of $C_{41}H_{76}N_2O_{15}$ from each tablet. Not less than 80% of the labelled amount is dissolved.

Other requirements Comply with the general requirements for dispersible tablets (Appendix I A).

Assay Weigh accurately and powder finely 10 tablets, triturate an accurately weighed quantity, equivalent to about 50 mg of roxithromycin, add quantity mobile phase, ultrasonic for 20 minutes, dilute with mobile phase to produce a solution of 1 mg of roxithromycin per ml, filter, take the successive filtrate as the test solution and carry out the test for the Assay as described under Roxithromycin.

Category As described under Roxithromycin.

Strength (1) 50 mg (2) 75 mg (3) 150 mg

Storage Preserve in tightly closed containers, stored in a dry place.

Roxithromycin for Suspension

Roxithromycin for suspension contains not less than 90.0% and not more than 110.0% of the labelled amount of roxithromycin ($C_{41}H_{76}N_2O_{15}$).

Description Powder; odour fragrant, taste, sweet.

Identification The retention time of principal peak of the solution being examined in the chromatogram obtained in the Assay is identical with that the principal peak of the reference solution correspondingly.

Alkalinity Weigh a quantity of the substance being examined, equivalent to about 15 mg of roxithromycin, add 10 ml of water, shake thoroughly, pH 7.0-9.0. (Appendix VI H).

Loss on drying When dried in vacuum to constant weight at 80°C, loses not more than 2.0% of its weight (Appendix VII L).

Other requirements Complies with the general requirements for oral suspensions (Appendix I O) except of ratio of sedimental volume.

Assay Weigh accurately and powder finely the mixed contents obtained in the test for weight variation of contents, dissolve accurately a quantity of powdered mixed contents in mobile phase, ultrasonic for 20 minutes, dilute with mobile phase to produce a solution of 0.5 mg per ml. Filter and use the successive filtrate as the test solution. Carry out the Assay described under Roxithromycin.

Category As described under Roxithromycin.

Strength (1) 25 mg (2) 50 mg (3) 75 mg

Storage Preserve in tightly closed containers, stored in a dry place and protected from light.

Roxithromycin Granules

Roxithromycin Granules contain not less than 90.0% and not more than 110.0% of the labelled amount of roxithromycin ($C_{41}H_{76}N_2O_{15}$).

Description Suspension granules; taste, slightly sweet. or tasteless coated granules with white or almost white core.

Identification The retention time of principal peak of the substance being examined in the chromatogram obtained in the Assay is identical with that of the principal peaks of the reference solution.

Dissolution Carry out the dissolution test (Appendix XC method 1), using hydrochloric acid solution (1→1000) 900 ml as the dissolution medium (600 ml for strength 50 mg, 500 ml for strength 25 mg), adjust the rotational speed of the basket to 100 rpm. Withdraw the solution after exactly 45 minutes and filter, dilute an accurately measured quantity of the successive filtrate with the dissolution medium to produce a solution of 80 µl of roxithromycin per ml (50 µg for strength 25 mg) as the test solution. Dissolve an accurately weighed quantity of the mixed contents obtained in the test for weight variation of contents, equivalent to about 50 mg of roxithromycin (using 1 ml of ethanol for 5 mg of roxithromycin), and dilute with the dissolution medium to produce a solution of 80 µg or 50 µg per ml and filter, using the successive filtrate as the reference solution. Measure accurately 5 ml of each of the test solution and reference solution separately, add 5 ml of sulfuric acid solution (75→100) respectively, accurately measured mix well, allow to stand for 30 minutes, cool to room temperature. Measure the absorbances of the resulting solutions at 482 nm (Appendix IV A), calculate the dissolution of $C_{41}H_{76}N_2O_{15}$ from each container. Not less than 70% of the labelled amount is dissolved (for coated granules).

Loss on drying When dried to constant weight at 105°C,

loses not more than 2.0% of its weight (Appendix VIII L).

Other requirements Comply with the general requirements for granules (Appendix I N).

Assay Dissolve an accurately weighed quantity of the powdered and mixed contents in the test for weight variation of contents in ethanol (using 1 ml of ethanol for 5 mg of roxithromycin), dilute with phosphate BS (pH 7.8) to produce a solution of 1000 Units per ml, mix well and allow to stand. Measure accurately a quantity of the supernatant liquid and carry out the Assay described under Roxithromycin.

Category As described under Roxithromycin.

Strength (1) 25 mg (2) 50 mg
(3) 75 mg (4) 150 mg

Storage Preserve in tightly closed containers, stored in a dry place.

triturate an accurately weighed quantity, equivalent to about 50 mg of roxithromycin, add quantity mobile phase, in an ultrasonic bath for 20 minutes, dilute with mobile phase to produce a solution of 1 mg roxithromycin per ml, filter, take the successive filtrate as test solution and carry out the Assay as described under Roxithromycin.

Category As described under Roxithromycin.

Strength (1) 50 mg (50000 units)
(2) 75 mg (75000 units)
(3) 150 mg (150000 units)

Storage Preserve in tightly closed containers, stored in a dry place.

Roxithromycin Tablets

Roxithromycin Tablets contain not less than 90.0% and not more than 110.0% of the labelled amount of Roxithromycin ($C_{41}H_{76}N_2O_{15}$).

Description White or almost white tablets or film coated tablets with white or almost white core.

Identification The retention time of principal peak of the solution being examined in the chromatogram obtained in the Assay is identical with that the principal peak of the reference solution correspondingly.

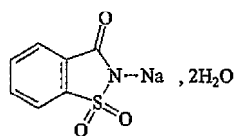
Dissolution Carry out the dissolution test (Appendix X C, method 1), using hydrochloric acid solution (1→1000) 900 ml as the dissolution medium (600 ml for strength 50 mg), adjust the rotational speed of the basket to 100 rpm. Withdraw the solution after exactly 45 minutes and filter, dilute an accurately measured quantity of the successive filtrate with the dissolution medium to produce a solution of 80 µg of roxithromycin per ml. Dissolve a quantity of 10 powdered tablets, equivalent to about the average weight of one tablet, in ethanol (1 ml of ethanol per 5 mg roxithromycin), dilute with the dissolution medium and filter, dilute an accurately measured quantity of the successive filtrate with the dissolution medium to produce a solution of 80 µg of roxithromycin per ml according to the labelled amount. Measure accurately 5 ml each of the two solutions separately, add 5 ml of sulfuric acid solution (75→100), measured accurately, mix well, allow it to stand for 30 minutes, cool to room temperature. Measure the absorbances of the resulting solutions at 482 nm (Appendix IV A), calculate the dissolution of $C_{41}H_{76}N_2O_{15}$ from each tablet. Not less than 80% of the labelled amount is dissolved.

Related substances Dissolve a quantity of powdered tablets in mobile phase to produce a solution of 2 mg per 1 ml, filter and use the successive filtrate as the test solution. Measure accurately 1 ml to a 100 ml volumetric flask, dilute with mobile phase to volume, mix well as reference solution. Carry out the Related substances as described under Roxithromycin. The area of each impurity peak in the chromatogram obtained with test solution is not greater than 2.5 times of the area of the principal peak in the chromatogram obtained with reference solution (2.5%).

Other requirements Comply with the general requirements for tablets (Appendix I A).

Assay Weigh accurately and powder finely 10 tablets,

Saccharin Sodium



$C_7H_4NNaO_3S \cdot 2H_2O$ 241.19

[6155-57-3]

Saccharin Sodium is the sodium salt of 1,2-benzisothiazolin-3 (2H)-one-1,1-dioxide dihydrate. It contains not less than 99.0% of $C_7H_4NNaO_3S$, calculated on the dried basis.

Description Colourless crystals or a white crystalline powder; odourless or with a faintly aromatic odour; taste, intensely sweet with bitter. Efflorescent. Freely soluble in water; sparingly soluble in ethanol.

Identification (1) Dissolve about 0.3 g in 5 ml of water, add 1 ml of dilute hydrochloric acid; a crystalline precipitate is produced. Filter, wash the precipitate with water and dry at 105°C for 2 hours, it melts at 226-230°C (Appendix VI C). (2) Mix 20 mg with 40 mg of resorcinol, add 0.5 ml of sulfuric acid, heat over a small flame until it assumes a dark green colour. Allow it to cool, add 10 ml of water and an excess of sodium hydroxide TS; a fluorescent green liquid is produced.

(3) The residue left on ignition yields the reactions characteristic of sodium salts (Appendix III).

(4) The infrared absorption spectrum (Appendix IV C) is concordant with the reference spectrum of saccharin sodium (Appendix XVI).

Acidity or alkalinity A solution of 1.0 g in 10 ml of water is neutral or alkaline to litmus paper, but exhibits no red colour to phenolphthalein IS.

Ammonium salt Dissolve 0.40 g in 20 ml of ammonia-free water, add 1 ml of alkaline potassium mercuric-iodide TS, mix well and allow to stand for 5 minutes. Any colour produced is not more intense than that of a reference solution prepared in the same manner with 0.10 ml of ammonium chloride solution. 0.966 g ammonium chloride, previously dried to constant weight at 105°C, is dissolved in ammonia-free water to make 1000 ml (0.0025%).

Benzoate and salicylate Dissolve 0.50 g in 10 ml of water, acidify with 5 drops of acetic acid, add 3 drops of ferric chloride TS; no precipitate or violet colour is produced.

Toluenesulfonamide Carry out the method for gas chromatography (Appendix V E), using a column packed with 1.5% polyethylene glycol adipate containing silicone (OV-17) as the stationary phase, and maintain the column temperature at 180°C.

Dissolve a quantity of *o*- and *p*-Toluenesulfonamide CRS, accurately weighed, in dichloromethane to produce a solution containing 50 µg each of *o*-Toluenesulfonamide and 50 µg of *p*-Toluenesulfonamide per ml as reference standard solution. Dissolve about 2.0 g of saccharin sodium, accurately weighed, in 8.0 ml of 5% solution of sodium carbonate, then add 10 g of kieselguhr [weigh 100 g of kieselguhr (pass through No. 9 sieve), add 800 ml of hydrochloric acid, stir occasionally, allow to immerse for 12 hours, discard the acid solution. Repeat the operation for 3 times using hydrochloric acid, allow to immerse for 1 hour each time. Wash with water till the solution yields neutral reaction. Transfer the kieselguhr to 300 ml of methanol and filter,

dried at 80°C], mix well, pack into a 25 mm × 250 mm chromatography tube. Carry out the method for column chromatography (Appendix V C, method 2), using dichloromethane to elute about 30 minutes. Collect 50 ml of eluent, evaporate to almost dryness, add dichloromethane to produce 1.0 ml as the test solution. Inject the two solutions to operate the column respectively and calculate the content of toluenesulfonamide, the sum is not more than 0.0025%.

Loss on drying When dried to constant weight at 105°C, loses not more than 0.5% of its weight upon drying.

Heavy metals Dissolve 2.0 g in 48 ml of water in a beaker, add 2 ml of hydrochloric acid solution (9→100), stir and scratch the inside of the beaker with a glass rod until crystallization begins. Allow to stand for 1 hour, filter. Carry out the limit test for heavy metals (Appendix VIII H, method 1) using 25 ml of the filtrate; not more than 0.001%.

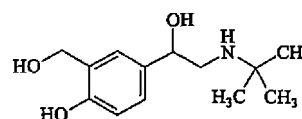
Arsenic Transfer 1 g to a crucible containing about 1 g of anhydrous sodium carbonate on the bottom and around the inner walls. Moisten with a small quantity of water. Evaporate to dryness on a water bath, gently ignite to carbonize it and continue to ignite at 500-600°C until all black particles have disappeared. Cool, dissolve the residue in 5 ml of hydrochloric acid and 23 ml of water. Carry out the limit test for arsenic (Appendix VIII J, method 1); not more than 0.0002%.

Assay Dissolve about 0.2 g, accurately weighed, in 20 ml of glacial acetic acid, add 1 drop of crystal violet IS and titrate with perchloric acid (0.1 mol/L) VS until the colour changes to bluish-green. Perform a blank determination and make any necessary correction. Each ml of perchloric acid (0.1 mol/L) VS is equivalent to 20.52 mg of $C_7H_4NNaO_3S$.

Category Diagnostic and sweetener.

Storage Preserve in tightly closed containers.

Salbutamol



$C_{13}H_{21}NO_3$ 239.31

[18559-94-9]

Salbutamol is 1-(4-hydroxy-3-hydroxymethylphenyl)-2-(tert-butylamino) ethanol. It contains not less than 98.5% of $C_{13}H_{21}NO_3$, calculated on the dried basis.

Description White crystalline powder; odourless; almost tasteless. Soluble in ethanol; sparingly soluble in water; insoluble in ether.

Melting range 154-158°C, with decomposition (Appendix VI C).

Identification (1) Dissolve about 20 mg in 2 ml of water, add 2 drops of ferric trichloride TS and shake; a violet colour is produced which turns to orange-red on addition of sodium bicarbonate TS.

(2) Dissolve about 10 mg in 20 ml of 0.4% borax solution, add 1 ml of 3% 4-aminoantipyrine solution and 1 ml of 2% potassium ferricyanide solution. Add 10 ml of chloroform, shake and allow to stand; an orange-red colour is produced in the chloroform layer.

(3) The light absorption of a solution of 0.08 mg per ml in

0.1 mol/L hydrochloric acid solution, exhibits a maximum at 276 nm (Appendix IV A).

Colour of ethanol solution A solution of 0.40 g in 10 ml of dehydrated ethanol is made by warming in a water bath. Any colour produced is not more intense than that of reference solution (to 0.5 ml of yellow stock Reference Solution add 10 ml of dehydrated ethanol) (Appendix IX A, method 1).

Related substances Carry out the method for thin-layer chromatography (Appendix V B), using silica gel G as the coating substance and a mixture of ethyl acetate-isopropanol-water-concentrated ammonia (50 : 30 : 16 : 4) as the mobile phase. Apply separately to the plate 10 µl each of two solutions in methanol containing (1) 10 mg; (2) 0.10 mg of the substance being examined per ml. After developing and removal of the plate, dry it in air. Place the plate in an atmosphere saturated with diethylamine for 5 minutes and spray with diazotized sulfanilic acid solution. Any spot other than the principal spot in the chromatogram obtained with solution (1), is not more intense than the principal spot obtained with solution (2).

Loss on drying When dried to constant weight at 105°C, loses not more than 0.5% of its weight (Appendix VIII L).

Residue on ignition Not more than 0.1% (Appendix VIII N).

Assay Dissolve about 0.2 g, accurately weighed, in 25 ml of glacial acetic acid, add a drop of crystal violet IS, titrate with perchloric acid (0.1 mol/L) VS until the colour changes to blue. Perform a blank determination and make any necessary correction. Each ml of perchloric acid (0.1 mol/L) VS is equivalent to 23.93 mg of $C_{13}H_{21}NO_3$.

Category β_2 -Adrenergic receptor activating agent.

Storage Preserve in tightly closed containers, protected from light.

Preparation Salbutamol Aerosol

Salbutamol Aerosol

Salbutamol Aerosol of solution type or suspension type is packed in a tightly closed containers fitted with meter-dose valve system. It contains not less than 90.0% and not more than 120.0% of the labelled amount of salbutamol, ($C_{13}H_{21}NO_3$). The concentration of salbutamol in the liquid is not less than 80% (g/g) and not more than 130% (g/g) of the labelled concentration.

Description Solution type: a clear, colourless to pale yellow liquid; suspension type: a white suspension.

Identification Punch a small hole on the aluminium cover of one container, with a syringe needle, remove the aluminium cover after complete evaporation of the propellant, weigh a quantity equivalent to about 5 mg of salbutamol, add 10 ml of 2% borax solution, 1 ml of 3% 4-aminoantipyrine solution and 2 ml of 2% potassium ferricyanide solution; the solution becomes orange-red, then shake with 5 ml of chloroform, and allow to stand; an orange-red colour is produced in the chloroform layer.

Other requirements Complies with the general requirements for aerosols (Appendix I L).

Assay Remove the cover of one container, weigh accurately, punch a small hole on the aluminium cover and insert a syringe needle connecting to a dry rubber tubing, keep the needle without contact the liquid surface. Dip the other end of the

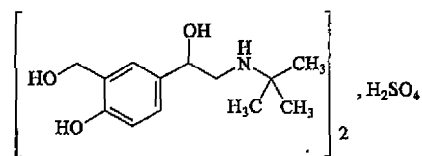
tubing to 5 ml of ethanol contained in a 50 ml volumetric flask, allow the propellant to evaporate slowly. Remove the aluminium cover, and valve, transfer the content to above 50 ml volumetric flask. Wash the aluminium cover, valve and container with ethanol for several times, combine the washings to a small beaker, evaporate to dryness on a water bath, wash the residue with 0.1 mol/L hydrochloric acid solution and transfer to above volumetric flask, dilute with 0.1 mol/L hydrochloric acid to volume, mix well, filter. Measure accurately 5 ml of successive filtrate to a 50 ml volumetric flask, dilute with 0.1 mol/L hydrochloric acid solution to volume, mix well, as the test solution. Weigh accurately about 28 mg of salbutamol CRS (suspension type using 20 mg), in a 50 ml volumetric flask, add 0.1 mol/L hydrochloric acid solution to dissolve salbutamol and dilute to volume, mix well. Measure accurately 5 ml to a 50 ml volumetric flask, dilute with 0.1 mol/L hydrochloric acid solution to volume, mix well, as the reference solution. Measure the absorbance of the two solutions at 276 nm (Appendix IV A). Calculate the content of salbutamol. Weigh accurately the weight of container, aluminium cover and valve after washing clean and dried, subtracted from the original weight of the container being the weight of salbutamol; the concentration may be obtained from the ratio of content of salbutamol in each container. Repeat the Assay with another two containers, if only one of the two results of the content and the concentration result meets the requirement, all results should comply with the requirements.

Category β_2 -Adrenergic receptor activating agent.

Strength Solution type: 14 g per container, containing 28 mg of salbutamol, liquid concentration: 0.2% (g/g), spraying dose: 0.14 mg
Suspension type: 14 g per container, containing 20 mg of salbutamol, liquid concentration: 0.14% (g/g), spraying dose: 0.10 mg
Suspension type: 20.4 g per container, containing 24.0 mg of salbutamol, liquid concentration: 0.1176% (g/g), spraying dose: 0.10 mg

Storage Preserve in well closed containers, stored in cool place, protected from light.

Salbutamol Sulfate



($C_{13}H_{21}NO_3$)₂ · H₂SO₄ 576.71

[51027-70-9]

Salbutamol Sulfate is 1-(4-hydroxy-3-hydroxy-methylphenyl)-2-(tert-butyl-amino) ethanol sulfate (2 : 1) (salt). It contains not less than 98.0% of ($C_{13}H_{21}NO_3$)₂ · H₂SO₄, calculated on the dried basis.

Description A white or almost white powder; odourless; taste, slightly bitter. Freely soluble in water; very slightly soluble in ethanol; practically insoluble in chloroform or ether.

Identification (1) Dissolve 20 mg in 2 ml of water, add 1 drop of ferric chloride TS and shake; a violet colour is produced which turns to cloudy orange yellow on addition of sodium bicarbonate TS.

(2) Dissolve about 10 mg in 20 ml of 0.4% borax solution, add 1 ml of 3% 4-aminoantipyrine solution and 1 ml of 2% potassium ferricyanide solution. Add 10 ml of chloroform, shake and allow it to stand; an orange-red colour is produced in the chloroform layer.

(3) The light absorption of a solution of 0.08 mg per ml in water exhibits a maximum at 276 nm (Appendix IV A).

(4) The infrared absorption spectrum (Appendix IV C) is concordant with the reference spectrum of Salbutamol sulfate (Appendix XVI).

(5) The aqueous solution yields the reactions characteristic of sulfates (Appendix III).

Clarity and colour of solution A solution of 0.5 g in 10 ml of water is clear and colourless. Any opalescence produced is not more pronounced than that of reference suspension 1 (Appendix IX B) and any colour produced is not more intense than that of reference solution Y₂ (Appendix IX A, method 1).

Related substances Carry out the method for thin-layer chromatography (Appendix V B), using silica gel G as the coating substance and a mixture of concentrated ammonia solution-water-isopropanol-ethyl acetate (4 : 16 : 30 : 50) as the mobile phase. Apply separately to the plate 4 µl each of two solutions of the substance being examined in water containing (1) 50 mg per ml, (2) 0.50 mg per ml. After developing and removal of the plate, allow it to dry in air. Place the plate in an atmosphere saturated with diethylamine for 5 minutes and spray with diazotised sulfanilic acid solution. Any spot in the chromatogram obtained with solution (1), other than the principal spot, is not more intense than the principal spot obtained with solution (2).

Loss on drying When dried in vacuum to constant weight at 60°C, loses not more than 0.5% of its weight (Appendix VIII L).

Residue on ignition Not more than 0.1% (Appendix VIII N).

Assay Dissolve about 0.4 g, accurately weighed, in 10 ml of glacial acetic acid on gentle heating and cool. Add 15 ml of acetic anhydride and a drop of crystal violet IS, titrate with perchloric acid (0.1 mol/L) VS until the colour changes to bluish-green. Perform a blank determination and make any necessary correction. Each ml of perchloric acid (0.1 mol/L) VS is equivalent to 57.67 mg of (C₁₃H₂₁NO₃)₂ · H₂SO₄.

Category β-Adrenergic receptor activating agent.

Storage Preserve in tightly closed containers, protected from light.

Preparation (1) Salbutamol Sulfate Capsules
(2) Salbutamol Sulfate Injection
(3) Salbutamol Sulfate Sustained-release Tablets
(4) Salbutamol Sulfate Sustained-release Capsules
(5) Salbutamol Sulfate Tablets

Salbutamol Sulfate Capsules

Salbutamol Sulfate Capsules contain not less than 90.0% and not more than 110.0% of the labelled amount of salbutamol sulfate [(C₁₃H₂₁NO₃)₂ · H₂SO₄].

Identification To the powdered contents of 20 capsules, add 20 ml of water, shake to dissolve and filter. The filtrate complies with tests for Identification (1), (2), (3), (5) described under Salbutamol Sulfate.

Loss on drying When dried in vacuum at 60°C over

phosphorus pentoxide to constant weight, loses not more than 7.0% of its weight. (Appendix VIII L).

Other requirements Comply with the general requirements for capsules (Appendix I E).

Assay Weigh accurately the mixed powered contents obtained in the test for weight variation of contents, equivalent to about 8 mg of salbutamol sulfate, to a 100 ml volumetric flask, add about 50 ml of water, shake to dissolve salbutamol sulfate. Dilute to volume with water, mix well and filter (repeat filter with the same filter paper if the filtrate is not clear). Measure the absorbance of the successive filtrate at 276 nm (Appendix IV A), calculate the content of (C₁₃H₂₁NO₃)₂ · H₂SO₄, taking 59 as the value of A (1%, 1 cm).

Category As described under salbutamol sulfate.

Strength 2.4 mg (equivalent to 2 mg of salbutamol)

Storage Preserve in tightly closed containers, protected from light.

Salbutamol Sulfate Injection

Salbutamol Sulfate Injection is a sterile solution of salbutamol sulfate in Water for Injection. It contains not less than 90.0% and not more than 110.0% of the labelled amount of salbutamol sulfate [(C₁₃H₂₁NO₃)₂ · H₂SO₄].

Description A clear, colourless liquid.

Identification (1) Evaporate a quantity, equivalent to about 2.4 mg of salbutamol sulfate, to 1 ml on a water bath, add 2 drops of ferric chloride TS and mix well, a violet colour is produced, which turns to turbid orange-yellow on addition of sodium bicarbonate TS.

(2) Evaporate a quantity, equivalent to about 2.4 mg of salbutamol sulfate, to 3 ml on a water bath, add 15 ml of 0.4% borax solution, 1 ml of 3% 4-aminoantipyrine solution, 1 ml of 2% potassium ferricyanide solution and 5 ml of chloroform, shake, allow to stand. An orange-red colour is produced in the chloroform layer.

(3) The light absorption of a solution obtained in the Assay exhibits a maximum at 276 nm (Appendix IV A).

(4) Yields the reactions characteristic of sulfates (Appendix III).

pH value 3.0-4.5 (Appendix VI H).

Other requirements Complies with the general requirements for injections (Appendix I B).

Assay Measure accurately a quantity equivalent to about 2.4 mg of salbutamol sulfate into a 25 ml volumetric flask, dilute with water to volume and mix well. Measure the absorbance of the solution at 276 nm (Appendix IV A), calculate the content of (C₁₃H₂₁NO₃)₂ · H₂SO₄, taking 59 as the value of A (1%, 1 cm).

Category As described under salbutamol sulfate.

Strength 2 ml : 0.48 mg (equivalent to 0.4 mg of salbutamol)

Storage Preserve in well closed containers, protected from light.

Salbutamol Sulfate Sustained-release Capsules

Salbutamol Sulfate Sustained-release Capsules contain not less than 90.0% and not more than 110.0% of the labelled amount of salbutamol ($C_{13}H_{21}NO_3$).

Description Capsules containing white or almost white pills.

Identification (1) The retention time of the principle peak of the substance being examined in the chromatogram obtained in the Assay is identical with that of the principle peak of salbutamol sulfate CRS in the chromatogram of the reference solution.

(2) Weigh a quantity of powdered contents, equivalent to about 20 mg of salbutamol, add 10 ml of water and shake to dissolve salbutamol sulfate. The filtrate yields the reactions characteristic of sulfates (Appendix III B).

Content uniformity Comply with the requirements for content uniformity (Appendix X E). Triturate the content of 1 capsule in a mortar. Add a quantity amount of 0.1 mol/L hydrochloric acid, triturate and transfer into a 50 ml (for strength 4 mg) or a 100 ml volumetric flask (for strength 8 mg), in an ultrasonic bath for 15 minutes, cool, dilute with 0.1 mol/L hydrochloric acid to the volume, mix well and filter. Carry out the procedure as described under the Assay, calculate the content of $C_{13}H_{21}NO_3$.

Drug Release Carry out the method for drug release test (Appendix X D, method 1) and use the apparatus for dissolution test (Appendix X C, method 2), using 500 ml of phosphate BS [Dissolve 6.8 g of potassium dihydrogen phosphate in 900 ml water, adjust to pH 3 ± 0.5 with phosphoric acid, dilute with water to 1000 ml] as the release medium, adjust the rotation speed of the paddle to 100 rpm. Withdraw a sample of 5 ml of the solution at exact 1, 4 and 8 hours respectively, filter and supply 5 ml of release medium accordingly in the vessel immediately. Carry out the chromatographic conditions as described under the Assay. Accurately inject 20 μ l of the successive filtrate into the column and record the chromatogram. Dissolve an accurately weighed quantity of salbutamol sulfate CRS in release medium to produce a solution of 8 μ g per ml (for strength 4 mg) or 16 μ g per ml (for strength 8 mg), measure in the same manner. Calculate the content of $C_{13}H_{21}NO_3$ dissolved from each capsule at 1, 4 and 8 hours separately by multiplying the percentage content of $C_{13}H_{21}NO_3 \cdot H_2SO_4$ by 0.8299. The dissolution complies with the following requirements; the quantity dissolved of each capsule is less than 40%, 45%-80% and over 75% of the labelled amount at 1, 4 and 8 hours respectively.

Other requirements Comply with the general requirements for capsules (Appendix I E).

Assay Carry out the method for high performance liquid chromatography (Appendix V D), using a column packed with octadecylsilane bonded silica gel and a mixture of 0.005 mol/L ammonium biphosphate solution (pH 3.0)-methanol (75 : 25) as the mobile phase. Detection wavelength is 224 nm and the number of theoretical plates of the column is not less than 2000, calculated with reference to the peak of salbutamol sulfate.

Procedure Weigh accurately the contents of 10 capsules, triturate and mix well. Weigh accurately a quantity of powder, equivalent to about 8 mg of salbutamol, in a 100 ml volumetric flask, add a quantity of 0.1 mol/L hydrochloric

acid, in an ultrasonic bath for 15 minute to dissolve salbutamol sulfate and dilute with 0.1 mol/L hydrochloric acid to volume, mix well and filter. Accurately inject 20 μ l of the successive filtrate into the column and record the chromatogram. Dissolve an accurately weighed quantity of salbutamol sulfate CRS in 0.1 mol/L hydrochloric acid to produce a solution of 80 μ g per ml, measure in the same manner. Calculate the content of $C_{13}H_{21}NO_3$ by multiplying the percentage content of $C_{13}H_{21}NO_3 \cdot H_2SO_4$ by 0.8299.

Category As described under Salbutamol Sulfate.

Strength (1) 4 mg (2) 8 mg ($C_{13}H_{21}NO_3$)

Storage Preserve in tightly closed containers, stored in a dry place and protected from light.

Salbutamol Sulfate Sustained-release Tablets

Salbutamol Sulfate Sustained-release Tablets contain not less than 90.0% and not more than 110.0% of the labelled amount of salbutamol ($C_{13}H_{21}NO_3$).

Description White or almost white tablets.

Identification (1) Weigh a quantity of powdered tablets, equivalent to about 50 mg of salbutamol, add 2 ml of water and shake to dissolve salbutamol sulfate. Filter and add 1 drop of ferric chloride to a proper amount of filtrate, shake, a violet colour is produced. Add drops of sodium bicarbonate TS, an orange-yellow turbidity is produced.

(2) Weigh a quantity of powdered tablets, equivalent to about 10 mg of salbutamol, add 20 ml of 0.4% sodium borate solution and shake to dissolve salbutamol sulfate. Add 1 ml of 3% 4-aminodimethyloxycinchin solution and 1 ml of 2% potassium ferricyanide solution. Add 10 ml of chloroform, shake and allow to stand for stratification. An orange-red colour is produced in the chloroform layer.

(3) The retention time of the principle peak of the substance being examined in the chromatogram obtained in the Assay is identical with that of the principle peak of salbutamol sulfate CRS in the chromatogram of the reference solution.

(4) The filtrate obtained in the test (1) for Identification yields the reactions characteristic of sulfates (Appendix III).

Content uniformity Comply with the requirements for content uniformity (Appendix X E). Triturate 1 tablet in a mortar and transfer with water in portions to a 100 ml volumetric flask. Shake to dissolve salbutamol sulfate and dilute with water to volume, mix well and filter. Carry out the procedure as described under the Assay beginning at the words "Accurately inject 20 μ l of the successive filtrate into the column...", calculate the content of $C_{13}H_{21}NO_3$.

Drug Release Carry out the method for drug release test (Appendix X D) and use the apparatus for dissolution test (Appendix X C, method 3), using 250 ml of hydrochloric acid (9 \rightarrow 1000) as the release medium in the first 2 hours, then changed by 250 ml of phosphate BS (pH 6.8), adjust the rotation speed of the paddle to 100 rpm. Withdraw a sample of 5 ml of the solution at exact 2, 4 and 8 hours respectively, filter and supply 5 ml of phosphate BS (pH 6.8) accordingly in the vessel immediately. Carry out the chromatographic conditions as described under the Assay. Accurately inject 20 μ l of the successive filtrate into the column and record the chromatogram. Respectively dissolve an accurately weighed quantity of salbutamol sulfate CRS in hydrochloric acid (9 \rightarrow 1000) and phosphate BS (pH 6.8) to produce a solution of 32 μ g per ml, measure in the same manner. Calculate the content of $C_{13}H_{21}NO_3$ dissolved from

each capsule at 2, 4 and 8 hours separately by multiplying the percentage content of $C_{13}H_{21}NO_3 \cdot H_2SO_4$ by 0.8299. The dissolution complies with the following requirements; the quantity dissolved of each tablet is 35%-55%, 55%-75% and over 75% of the labelled amount at 2, 4 and 8 hours respectively.

Other requirements Comply with the general requirements for tablets (Appendix I A).

Assay Carry out the method for high performance liquid chromatography (Appendix V D), using a column packed with octadecylsilane bonded silica gel and a mixture of phosphate BS [Dissolve 9.77 g of sodium dihydrogen phosphate in 1000 ml of water, adjust to pH 3.10 ± 0.05 with phosphoric acid] -methanol (85 : 15) as the mobile phase. Detection wavelength is 276 nm and the number of theoretical plates of the column is not less than 2000, calculated with reference to the peak of salbutamol sulfate.

Procedure Weigh accurately 20 tablets and powder. Weigh accurately a quantity, equivalent to about 8 mg of salbutamol, in a 100 ml volumetric flask, add a quantity of water, shake to dissolve salbutamol sulfate and dilute with water to volume, mix well and filter. Accurately inject 20 μ l of the successive filtrate into the column and record the chromatogram. Dissolve an accurately weighed quantity of salbutamol sulfate CRS in water to produce a solution of 80 μ g per ml, measure in the same manner. Calculate the content of $C_{13}H_{21}NO_3$ by multiplying the percentage content of $C_{13}H_{21}NO_3 \cdot H_2SO_4$ by 0.8299.

Category As described under Salbutamol Sulfate.

Strength 8 mg ($C_{13}H_{21}NO_3$)

Storage Preserve in tightly closed containers, stored in a dry place and protected from light.

Salbutamol Sulfate Tablets

Salbutamol Sulfate Tablets contain not less than 90.0% and not more than 110.0% of the labelled amount of salbutamol sulfate [$(C_{13}H_{21}NO_3)_2 \cdot H_2SO_4$].

Description White tablets.

Identification Powder 20 tablets, extract with 20 ml of water and filter. The filtrate complies with the tests (1), (2), (3) and (5) for Identification described under Salbutamol Sulfate.

Content uniformity Comply with the requirements for content uniformity (Appendix X E). Shake 1 tablet in a 25 ml volumetric flask with a quantity of mobile phase to dissolve salbutamol sulfate. Dilute to volume with mobile phase, mix well and filter. Carry out the method as described under Assay beginning at the words "Inject 20 μ l of the successive filtrate into the column...", calculate the content of $(C_{13}H_{21}NO_3)_2 \cdot H_2SO_4$.

Other requirements Comply with the general requirements for tablets (Appendix I A).

Assay Carry out the method for high performance liquid chromatography (Appendix V D), using a column packed with octadecylsilane bonded silica gel and a mixture of sodium dihydrogen phosphate solution (Dissolve 11.04 g of sodium dihydrogen phosphate ($NaH_2PO_4 \cdot 2H_2O$) in water in a 1000 ml volumetric flask and dilute to volume and adjusting to pH 3.10 ± 0.05 with phosphoric acid) -methanol (85 : 15) as the mobile phase. Detection wavelength is 276 nm

and the number of the theoretical plates of the column is not less than 3000, calculated with reference to the peak of salbutamol sulfate.

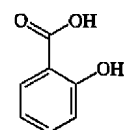
Procedure Weigh accurately and powder 10 tablets. Add a sufficient quantity of mobile phase to an accurately weighed quantity, equivalent to about 4.8 mg of salbutamol sulfate, in a 50 ml volumetric flask, shake to dissolve salbutamol sulfate. Dilute to volume with mobile phase, mix well and filter. Inject 20 μ l of the successive filtrate into the column, record the chromatogram. Dissolve a quantity of salbutamol sulfate CRS in mobile phase to produce a solution of 96 μ g per ml, repeat the operation. Calculate the content of $(C_{13}H_{21}NO_3)_2 \cdot H_2SO_4$ by external method.

Category As described under Salbutamol Sulfate.

Strength (1) 0.6 mg (equivalent to 0.5 mg of salbutamol)
(2) 2.4 mg (equivalent to 2 mg of salbutamol)

Storage Preserve in tightly closed containers, protected from light.

Salicylic Acid



$C_7H_6O_3$ 138.12

[69-72-7]

Salicylic Acid is 2-hydroxy-benzoic acid. It contains not less than 99.5% of $C_7H_6O_3$.

Description White needle crystals or a white crystalline powder; odourless or almost odourless; taste, slightly sweet then uncomfortable. The aqueous solution exhibits acid reaction.

Freely soluble in ethanol or ether; soluble in boiling water; sparingly soluble in chloroform; slightly soluble in water.

Melting range 158-161°C (Appendix VI C).

Identification (1) To the aqueous solution add 1 drop of ferric chloride TS, a violet colour is produced.

(2) The infrared absorption spectrum (Appendix IV C) is concordant with the reference spectrum of salicylic acid (Appendix XVI).

Phenol Dissolve 0.10 g in 2 ml of ethanol, add 0.7 ml of sodium hydroxide TS and 2 ml of ammonia-ammonium chloride BS (pH 10.0), then add 0.5 ml of 2% 4-amino-antipyrine solution, mix well. Add 0.25 ml of potassium ferricyanide TS, mix well. Extract with 10, 5 and 5 ml of chloroform and combine the chloroform solution. Any colour produced is not more intense than that of a reference solution using 1.0 ml (0.10 g/ml) of phenol standard solution (0.10%).

Residue on ignition Not more than 0.1% (Appendix VII N).

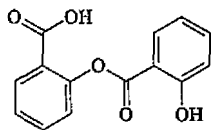
Heavy metals Dissolve 1.0 g in 23 ml of ethanol, add 2 ml of acetate BS (pH 3.5). Carry out the limit test for heavy metals (Appendix VII H, method 1): Not more than 0.001%.

Assay Dissolve about 0.3 g, accurately weighed, in 25 ml of neutral dilute ethanol (neutral to phenolphthalein IS), add 3 drops of phenolphthalein IS, titrate with sodium hydroxide (0.1 mol/L) VS. Each ml of sodium hydroxide (0.1 mol/L) VS is equivalent to 13.81 mg of $C_7H_6O_3$.

Category Antiseptic, Disinfectant.

Storage Preserve in tightly closed containers.

Salsalate



$C_{14}H_{10}O_5$ 258.22

[552-94-3]

Salsalate is 2-hydroxybenzoic acid-2-carboxyl-phenyl ester. It contains not less than 99.0% of $C_{14}H_{10}O_5$, calculated on the dried basis.

Description White crystalline powder; odourless; taste, slightly bitter.

Freely soluble in ethanol or ether, practically insoluble in water.

Melting range 140-146°C (Appendix VI C).

Identification To about 0.5 g add 5 ml of sodium hydroxide TS, boil, the solution yields the reactions characteristic of salicylates (Appendix III).

Chloride To 1.0 g add 20 ml of water, shake and filter, measure 4 ml of the successive filtrate, carry out the limit test for chloride (Appendix VIII A). Any opalescence produced is not more pronounced than that of a reference using 1 ml of sodium chloride standard solution (0.005%).

Sulfate To 5 ml of the filtrate obtained in the test for chloride add 1 ml of dilute hydrochloric acid and 3 ml of barium chloride TS; no opalescence is produced.

Salicylic acid Dissolve 1.0 g of the substance being examined in 20 ml of chloroform as test solution. Transfer 25 mg of salicylic acid, accurately weighed, to a 100 ml volumetric flask, and dissolve in chloroform, dilute to volume and mix well, accurately measure 20 ml of the resulting as the reference solution. Transfer the above two solutions in the separators respectively, and extract with four 20 ml portions of ferric nitrate solution [dissolve 1 g of ferric nitrate with nitric acid solution (0.1→100) and dilute to 1000 ml]. Filter the ferric nitrate solution to a 100 ml volumetric flask and dilute to volume with ferric nitrate solution, mix well. Measure the absorbance at 530 nm (Appendix IV A). The absorbance of test solution is not more than that of reference solution.

Loss on drying When dried in vacuum over phosphorus pentoxide to constant weight, loses not more than 0.5% of its weight (Appendix VIII L).

Residue on ignition Not more than 0.1% (Appendix VIII N).

Heavy metals To 5 ml filtrate obtained in the test for chloride add a few drops of sodium sulfide TS; no colour is produced.

Assay Dissolve about 0.5 g, accurately weighed, in 40 ml of ethanol, add 0.2 ml of phenolphthalein IS, titrate with sodium hydroxide (0.1 mol/L) VS. Perform a blank determination and make any necessary correction. Each ml of sodium hydroxide (0.1 mol/L) VS is equivalent to 25.82 mg of $C_{14}H_{10}O_5$.

Category Anti-inflammatory, analgesic, non-steroids anti-inflammatory agent.

Storage Preserve in tightly closed containers, protected from light.

Preparation Salsalate Tablets

Salsalate Tablets

Salsalate Tablets contain not less than 95.0% and not more than 105.0% of the labelled amount of salsalate ($C_{14}H_{10}O_5$).

Description White tablets.

Identification To a quantity of the powdered tablets equivalent to about 0.3 g of salsalate add 5 ml of sodium hydroxide TS, shake to dissolve salsalate, filter, boil the filtrate. The filtrate complies with the test for Identification described under Salsalate.

Salicylic acid Transfer a quantity of the powdered tablets equivalent to about 0.3 g of salsalate, accurately weighed, to a separator, dissolve with 50 ml of chloroform, add 2.5 ml of 1 mol/L hydrochloric acid and 7.5 ml of water, shake. Filter the chloroform, and wash with 10 ml chloroform. Combine the chloroform as the test solution. Transfer 45 mg of salicylic acid, accurately weighed, to a 50 ml volumetric flask. Dissolve with chloroform and dilute to volume, and mix well. Accurately measure 5 ml of the solution, add 50 ml of chloroform, take the resulting solution as the reference solution. Transfer the above two solution in the separators respectively, and extract with four 20 ml portions of ferric nitrate solution [dissolve 1 g of ferric nitrate with nitric acid solution (0.1→100) and dilute to 1000 ml]. Filter the ferric nitrate solution to a 100 ml volumetric flask, and dilute to volume with ferric nitrate solution, mix well. Measure the absorbance at 530 nm (Appendix IV A). The absorbance of test solution is not more than that of reference solution.

Other requirements Comply with the general requirements for tablets (Appendix I A).

Assay Weigh accurately and powder 20 tablets. Dissolve a quantity, accurately weight, equivalent to about 0.3 g of salsalate, in 40 ml of ethanol with shaking, add 0.2 ml of phenolphthalein IS, titrate with sodium hydroxide (0.1 mol/L) VS. Perform a blank determination and make any necessary correction. Each ml of sodium hydroxide (0.1 mol/L) VS is equivalent to 25.82 mg of $C_{14}H_{10}O_5$.

Category As described under Salsalate.

Strength 0.3 g

Storage Preserve in tightly closed containers, protected from light.

Saponated Cresol Solution

Saponated Cresol Solution contains not less than 85.0% and not more than 110.0% of the labelled amount of Cresol (C_7H_8O).

Formula	Cresol	500 ml
	Vegetable oil	173 g
	Sodium hydroxide	sufficient (about 27 g)
	Water	sufficient quantity

To make 1000 ml

Processing Dissolve sodium hydroxide in 100 ml of water,

cool and add the solution to vegetable oil with constant stirring to form a uniform emulsion. Allow it to cool for 30 minutes, warm gently by indirect steam or water bath. Continue to stir when the saponified matter becomes darker and transparent. The saponification process is complete if a sample complies with the test for unsaponified matter. Add cresol while hot with constant stirring, cool, add water to produce 1000 ml. Fatty acids of low or medium molecular weight may be used instead of vegetable oils.

Description A yellowish-brown to reddish-brown viscous liquid with odour of cresol.

Miscible with ethanol to form clear liquid.

Alkalinity Dilute 1.0 ml with 20 ml of neutral ethanol (neutral to phenolphthalein IS), add 1 ml of phenolphthalein IS, any red colour produced requires not more than 1.0 ml of 0.5% /L. V g.

Unsaponified matter A solution of 5 ml in 95 ml of water is clear. Any opalescence produced is not more pronounced than that of a reference solution (prepared by mixing of 6 ml of potassium sulfate standard solution with 80 ml of water and 1 ml of dilute hydrochloric acid, match the colour of the solution with cobaltic chloride solution CS and concentrate caramel solution, then add 3 ml of 25% barium chloride solution and water to produce 100 ml, mix well, compared after 10 minutes).

Minimum fill Complies with the requirements for minimum fill (Appendix X F).

Assay Carry out the method for gas chromatography (Appendix V E), using a column packed with 4%-10% polyethylene glycol adipate containing 2% phosphoric acid as the stationary phase, and maintain the column temperature at 145°C. The number of theoretical plates of the column is not less than 400, calculate with reference to the peak of *o*-cresol, and the resolution factor between the peaks of *o*-cresol and the internal standard substance complies with the related requirements.

Dissolve about 1.3 g of salicylaldehyde, accurately weighed, in ether in a 50 ml volumetric flask and dilute to volume, mix well as internal standard solution.

Dissolve about 0.65 g of *o*-cresol CRS, accurately weighed, in ether in a 25 ml volumetric flask and dilute to volume, mix well, as reference solution. Measure accurately 5 ml each of the reference solution and internal standard solution into a test tube with stopper, mix well. Inject 1 µl of the resulting solution into the column, calculate the correction factor for *o*-cresol, multiply by 1.042, that represents the correction factor for *p*-cresol and *m*-cresol.

Procedure Measure accurately 2 ml with a "to contain" pipet into a separator, add 0.1 ml of hydrochloric acid, mix well, add 3 ml of water, mix well again. Add accurately 20 ml of ether, shake gently, allow to stand, discard the aqueous layer, add 5 ml of water, and shaking gently, allow to stand and discard the aqueous layer again. Mix well 5 ml each of the ether extract and 5 ml of internal standard solution, both accurately measured, in a test tube with stopper. Inject 1 µl of the resulting solution into the column. Calculate the content of cresol as follows.

$$\% \text{ of the labelled amount} = \frac{(A_1 f_1 + A_2 f_2) \cdot W}{A \times 5 \times 0.52} \times 100\%$$

Where A is peak area of the internal standard substance;

A₁ is peak area of *o*-cresol;

A₂ is peak area of *m*-cresol and *p*-cresol;

f₁ is correction factor of *o*-cresol;

f₂ is correction factor of *m*-cresol and *p*-cresol;

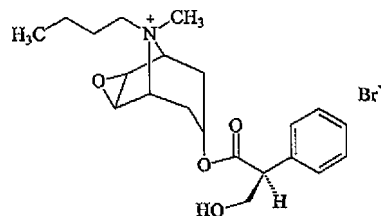
W is weight of the internal standard (g);

0.52 is the content of cresol (g/ml) in the formula.

Category As described under Cresol.

Storage Preserve in tightly closed containers, protected from light.

Scopolamine Butylbromide



C₂₁H₃₀BrNO₄ 440.38

[149-64-4]

Scopolamine Butylbromide is (1*S*,3*S*,5*R*,6*R*,7*S*,8*S*)-6,7-epoxy-8-butyl-3-[(*S*)-tropoyloxy] tropanium bromide. It contains not less than 99.0% of C₂₁H₃₀BrNO₄, calculated on the dried basis.

Description A white or almost white crystalline powder; odourless or almost odourless.

Freely soluble in water or chloroform, sparingly soluble in ethanol.

Specific optical rotation -18° to -20°, in a solution of about 0.1 g per ml in water.

Identification (1) The light absorption of a solution of 1 mg per ml in hydrochloric acid solution (0.01 mol/L) exhibits maxima at 252 nm, 257 nm, and 264 nm (Appendix IV A).

(2) The infrared absorption spectrum (Appendix IV C) is concordant with the reference of scopolamine butylbromide (Appendix XVI).

(3) Yields the reactions characteristic of tropane alkaloids (Appendix III).

(4) The aqueous solution yields the reactions characteristic of bromides (Appendix III).

Acidity A solution of 0.1 g per ml in water, pH 5.5-6.5 (Appendix VI H).

Clarity of solution A solution of 0.5 g in 15 ml of water is clear.

Scopolamine and related substances Dissolve a quantity in the mobile phase to produce a solution of 2.5 mg per ml as the test solution; dissolve a quantity of scopolamine hydrobromide CRS in the mobile phase to produce a solution of 0.01 mg per ml as the reference solution. Carry out the method for high performance liquid chromatography (Appendix V D), using a column packed with octadecylsilane bonded silica gel and 0.008 mol/L sodium laurylsulfate in a mixture of 0.004% phosphoric acid-acetonitrile (50 : 50) as the mobile phase. Detection wavelength is 210 nm and the number of the theoretical plates of the column is not less than 3000, calculated with reference to the peak of scopolamine butylbromide, the resolution factor between the peaks of scopolamine butylbromide and scopolamine hydrobromide complies with the related requirements. Inject 10 µl of the reference solution into the column, adjust the attenuation so that the principal peak height in the chromatogram is about 20% of the full scale of the chat. Inject separately 10 µl of the reference solution and the test solution into the column, and record the chromatogram for twice the retention time of the principal peak. The peak area of scopolamine hydrobromide is not greater than that of the principal peak in

the chromatogram obtained with the reference solution (0.4%); The sum of the areas of all impurity peaks other than the bromine peak near the solvent is not greater than twice the area of the principal peak in the chromatogram obtained with the reference solution.

Loss on drying When dried to constant weight at 105°C, loses not more than 2.5% of its weight (Appendix VIII L).

Residue on ignition Not more than 0.1% (Appendix VIII N).

Assay Dissolve about 0.3 g, previously dried to constant weight at 105°C and accurately weighed, in 20 ml of glacial acetic acid, heat gently if necessary, add 5 ml of mercuric acetate TS and 1 drop of crystal violet IS. Titrate with perchloric acid (0.1 mol/L) VS until the colour changes to pure blue. Perform a blank determination and make any necessary correction. Each ml of perchloric acid (0.1 mol/L) VS is equivalent to 44.04 mg of $C_{21}H_{30}BrNO_4$.

Category Anticholinergic.

Storage Preserve in tightly closed containers, protected from light.

Preparations (1) Scopolamine Butylbromide Capsules
(2) Scopolamine Butylbromide Injection

Scopolamine Butylbromide Capsules

Scopolamine Butylbromide Capsules contain not less than 90.0% and not more than 110.0% of the labelled amount of scopolamine butylbromide ($C_{21}H_{30}BrNO_4$).

Identification (1) To a quantity of the contents of the capsules equivalent to about 50 mg of scopolamine butylbromide add 20 ml of chloroform, shake to dissolve scopolamine butylbromide. Filter and evaporate the filtrate to dryness on a water bath, dissolve the residue in 50 ml of hydrochloric acid solution (0.01 mol/L), the light absorption of the resulting solution exhibits maxima at 252 nm, 257 nm and 264 nm (Appendix IV A).

(2) Dissolve a quantity of the contents of the capsules equivalent to about 10 mg of scopolamine butylbromide in 5 ml of chloroform with shaking, filter it rapidly, evaporate the filtrate to dryness on a water bath, the residue yields the reaction characteristic of tropane alkaloids (Appendix III).

(3) The aqueous solution yields the reactions characteristic of bromides (Appendix III).

Related substances Carry out the method for thin-layer chromatography (Appendix V B), using silica gel G as the coating substance and a mixture of acetone-concentrated ammonia solution (95 : 3) as the mobile phase. Apply separately to the plate 20 µl of each of two solutions containing (1) 0.10 g of the substance being examined per ml in chloroform (dissolve a quantity of the contents of the capsules equivalent to about 0.10 g of scopolamine butylbromide in 10 ml of chloroform with shaking, filter and wash the residue with 5 ml of chloroform, combine the washing and filtrate, evaporate to dryness on a water bath, dissolve the residue in 1 ml of chloroform.). (2) 0.5 mg of scopolamine butylbromide CRS per ml in ethanol. After developing and removal of the plate, dry it in air and spray with dilute potassium iodobismuthate TS. Not more than 1 spot, other than the principal spot, obtained with solution (1) is observed, and it is not more intense than the principal spot obtained with solution (2).

Content uniformity Comply with the requirements for content uniformity (Appendix X E). Transfer the content

of 1 capsule to a 25 ml volumetric flask, wash the shell with water in divided portions, transfer the washings to the same volumetric flask, add 15 ml of water, shake thoroughly to dissolve scopolamine butylbromide, dilute with water to volume, mix well and allow to stand, use the supernatant liquid as the test solution. Carry out the procedure as described under the Assay. Calculate the content of $C_{21}H_{30}BrNO_4$.

Other requirements Comply with the general requirements for capsules (Appendix I E).

Assay Carry out the method for high performance liquid chromatography (Appendix V D), using a column packed with octadecylsilane bonded silica gel and 0.008 mol/L sodium laurylsulfate in a mixture of 0.004% phosphoric acid-acetonitrile (50 : 50) as the mobile phase. Detection wavelength is 210 nm and the number of the theoretical plates of the column is not less than 3000, calculated with reference to the peak of scopolamine butylbromide, the resolution factor between the peaks of scopolamine butylbromide and scopolamine hydrobromide complies with the related requirements.

Procedure Weigh and mix the contents of 20 capsules, dissolve a quantity, weighed accurately, equivalent to about 20 mg of scopolamine butylbromide in the mobile phase to produce a solution of 0.4 mg per ml, filter. Inject 20 µl of the successive filtrate into the column, record the chromatogram; Dissolve a quantity of scopolamine butylbromide CRS, weighed accurately, in the mobile phase to produce a solution of 0.4 mg per ml, repeat the test, calculate the content of $C_{21}H_{30}BrNO_4$ with respect to the peak area by external standard method.

Category As described under Scopolamine Butylbromide.

Strength 10 mg

Storage Preserve in tightly closed containers, protected from light.

Scopolamine Butylbromide Injection

Scopolamine Butylbromide Injection is a sterile solution of Scopolamine Butylbromide in Water for Injection. It contains not less than 93.0% and not more than 107.0% of the labelled amount of scopolamine butylbromide ($C_{21}H_{30}BrNO_4$).

Description A clear, colourless liquid.

Identification (1) Complies with the test (1) and (4) for Identification described under Scopolamine Butylbromide.

(2) Evaporate 0.5 ml of the injection to dryness on a water bath, the residue yields the reactions characteristic of tropane alkaloids (Appendix III).

pH value 3.7-5.5 (Appendix VI H).

Scopolamine and related substance Dilute a quantity with the mobile phase to produce two solutions containing scopolamine hydrobromide 2 mg per ml (1) and 40 µg per ml (2) respectively; dissolve a quantity of scopolamine hydrobromide CRS in the mobile phase to produce a solution of 20 µg per ml (3). Carry out the method as described under the Assay. Inject 10 µl of solution (3) into the column, adjust the attenuation so that the principal peak height in the chromatogram is about 20% of the full scale of the chat. Inject separately 10 µl of the three solutions into the column, and record the chromatogram for twice the retention time of the principal peak. The peak area of the

scopolamine hydrobromide is not greater than that of the principal peak in the chromatogram obtained with the solution (3) (1.0%); The sum of the areas of all impurity peaks other than the bromine peak near the solvent is not greater than twice the area of the principal peak in the chromatogram obtained with the solution (2).

Other requirements Complies with the general requirements for injections (Appendix I B).

Assay Carry out the method for high performance liquid chromatography (Appendix V D), using a column packed with octadecylsilane bonded silica gel and 0.008 mol/L sodium laurylsulfate in a mixture of 0.004% phosphoric acid-acetonitrile (50 : 50) as the mobile phase. Detection wavelength is 210 nm and the number of the theoretical plates of the column is not less than 3000, calculated with reference to the peak of scopolamine butylbromide, the resolution factor between the peaks of scopolamine butylbromide and scopolamine hydrobromide complies with the related requirements.

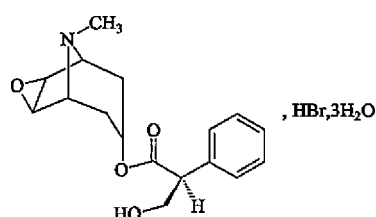
Procedure Measure accurately a quantity, dilute with the mobile phase to produce a solution of 0.4 mg per ml. Inject 20 μ l into the column, record the chromatogram. Dissolve a quantity of scopolamine butylbromide CRS, weighed accurately, in the mobile phase to produce a solution of 0.4 mg per ml, repeat the test, calculate the content of $C_{17}H_{21}NO_4 \cdot HBr$ with respect to the peak area by external standard method.

Category As described under Scopolamine Butylbromide.

Strength 1 ml : 20 mg

Storage Preserve in tightly closed containers, protected from light.

Scopolamine Hydrobromide



$C_{17}H_{21}NO_4 \cdot HBr \cdot 3H_2O$ 438.32 [114-49-8]

Scopolamine Hydrobromide is 6 β , 7 β -epoxy-1 α H, 5 α H-tropane-3 α -ol (-) trobate (ester) hydrobromide trihydrate. It contains not less than 99.0% of $C_{17}H_{21}NO_4 \cdot HBr$, calculated on the dried basis.

Description Colourless crystals or a white, crystalline powder; odourless; slightly efflorescent. Freely soluble in water; sparingly soluble in ethanol; very slightly soluble in chloroform; insoluble in ether.

Melting range 195-199°C, with decomposition (Appendix VI C).

Specific optical rotation -24° to -27° , in a solution of 50 mg per ml in water (Appendix VI E).

Identification (1) Dissolve 10 mg in 1 ml of water in a separator, add ammonia TS to make the solution alkaline, extract with 5 ml of chloroform. Evaporate the chloroform extract to dryness on a water bath. To the residue add 1.5 ml of the ethanolic solution of mercuric chloride (to 2 g of

mercuric chloride add 60% ethanol to produce 100 ml), a white precipitate is produced (distinction from atropine and homatropine).

(2) The infrared absorption spectrum (Appendix IV C) is concordant with the reference spectrum of scopolamine hydrobromide (Appendix XVI).

(3) Yields the reactions characteristic of tropane alkaloids (Appendix III).

(4) The aqueous solution yields the reactions characteristic of bromides (Appendix III).

Clarity of solution A solution of 0.50 g in 15 ml of water is clear.

Acidity Dissolve 0.50 g in 10 ml of water, pH 4.0-5.5 (Appendix VI H).

Other alkaloids Divide a solution of 0.10 g in 2 ml of water into two equal parts. To one part add 2-3 drops of ammonia TS, no turbidity is produced. To the other part add a few drops of potassium hydroxide TS, an almost white turbidity is produced which disappears immediately.

Readily oxidizable substances Dissolve 0.15 g in 5 ml of water, at 15-20°C, add 0.05 ml of potassium permanganate (0.02 mol/L) VS, the red colour is not completely discharged in 10 minutes.

Loss on drying When dried at 60°C for 1 hour and then at 105°C to constant weight, loses not more than 13.0% of its weight (Appendix VIII L).

Assay Dissolve about 0.3 g, previously dried to constant weight at 105°C and accurately weighed, in 20 ml of glacial acetic acid, heat gently if necessary, add 5 ml of mercuric acetate TS and 1 drop of crystal violet IS. Titrate with perchloric acid (0.1 mol/L) VS until the solution becomes pure blue. Perform a blank determination and make any necessary correction. Each ml of perchloric acid (0.1 mol/L) VS is equivalent to 38.43 mg of $C_{17}H_{21}NO_4 \cdot HBr$.

Category Anticholinergic agent.

Storage Preserve in tightly closed containers, protected from light.

Preparations (1) Scopolamine Hydrobromide Injection
(2) Scopolamine Hydrobromide Tablets

Scopolamine Hydrobromide Injection

Scopolamine Hydrobromide Injection is a sterile solution of Scopolamine Hydrobromide in Water for Injection. It contains not less than 90.0% and not more than 110.0% of the labelled amount of scopolamine hydrobromide ($C_{17}H_{21}NO_4 \cdot HBr \cdot 3H_2O$).

Description A clear, colourless liquid.

Identification (1) Evaporate a quantity equivalent to about 2.5 mg of scopolamine hydrobromide to dryness on a water bath. Triturate the residue with 0.5 ml of ethanol to dissolve scopolamine hydrobromide (Solution 1). Dissolve scopolamine hydrobromide CRS in ethanol to prepare a solution of 5 mg per ml (Solution 2). Carry out the method for ascending paper chromatography (Appendix V A), using a piece of chromatographic paper impregnated with a buffer solution (dissolve 0.76 g of anhydrous disodium hydrogen phosphate and 0.18 g of anhydrous potassium dihydrogen phosphate in water to produce 100 ml) and dried in air. Using water saturated *n*-butanol as the mobile phase. Apply to the paper 10 μ l each of the above two solutions;

after developing and removal of the paper, dry it at 105°C for 20 minutes, cool, spray with dilute potassium iodobismuthate TS. The principal spot in the chromatogram obtained with solution (1) is similar in position and colour to that in the chromatogram obtained with solution (2).

(2) Evaporate the ethanol solution obtained in Identification test (1) to dryness on a water bath. The residue yields the reactions characteristic of tropane alkaloids (Appendix III).

(3) Yields the reactions characteristic of bromides (Appendix III).

pH value 3.0-5.0 (Appendix VI H).

Other requirements Complies with the general requirements for injections (Appendix I B).

Assay Measure accurately a quantity equivalent to about 3 mg of scopolamine hydrobromide to a 50 ml volumetric flask, dilute with water to volume and mix well. Carry out the Assay described under Scopolamine Hydrobromide Tablets.

Category As described under Scopolamine Hydrobromide.

Strength (1) 1 ml : 0.3 mg (2) 1 ml : 0.5 mg

Storage Preserve in well closed containers, protected from light.

Scopolamine Hydrobromide Tablets

Scopolamine Hydrobromide Tablets contain not less than 90.0% and not more than 110.0% of the labelled amount of scopolamine hydrobromide ($C_{17}H_{21}NO_4 \cdot HBr \cdot 3H_2O$).

Description White tablets.

Identification (1) Extract a quantity of the finely powdered tablets equivalent to about 3 mg of scopolamine hydrobromide with 2 ml of ethanol and centrifuge, using the supernatant liquid as the test solution; Dissolve scopolamine hydrobromide CRS in ethanol to prepare a solution of 4.5 mg per ml as the reference solution. Carry out the method for ascending paper chromatography (Appendix V A), using a piece of chromatographic paper impregnated with a buffer solution (dissolve 0.76 g of anhydrous disodium hydrogen phosphate and 0.18 g of anhydrous potassium dihydrogen phosphate in water to produce 100 ml) and dried in air. Using water saturated *n*-butanol as the mobile phase. Apply to the paper 30 μ l of the test solution and 10 μ l of the reference solution; after developing and removal of the paper, dry it at 105°C for 20 minutes, cool, spray with dilute potassium iodobismuthate TS. The principal spot in the chromatogram obtained with the test solution is similar in position and colour to that in the chromatogram obtained with the reference solution.

(2) Evaporate the ethanolic solution obtained in Identification test (1) to dryness on a water bath. The residue yields the reactions characteristic of tropane alkaloids (Appendix III).

(3) Shake a quantity of the fine powder with water and filter, the filtrate yields the reactions characteristic of bromides (Appendix III).

Content uniformity Comply with the requirements for content uniformity (Appendix X E).

Triturate 1 tablet with 5 ml, measured accurately, of water to dissolve scopolamine hydrobromide and centrifuge. Carry out the procedure described under Assay, using the supernatant liquid as the test preparation.

Other requirements Comply with the general requirements for tablets (Appendix I A).

Assay Weigh accurately and powder 20 tablets. Weigh

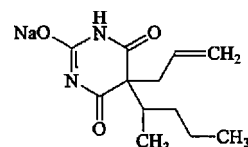
accurately a quantity of the powder equivalent to about 3 mg of scopolamine hydrobromide to a 50 ml volumetric flask, add water to dissolve scopolamine hydrobromide and dilute to volume, mix well and filter, use the successive filtrate as the test solution. Dissolve a quantity of scopolamine Hydrobromide CRS, accurately weighed, and dilute with water to produce a solution of 60 μ g per ml as the reference solution. Measure accurately 2 ml each of the reference solution and test solution to two separators each containing 10 ml of chloroform, accurately measured, add 4.0 ml of bromocresol green solution [dissolve 50 mg of bromocresol green and 1.021 g of potassium hydrogen phthalate in 1.6 ml of hydrochloric acid (0.2 mol/L) VS and add water to produce 100 ml, filter if necessary]. Extract with shaking, allow to stand to separate the chloroform layers. Measure the absorbances of the chloroform solutions at 420 nm (Appendix IV A), calculate the content of $C_{17}H_{21}NO_4 \cdot HBr \cdot 3H_2O$ by multiplying the result with 1.141.

Category As described under Scopolamine Hydrobromide.

Strength 0.3 mg

Storage Preserve in tightly closed containers, protected from light.

Secobarbital Sodium



$C_{12}H_{17}N_2NaO_3$ 260.27

[309-43-3]

Secobarbital Sodium is 5-(1-methylbutyl)-5-(2-propenyl)-2,4,6-(1*H*,3*H*,5*H*)-pyrimidinetrione monosodium salt. It contains not less than 98.5% of $C_{12}H_{17}N_2NaO_3$, calculated on the dried basis.

Description A white powder; odourless; taste, bitter; hygroscopic

Very soluble in water; soluble in ethanol; insoluble in ether.

Identification (1) Dissolve 1 g in 100 ml of water, add 5 ml of dilute acetic acid, stir vigorously, add 200 ml of water, boil to dissolve (no oily substance remaining on the surface of the solution). Cool, allow to stand until crystallizes and filter. The crystals, dried at 70°C, melt at about 97°C (Appendix VI C).

(2) Dissolve 0.1 g in 10 ml of water, add 2 ml of iodine TS, a yellowish-brown colour is produced which disappears within 5 minutes.

(3) The infrared absorption spectrum (Appendix IV C) is concordant with the reference spectrum of secobarbital sodium (Appendix XVI).

(4) Yields the reactions characteristic of malonylureas (Appendix III).

Clarity of solution A solution of 1.0 g in 10 ml of freshly boiled and cooled water is clear.

Neutral and basic substances Complies with the test for neutral and basic substances described under Phenobarbital, using 1.0 g.

Loss on drying When dried to constant weight at 105°C, loses not more than 3.0% of its weight (Appendix VIII L).

Heavy metals Carry out the limit test for heavy metals (Appendix VIII H, method 3); use 1.0 g; not more than

0.002%.

Assay Dissolve 0.1 g, accurately weighed, in a 250 ml iodine flask with 10 ml of water on shaking. Add accurately 25 ml of bromine (0.05 mol/L) VS and 5 ml of hydrochloric acid, stopper the flask immediately and shake for 1 minute, allow to stand in dark for 15 minutes. Add 10 ml of potassium iodide TS, stopper the flask immediately and mix well. Titrate with sodium thiosulfate (0.1 mol/L) VS and add starch IS toward the end of titration and continue the titration until the blue colour disappears. Perform a blank determination and make any necessary correction. Each ml of bromine (0.05 mol/L) VS is equivalent to 13.01 mg of $C_{12}H_{17}N_2NaO_3$.

Category Hypnotic agent.

Storage Preserve in tightly closed containers.

Preparation Secobarbital Sodium Capsules

Secobarbital Sodium Capsules

Secobarbital Sodium Capsules contain not less than 90.0% and not more than 110.0% of the labelled amount of secobarbital sodium ($C_{12}H_{17}N_2NaO_3$).

Identification (1) The contents of the capsules yields the reactions characteristic of malonylureas (Appendix III). (2) The residue obtained by incineration of the contents yields the reactions characteristic of sodium (Appendix III).

Other requirements Comply with the general requirements for capsules (Appendix I E).

Assay Weigh accurately a quantity obtained in the test for weight variation of contents equivalent to about 0.1 g of secobarbital sodium. Carry out the Assay described under Secobarbital Sodium. Each ml of bromine (0.05 mol/L) VS is equivalent to 13.01 mg of $C_{12}H_{17}N_2NaO_3$.

Category As described under Secobarbital Sodium.

Strength 0.1 g

Storage Preserve in tightly closed containers, stored in dry place.

Selenium Sulfide

SeS_2 143.09 [7488-56-4]

Selenium Sulfide contains not less than 52.0% and not more than 55.5% of selenium (Se).

Description An orange-yellow to orange-red powder with a slight odour of hydrogen sulfide. Practically insoluble in water or organic solvents.

Identification (1) To 10 ml of the nitrified solution obtained in the Assay, add 5 ml of water and 5 g of urea, heat to boiling, cool and add 2 ml of potassium iodide TS. A slightly yellow to orange colour is produced which darkens rapidly on standing.

(2) Allow the coloured solution obtained under the Identification (1) to stand for 10 minutes and filter. To the filtrate add 10 ml of barium chloride TS; a precipitate is produced.

Soluble selenium compounds *Reference preparation* Dissolve sodium selenite CRS, accurately weighed, in nitric acid solution (1→30) to produce a solution containing about

1 mg per ml of selenium. Transfer 5 ml of the solution, accurately measured, to a 250 ml volumetric flask, dilute with water to volume and mix well; measure accurately 5 ml of the solution into a 200 ml volumetric flask, dilute with water to volume and mix well (each ml is equivalent to 0.5 µg of Se).

Test preparation To 5.0 g, in a 150 ml flask, add 50.0 ml of water, allow to stand for 1 hour with frequent shaking and filter. Use the filtrate as a test solution.

Procedure To each of 10 ml of the reference solution and the test solution, add 2 ml of 2.5 mol/L formic acid solution, dilute to 50 ml with water, adjust, if necessary, to pH 2.0 to 3.0 with the 2.5 mol/L formic acid solution and mix well. Add 2 ml of a freshly prepared 0.5% solution of diaminobenzidine hydrochloride and mix well, allow to stand for 45 minutes and then adjust to pH 6.0 to 7.0 with ammonia TS. Transfer the solution to a separator, add 10 ml of toluene, accurately measured, and shake vigorously for 1 minute, allow the layers to separate and discard the aqueous phase. Measure the absorbances of the toluene layers at 420 nm (Appendix IV A). The absorbance of the test solution is not greater than that of the reference solution (0.0005%).

Assay To about 0.1 g, accurately weighed, add 25 ml of fuming nitric acid and heat on a water bath for about 1 hour until it is thoroughly nitrified. Cool and transfer the solution to a 100 ml volumetric flask, dilute with water to volume and mix well. To 20 ml, accurately measured, add 10 g of urea and 25 ml of water and heat to boiling. Cool, add 10 ml of potassium iodide TS and 3 ml of starch IS and titrate immediately with sodium thiosulfate (0.05 mol/L) VS until the colour changes from reddish-brown to orange-red. Each ml of sodium thiosulfate (0.05 mol/L) VS is equivalent to 0.987 mg of Se.

Category Antiseborrheic.

Storage Preserve in tightly closed containers, protected from light.

Preparation Selenium Sulfide Lotion

Selenium Sulfide Lotion

Selenium Sulfide Lotion is a suspension of Selenium Sulfide. It contains not less than 90.0% and not more than 110.0% of the labelled amount of Selenium Sulfide (SeS_2).

Description A viscous, orange-yellow suspension with a sweet odour.

Identification Complies with the tests for the Identification described under Selenium Sulfide, using 10 ml of the filtrate obtained in the Assay.

pH value To 25 g, add 50 ml of water and mix well, pH 3.0-5.0 (Appendix VI H).

Other requirements Complies with the general requirements for lotion (Appendix I S).

Assay To a well-mixed and accurately weighed quantity, equivalent to about 100 mg of Selenium Sulfide, add 25 ml of fuming nitric acid, heat on a water bath for 2 hours, cool and transfer the solution to a 100 ml volumetric flask, dilute with water to volume and mix well. Filter and to 20 ml of the successive filtrate, accurately measured, carry out the Assay described under Selenium Sulfide beginning at the words "add 10 g of urea...". Each ml of sodium thiosulfate

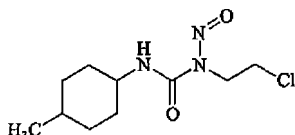
(0.05 mol/L) VS is equivalent to 1.789 mg of SeS_2 .

Category As described under Selenium Sulfide.

Strength (1) 50 g : 1.25 g (2) 100 g : 2.5 g

Storage Preserve in tightly closed containers, stored in a cool and dark place.

Semustine



$\text{C}_{10}\text{H}_{18}\text{ClN}_3\text{O}_2$ 247.72

[13909-09-6]

Semustine is 1-(2-chloroethyl)-3-(4-methylcyclohexyl)-1-nitrosourea. It contains not less than 97.0% and not more than 103.0% of $\text{C}_{10}\text{H}_{18}\text{ClN}_3\text{O}_2$, calculated on the dried basis.

Description A pale yellow with slightly reddish crystalline powder; sensitive to light.

Very soluble in chloroform; soluble in ethanol or cyclohexane; practically insoluble in water.

Melting range 71-75°C (Appendix VI C).

Identification (1) Dissolve 10 mg in 5 ml of ethanol with shaking, add 2 ml of 1% sulfanilamide in dilute hydrochloric acid solution, heat in a water bath for 10 minutes, allow to cool. Add 2 ml of alkaline β -naphthol TS, an orange yellow colour is produced.

(2) The light absorption of the solution obtained in the Assay exhibits a maximum at 232 nm (Appendix IV A).

(3) To about 10 mg add 5 ml of sodium hydroxide TS, heat in a water bath for 5 minutes, the solution yields the reactions characteristic of chlorides (Appendix III).

Chloride To 0.25 g add 20 ml of water, shake thoroughly and filter. Wash the residue with 10 ml of water, combine the filtrate and washings, carry out the limit test for chlorides (Appendix III A). Any opalescence produced is not more pronounced than that of a reference solution using 5.0 ml of sodium chloride standard solution (0.02 %).

Related substances Carry out the method for thin-layer chromatography (Appendix V B), using silica HF_{254} as the coating substance and a mixture of cyclohexane-chloroform (1 : 3) as the mobile phase. Apply separately to the plate 10 μl each of two solutions in ethanol containing (1) 10 mg, (2) 0.1 mg of the substance being examined per ml. After developing and removal of the plate, dry it in air and examine under ultraviolet light (254 nm). Any spot, other than the principal spot in the chromatogram obtained with solution (1), is not more intense than the principal spot obtained with solution (2). Visualize in iodine vapour, no yellow colour exhibits at the original spot.

Loss on drying When dried in vacuum over phosphorous pentoxide for 4 hours, loses not more than 0.5 % of its weight (Appendix VIII L).

Residue on ignition Not more than 0.1% (Appendix VIII N).

Assay Protect from light throughout the operation. Dissolve an accurately weighed quantity in cyclohexane to produce a solution of about 20 μg per ml. Measure the absorbance at 232 nm (Appendix IV A), calculate the content of $\text{C}_{10}\text{H}_{18}\text{ClN}_3\text{O}_2$, taking 254 as the value of A

(1%, 1 cm).

Category Antineoplastic.

Storage Preserve in tightly closed containers, protected from light.

Preparation Semustine Capsules

Semustine Capsules

Semustine Capsules contain not less than 97.0% and not more than 110.0% of the labelled amount of semustine ($\text{C}_{10}\text{H}_{18}\text{ClN}_3\text{O}_2$).

Identification (1) Weigh a quantity of the contents equivalent to about 10 mg of semustine, comply with the test (1) for Identification described under Semustine.

(2) The light absorption of the solution obtained in the Assay exhibits a maximum at 232 nm (Appendix IV A).

Other requirements Comply with the general requirements for capsules (Appendix I E).

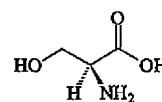
Assay Protect from light throughout the procedure. Weigh accurately a quantity of the mixed contents obtained in the test for Weight variation of contents, equivalent to about 25 mg of semustine, into a 50 ml volumetric flask, add a quantity of cyclohexane to dissolve semustine and shake well, dilute to volume, shake and filtrate. Transfer 2 ml of successive filtrate, accurately measured, into a 50 ml volumetric flask, dilute to volume with cyclohexane, mix well, and carry out the Assay as described under Semustine.

Category As described under Semustine.

Strength (1) 10 mg (2) 50 mg

Storage Preserve in tightly closed containers, protected from light and stored in a cool place.

Serine



$\text{C}_3\text{H}_7\text{NO}_3$ 105.09

[56-45-1]

Serine is (L)-2-amino-3-hydroxypropanoic acid. It contains not less than 98.5% of $\text{C}_3\text{H}_7\text{NO}_3$, calculated on the dried basis.

Description White crystals or a white, crystalline powder; odourless; taste, sweet.

Freely soluble in water; practically insoluble in ethanol, acetone or ether.

Specific optical rotation +14.0° to +16.0°, in a solution of 0.1 g per ml in hydrochloric acid solution (2 mol/L) (Appendix VI E).

Identification The infrared absorption spectrum (Appendix IV C) is concordant with the reference spectrum of serine (Appendix XVI).

Acidity Dissolve 0.30 g in 30 ml of water, pH 5.5-6.5 (Appendix VI H).

Transmittance of solution Dissolve 1.0 g in 20 ml of water, the transmittance at 430 nm is not less than 98.0%

(Appendix IV A).

Chloride Carry out the limit test for chloride (Appendix VIII A), using 0.25 g. Any opalescence produced is not more pronounced than that of a reference solution using 5.0 ml of sodium chloride standard solution (0.02%).

Sulfate Carry out the limit test for sulfate (Appendix VIII B), using 1.0 g. Any opalescence produced is not more pronounced than that of a reference solution using 2.0 ml of potassium sulfate standard solution (0.02%).

Ammonium Carry out the limit test for ammonium (Appendix VIII K), using 0.10 g. Any colour produced is not more intense than that of a reference solution using 2.0 ml of ammonium chloride standard solution (0.2%).

Other amino acids Carry out the method for thin-layer chromatography (Appendix V), using silica gel G as the coating substance and a mixture of *n*-butanol-water-glacial acetic acid (3 : 1 : 1) as the mobile phase. Apply separately to the plate 5 μ l of each of two solutions of the substance being examined in water containing (1) 6 mg per ml, (2) 30 μ g per ml. After developing and removal of the plate, dry in air and spray with ninhydrin solution (dissolve 1 g ninhydrin in 50 ml of acetone) and heat at 80°C until the colour is produced and examine immediately. Any spot, other than the principal spot in the chromatogram, obtained with solution (1) is not more intense than the principal spot obtained with solution (2).

Loss on drying When dried at 105°C for 3 hours, loses not more than 0.2% of its weight (Appendix VIII L).

Residue on ignition Not more than 0.1% (Appendix VIII N).

Iron Carry out the limit test for iron (Appendix VIII G), using 1.0 g. Any colour produced is not more intense than that of a reference solution using 1.0 ml of iron standard solution (0.001%).

Heavy metals Dissolve 2.0 g in 23 ml of water, add 2 ml of acetate BS (pH 3.5). Carry out the limit test for heavy metals (Appendix VIII H, method 1); not more than 0.001%.

Arsenic Dissolve 2.0 g in 23 ml of water, add 5 ml of hydrochloric acid. Carry out the limit test for arsenic (Appendix VIII J, method 1); not more than 0.0001%.

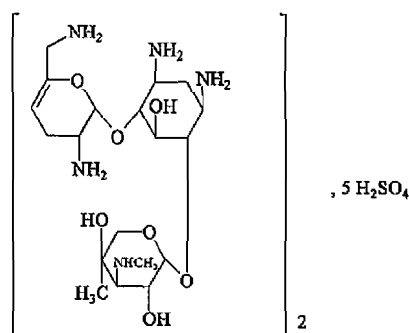
Bacterial endotoxin Carry out the test for bacterial endotoxin (Appendix XI E); less than 12.5 EU per g of serine (for parenteral administration).

Assay Dissolve about 0.1 g, accurately weighed, in 1 ml of dehydrated formic acid, add 25 ml of glacial acetic acid. Carry out the method for potentiometric titration (Appendix VII A), titrate with perchloric acid (0.1 mol/L) VS and perform a blank determination and make any necessary correction. Each ml of perchloric acid (0.1 mol/L) VS is equivalent to 10.51 mg of $C_{19}H_{37}N_5O_7$.

Category Amino acid.

Storage Preserve in tightly closed containers, protected from light.

Sisomicin Sulfate



$(C_{19}H_{37}N_5O_7)_2 \cdot 5H_2SO_4$ 1385.43 [53179-09-2]

Sisomicin Sulfate is O-3-deoxy-4-C-methyl-3-(methylamino)- β -L-arabinopyranosyl-(1 \rightarrow 4)-O-[2,6-diamino-2,3,4,6-tetrahydro-2H-pyran-4-enopyranosyl-(1 \rightarrow 6)]-2-deoxy-L-streptamine sulfate (2 : 5) (salt). It has a potency of not less than 580 Sisomicin Units per mg, calculated on the anhydrous basis.

Description A white or almost white powder; odourless; hygroscopic.

Freely soluble in water; insoluble in ethanol, acetone, chloroform or ether.

Specific optical rotation +100° to +110°, in a solution of 10 mg per ml in water (Appendix VI E).

Identification (1) Carry out the method for thin-layer chromatography (Appendix V B), using silica gel G as the coating substance and a mixture of chloroform-methanol-ammonia solution (5 : 12 : 6) as the mobile phase. Apply separately to the plate 5 μ l each of three solutions in water containing (1) 10 mg per ml of the substance being examined, (2) 10 mg per ml of sisomicin RS, and (3) 5 mg per ml of each of the substance being examined and sisomicin RS. After developing and removal of the plate, allow it to dry in air, and heat at 110°C for 15 minutes, cool, spray with a 1% solution of ninhydrin in *n*-butanol saturated with water (dissolve 1 g of ninhydrin in 100 ml of *n*-butanol containing 1 ml of pyridine). The colour and position of the principal spot in the chromatogram obtained with solution (1) correspond to that in the chromatogram obtained with solution (2), and the solution (3) shows only one principal spot.

(2) The aqueous solution yields the reactions characteristic of sulfates (Appendix III).

Acidity Dissolve a quantity in water to produce a solution of 40 mg per ml, pH 3.5-5.5 (Appendix VI H).

Clarity and colour of solution Dissolve 700 mg each of 5 portions in 5 ml water respectively, the solutions are clear and colourless; any opalescence produced is not more pronounced than that of reference suspension 1 (Appendix IX B); any colour produced is not more intense than that of reference solution Y₂ or YG₂ (Appendix IX A, method 1).

Water Not more than 15.0% (Appendix VIII M, method 1 A).

Residue on ignition Not more than 1.0% (Appendix VIII N).

Bacterial endotoxin Carry out the test for bacterial endotoxin

(Appendix XI E): less than 0.5 EU per 1000 Sisomicin Units.

Assay Carry out the Microbiological assay of antibiotics (Appendix XI A), using a solution of about 1000 Units per ml in phosphate BS (pH 7.8). The fiducial limit is not more than 7%. 1000 Sisomicin Units is equivalent to 1 mg of $C_{19}H_{37}N_5O_7$.

Category Aminoglycosides antibiotic.

Storage Preserve in tightly closed containers, stored in a place below -6°C .

Preparation Sisomicin Sulfate Injection

Sisomicin Sulfate Injection

Sisomicin Sulfate Injection is a sterile solution of sisomicin sulfate in Water for Injection. It contains not less than 90.0% and not more than 110.0% of the labelled amount of sisomicin ($C_{19}H_{37}N_5O_7$).

Description A clear, colourless or almost colourless liquid.

Identification Complies with the tests for Identification described under Sisomicin Sulfate.

pH value 3.0-5.5 (Appendix VI H).

Colour The solution is colourless; any colour produced is not more intense than that of reference solution Y_2 or YG_2 (Appendix IX A, method 1).

Sterility Dilute each vial with not less than 500 ml of 0.9% sterile Sodium Chloride Solution, the solution complies with the test for sterility (Appendix XI H, membrane filtration method).

Bacterial endotoxin Complies with the corresponding requirements described under Sisomicin Sulfate.

Other requirements Complies with the general requirements for injections (Appendix I B).

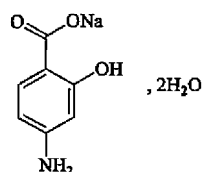
Assay Measure accurately a quantity and carry out the Assay described under Sisomicin Sulfate.

Category As described under Sisomicin Sulfate.

Strength (1) 1 ml : 50000 Units (2) 2 ml : 100000 Units

Storage Preserve in well closed containers, stored in a cool and dark place.

Sodium Aminosalicylate



$C_7H_6NNaO_3 \cdot 2H_2O$ 211.14 [65-49-6]

Sodium Aminosalicylate is sodium 4-amino-2-hydroxybenzoate dihydrate. It contains not less than 99.0% of $C_7H_6NNaO_3$, calculated on the dried basis.

Description White or almost white crystals, or a crystalline powder; odourless; taste, sweetish and saline. Very soluble in water; sparingly soluble in ethanol; insoluble in

ether.

Identification (1) Dissolve about 10 mg in 10 ml of water, acidify with 2 drops of dilute hydrochloric acid and add 1 drop of ferric chloride TS; a violet colour is produced; allow to stand for 3 hours, no precipitate is produced (distinction from 5-aminosalicylate).

(2) The infrared absorption spectrum (Appendix IV C) is concordant with the reference spectrum of sodium para-aminosalicylate (Appendix XVI).

(3) The aqueous solution yields the reactions characteristic of sodium salts (Appendix III).

Acidity or alkalinity A solution of 0.40 g in 20 ml of water, pH 6.5-8.5 (Appendix VI H).

Clarity and colour of solution Dissolve 1.0 g (for oral administration) or 2.0 g (for injection) in 10 ml of water, the solution is clear and colourless. Any opalescence produced is not more pronounced than that of reference suspension 1 (Appendix IX B); any colour produced is not more intense than that of the reference solution Y_6 (Appendix IX A, method 1).

Chloride Dissolve 1.0 g in 25 ml of water, add 2 ml of nitric acid, filter if necessary. Carry out the limit test for chlorides (Appendix VIII A), any opalescence produced is not more pronounced than that of a reference solution using 5.0 ml of sodium chloride standard solution (0.005%).

Sulfate Dissolve 1.0 g in 25 ml of water, add 2 ml of dilute hydrochloric acid, filter. Carry out the limit test for sulfates (Appendix VIII B), any opalescence produced is not more pronounced than that of a reference solution using 5.0 ml of potassium sulfate standard solution (0.05%).

3-Aminophenol To 3.0 g, finely powdered, in a 50 ml beaker add 25 ml of dehydrated ether, stir with a glass rod for 1 minute. Filter the ether extract with caution into a separator. Extract the residue with two portions of 25 ml dehydrated ether. Filter the extracts into the same separator, add 10 ml of water, 1 drop of methylorange IS and mix well. Titrate with hydrochloric acid (0.02 mol/L) VS. Perform a blank determination and make any necessary correction. The hydrochloric acid (0.02 mol/L) VS consumed is not more than 0.30 ml.

Sulfide Dissolve 0.50 g in 5 ml of water, add 5 ml of potassium iodide TS, 2 g of zinc granules and 5 ml of 1.6% stannous chloride solution in hydrochloric acid. Carry out the limit test for sulfides (Appendix VIII C); not more than 0.001%.

Loss on drying When dried to constant weight at 105°C , loses not more than 16.0%-17.5% of its weight (Appendix VIII L).

Iron Mix 1.0 g with 2 g of anhydrous sodium carbonate in a platinum crucible, ignite at about 740°C . Cool and dissolve the residue in 15 ml of dilute hydrochloric acid. Carry out the limit test for iron (Appendix VIII G), the solution is not more intense than a reference solution using 1.5 ml of iron standard solution (0.0015%).

Heavy metals Transfer 1.0 g to a platinum crucible, carry out the limit test for heavy metals (Appendix VIII H, method 2); not more than 0.001%.

Arsenic Transfer 1 g of anhydrous sodium carbonate to a platinum crucible, add 1.0 g of the substance being examined. Moisten with a few drops of water, dry, ignite gently to carbonize, then at $500-600^{\circ}\text{C}$ until free from carbon. Allow to cool, dissolve the residue in a mixture of 5 ml of hydrochloric acid and 23 ml of water. Carry out the limit test for arsenic (Appendix VIII J, method 1); not more than 0.0002%.

Pyrogens Complies with the test for pyrogens (Appendix XI D), using 20 mg per ml (for injection) per kg of the rabbit's weight dissolved in 10 ml of sterile water for injections.

Sterility Complies with the test for sterility (Appendix XI H, membrane filtration method) using 5 ml of a solution of 0.5 g (for injection) per ml in sterile water.

Assay Dissolve about 0.4 g, accurately weighed, in 180 ml of water and 15 ml of hydrochloric acid solution (1→2), carry out the method for dead-stop titration (Appendix VII A), titrate with sodium nitrite (0.1 mol/L) VS. Each ml of sodium nitrite (0.1 mol/L) VS is equivalent to 17.51 mg of $C_7H_5NNaO_3$.

Category Tuberculostatic agent.

Storage Preserve in hermetically sealed containers, protected from light.

Preparation (1) Sodium Aminosalicilate Enteric-coated Tablets
(2) Sodium Aminosalicilate for Injection

Sodium Aminosalicilate Enteric-coated Tablets

Sodium Aminosalicilate Enteric-coated Tablets contain not less than 95.0% and not more than 105.0% of the labelled amount of Sodium Aminosalicilate ($C_7H_5NNaO_3 \cdot 2H_2O$).

Description Enteric-coated tablets, with white or almost white core.

Identification To a quantity of the powdered tablets, with enteric coating removed, equivalent to about 1 g of sodium aminosalicilate, add 25 ml of water, filter and evaporate the filtrate to dryness, complies with the tests (1) and (3) for Identification described under sodium Aminosalicilate.

Other requirements Comply with the general requirements for tablets (Appendix I A).

Assay Weigh and powder 10 tablets. Transfer to a 500 ml volumetric flask with water, dilute to volume, shake thoroughly and filter. Measure accurately 50 ml of the successive filtrate, add 150 ml of water, 20 ml of dilute hydrochloric acid and 3 g of potassium bromide, carry out the method for dead-stop titration (Appendix VII A), titrate with sodium nitrate (0.1 mol/L) VS. Each ml of sodium nitrate (0.1 mol/L) VS is equivalent to 21.11 mg of $C_7H_5NNaO_3 \cdot 2H_2O$.

Category As described under Sodium Aminosalicilate.

Strength 0.5 g

Storage Preserve in tightly closed containers, protected from light.

Sodium Aminosalicilate for Injection

Sodium Aminosalicilate for Injection is a sterile crystalline powder of Sodium Aminosalicilate. It contains not less than 95.0% and not more than 105.0% of the labelled amount of sodium aminosalicilate ($C_7H_5NNaO_3 \cdot 2H_2O$), calculated

on the basis of the average weight of contents.

Description White or almost white crystals, or a crystalline powder.

Identification Complies with the tests (1) and (3) for Identification described under Sodium Aminosalicilate.

Colour of solution Dissolve the content of one container in water to produce a solution of 0.2 g per ml. The solution is not more intense than the reference solution Y_6 (Appendix IX A, method 1).

Loss on drying, Pyrogens, Sterility Complies with the related requirements described under Sodium Aminosalicilate.

Other requirements Complies with the general requirements for injections (Appendix I B).

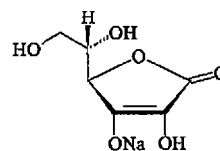
Assay Weigh accurately about 0.4 g of the mixed contents obtained in the test for weight variation of content, dissolve in 180 ml of water and 1.5 ml of hydrochloric acid solution (1→2). Carry out the method for dead-stop titration (Appendix VII A), titrate with sodium nitrite (0.1 mol/L) VS. Each ml of sodium nitrite (0.1 mol/L) VS is equivalent to 21.11 mg of $C_7H_5NNaO_3 \cdot 2H_2O$.

Category As described under Sodium Aminosalicilate.

Strength (1) 2 g (2) 4 g (3) 6 g

Storage Preserve in well closed containers, protected from light.

Sodium Ascorbate



$C_6H_7NaO_6$ 198.11

Sodium Ascorbate is the sodium salt of L-ascorbic acid. It contains not less than 99.0% of $C_6H_7NaO_6$, calculated on the dried basis.

Description White to very slightly yellow crystals or a crystalline powder; odourless; stable in atmosphere, darkens gradually on exposure to light. Freely soluble in water, very slightly soluble in ethanol, insoluble in chloroform or ether.

Specific optical rotation $+103^\circ$ to $+108^\circ$, in a solution of about 0.10 g per ml in water at $25^\circ C$ (Appendix VI E).

Identification (1) To 4 ml of the aqueous solution (1→50), add 1 ml of 0.1 mol/L hydrochloric acid solution and several drops of alkaline cupric tartrate TS, heat, a red precipitate is produced.

(2) The infrared absorption spectrum (Appendix IV C) is concordant with the spectrum of Sodium Ascorbate (Appendix XVI).

(3) The aqueous solution yields the reactions characteristic of sodium salts (Appendix III).

Acidity or alkalinity Dissolve 1.0 g in 10 ml of water, pH 7.0-8.0 (Appendix VI H).

Loss on drying When dried in vacuum over phosphorous pentoxide to constant weight at $60^\circ C$, loses not more than 0.25% of its weight (Appendix VIII L).

Heavy metals Carry out the limit test for heavy metals

(Appendix VIII H, method 2), using 1.0 g: not more than 0.002%.

Assay Dissolve about 0.2 g, accurately weighed, in a mixture of 100 ml of cooled water boiled freshly and 15 ml of 1 mol/L sulfuric acid solution, add 2 ml of starch IS, titrate with iodine (0.05 mol/L) VS until a blue colour persists for at least 30 seconds. Each ml of iodine (0.05 mol/L) VS is equivalent to 9.905 mg of $C_6H_7NaO_5$.

Category Vitamin.

Storage Preserve in tightly closed containers, protected from light.

Sodium Bicarbonate

$NaHCO_3$ 84.01

[144-55-8]

Sodium Bicarbonate contains not less than 99.5% and not more than 100.5% of $NaHCO_3$ (for injection), or not less than 99.0% of $NaHCO_3$ (for oral administration).

Description A white crystalline powder; odourless; taste, salty; decomposes slowly on exposure to moist air. The alkalinity of aqueous solution increases on standing, shaking or warming.

Soluble in water; insoluble in ethanol.

Identification Yields the reactions characteristic of sodium salts and bicarbonates (Appendix III).

Alkalinity Dissolve 0.20 g in 20 ml of water, the pH value is not greater than 8.6 (Appendix VI H).

Clarity of solution A solution of 1.0 g in 20 ml of water is clear (for injection); any opalescence produced is not more pronounced than that of reference suspension 2 (Appendix IX B), (for oral administration).

Chloride Dissolve 1.5 g (for injection) or 0.15 g (for oral administration) in 25 ml of water, acidify with nitric acid dropwise, heat in a water bath to expel carbon dioxide and allow to cool. Carry out the limit test for chlorides (Appendix VIII A). Any opalescence produced is not more pronounced than that of a reference solution using 3.0 ml of sodium chloride standard solution (0.002% for injection or 0.02% for oral administration).

Sulfate Dissolve 3.0 g (for injection) or 0.50 g (for oral administration) in 40 ml of water, acidify with hydrochloric acid dropwise, heat in a water bath to expel carbon dioxide and allow to cool. Carry out the limit test for sulfates (Appendix VIII B). Any opalescence produced is not more pronounced than that of a reference solution using 1.5 ml of potassium sulfate standard solution (0.005% for injection or 0.03% for oral administration).

Ammonium Heat 1.0 g in 10 ml of sodium hydroxide TS, the vapour evolved does not turn a moistened red litmus paper to blue.

Calcium Dissolve 1.0 g in 50 ml of freshly boiled and cooled water, add 1 ml of ammonia TS and 2 ml of ammonium oxalate TS, mix well and allow to stand for 1 hour. Any opalescence produced is not more pronounced than that of a reference solution using 1.0 ml of standard calcium solution (weigh 0.125 g of calcium carbonate to a 500 ml volumetric flask, add a mixture of 5 ml of water and 0.5 ml of hydrochloric acid, dilute with water to volume and mix well. Each ml is equivalent to 0.1 mg of Ca) (0.01% for injection).

Iron Dissolve 3.0 g (for injection) or 1.0 g (for oral

administration) in a quantity of water, acidify with dilute nitric acid, boil for 1 minute, cool and dilute with water to produce 25 ml. Carry out the limit test for iron (Appendix VIII G). Any colour produced is not more intense than that of a reference solution using 1.5 ml of iron standard solution (0.0005% for injection or 0.0015% for oral administration).

Heavy metals Dissolve 4.0 g in a mixture of 19 ml of dilute hydrochloric acid and 5 ml of water, boil for 5 minutes and allow to cool. Add 1 drop of phenolphthalein IS, then add ammonia TS dropwise until pink colour is produced. Add 2 ml of acetate BS (pH 3.5) and sufficient water to produce 25 ml. Carry out the limit test for heavy metals (Appendix VIII H, method 1): not more than 0.0005%.

Arsenic Dissolve 1.0 g in 23 ml of water, add 5 ml of hydrochloric acid, carry out the limit test for arsenic (Appendix VIII J, method 1): not more than 0.0002%.

Assay Dissolve about 1 g, accurately weighed, in 50 ml of water, add 10 drops of methyl red/bromocresol green IS, titrate with hydrochloric acid (0.5 mol/L) VS until the colour turns from green to purplish-red. Boil for 2 minutes, cool to room temperature and continue the titration until the colour turns from green to dark purple. Each ml of hydrochloric acid (0.5 mol/L) VS is equivalent to 42.00 mg of $NaHCO_3$.

Category Antacid.

Storage Preserve in tightly closed containers. Stored in a dry place.

Preparation (1) Sodium Bicarbonate Injection
(2) Sodium Bicarbonate Tablets

Sodium Bicarbonate Injection

Sodium Bicarbonate Injection is a sterile solution of Sodium Bicarbonate in Water for Injection. It contains not less than 95.0% and not more than 105.0% of the labelled amount of sodium bicarbonate ($NaHCO_3$).

It may contain suitable stabilizers.

Description A colourless, clear liquid.

Identification Yields the reactions characteristic of sodium salts and bicarbonates (Appendix III).

pH value 7.5-8.5 (Appendix VI H).

Pyrogens Complies with the test for pyrogens (Appendix XI D), using 10 ml per kg of the rabbit's weight.

Other requirements Complies with the general requirements for injections (Appendix I B).

Assay To a quantity equivalent to about 0.5 g of sodium bicarbonate, accurately measured, add water to produce 50 ml and 10 drops of methyl red/bromocresol green IS, titrate with hydrochloric acid (0.5 mol/L) VS until the colour turns from green to purplish-red. Boil for 2 minutes, cool to room temperature and continue the titration until the colour turns from green to dark purple. Each ml of hydrochloric acid (0.5 mol/L) VS is equivalent to 42.00 mg of $NaHCO_3$.

Category As described under Sodium Bicarbonate.

Strength (1) 10 ml : 0.2 g (2) 10 ml : 0.5 g
(3) 20 ml : 1 g (4) 100 ml : 5 g
(5) 250 ml : 12.5 g (6) 500 ml : 25 g

Storage Preserve in tightly closed containers.

Sodium Bicarbonate Tablets

Sodium Bicarbonate Tablets contain not less than 95.0% and not more than 105.0% of the labelled amount of sodium bicarbonate (NaHCO_3).

Description White tablets.

Identification Shake a quantity of the powdered tablets with water and filter. The filtrate yields the reactions characteristic of sodium salts and bicarbonates (Appendix III).

Carbonate To an accurately weighed quantity of the powdered tablets equivalent to 1.00 g of sodium bicarbonate add 100 ml of freshly boiled and ice cooled water, dissolve the sodium bicarbonate by swirling gently. Add 4-5 drops of phenolphthalein IS, no red colour is produced or becomes colourless on the addition of 1.30 ml of hydrochloric acid (0.5 mol/L) VS.

Other requirements Comply with the general requirements for tablets (Appendix I A), except the tablets disintegrate.

Assay Weigh accurately and powder 10 tablets. To a quantity of the powder equivalent to about 1 g of sodium bicarbonate, accurately weighed, add 50 ml of water and shake to dissolve. Add 10 drops of methyl red/bromocresol green IS, titrate with hydrochloric acid (0.5 mol/L) VS until the colour turns from green to purplish-red. Boil for 2 minutes, cool and continue the titration until the colour turns from green to dark purple. Each ml of hydrochloric acid (0.5 mol/L) VS is equivalent to 42.00 mg of NaHCO_3 .

Category As described under Sodium Bicarbonate.

Strength (1) 0.3 g (2) 0.5 g

Storage Preserve in tightly closed containers, stored in a dry place.

Sodium Chloride

NaCl 58.44 [7647-14-5]

Sodium Chloride contains not less than 99.5% of NaCl, calculated on the dried basis.

Description Colourless, transparent cubic crystals or a white crystalline powder; odourless; taste, salty. Freely soluble in water; practically insoluble in ethanol.

Identification The aqueous solution yields the reactions characteristic of sodium salts and chlorides (Appendix III).

Acidity or alkalinity Dissolve 5.0 g in 50 ml of water, add 2 drops of bromothymol blue IS; not more than 0.10 ml of sodium hydroxide (0.02 mol/L) VS or 0.20 ml of hydrochloric acid (0.02 mol/L) VS is required to change the colour of solution from yellow to blue or from blue or green to yellow.

Clarity of solution A solution of 5.0 g in 25 ml of water is clear.

Iodide Moisten 5.0 g in a porcelain evaporating dish by the dropwise addition of a freshly prepared starch mixture (mix 0.25 g of soluble starch with 2 ml of water, add boiling water to produce 25 ml with stirring, cool and add 2 ml of 0.025 mol/L sulfuric acid solution, 3 drops of sodium nitrite

TS and 25 ml of water and mix well). Examine the mixture in daylight; no particle shows any trace of blue colour within 5 minutes.

Bromide Dissolve 2.0 g in 10 ml of water, add 3 drops of hydrochloric acid and 1 ml of chloroform, and add 3 drops of freshly prepared 2% chloramine T solution with shaking. Any colour produced in the chloroform layer is not more intense than that of a reference solution using 1.0 ml of potassium bromide standard solution (weigh accurately 0.1485 g of potassium bromide, previously dried to constant weight at 105°C, add water to produce 100 ml of solution, mix well).

Sulfate Carry out the limit test for sulfates (Appendix VIII B), using 5.0 g. Any opalescence produced is not more pronounced than that of a reference solution using 1.0 ml of potassium sulfate standard solution (0.002%).

Barium Dissolve 4.0 g in 20 ml of water, filter and divide the filtrate into two equal portions. To one portion add 2 ml of dilute sulfuric acid and to the other portion add 2 ml of water, allow to stand for 15 minutes; both portions are equally clear.

Calcium Dissolve 2.0 g in 10 ml of water, add 1 ml of ammonia TS, mix well, add 1 ml of ammonium oxalate TS; no opalescence is produced within 5 minutes.

Magnesium Dissolve 1.0 g in 20 ml of water, add 2.5 ml of sodium hydroxide TS and 0.5 ml of 0.05% titan yellow solution and mix well. Any colour produced is not more intense than that of a reference solution using 1.0 ml of standard magnesium solution (dissolve 16.58 mg, accurately weighed, of magnesium oxide, previously ignited to constant weight at 800°C, in 2.5 ml of hydrochloric acid and dilute with water to produce 1000 ml, mix well) (0.001%).

Potassium Dissolve 5.0 g in 20 ml of water, add 2 drops of dilute acetic acid, add 2 ml of sodium tetraphenylboron solution (triturate 1.5 g of sodium tetraphenylboron with 10 ml of water, then add 40 ml of water triturate again and filter), add water to produce 50 ml. Any opalescence produced is not more pronounced than that of a reference solution using 12.3 ml of standard potassium sulfate solution (0.02%).

Loss on drying When dried to constant weight at 130°C, loses not more than 0.5% of its weight (Appendix VIII L).

Iron Carry out the limit test for iron (Appendix VIII G) using 5.0 g. Any colour produced is not more intense than that of a reference solution using 1.5 ml of iron standard solution (0.0003%).

Heavy metals Dissolve 5.0 g in 20 ml of water, add 2 ml of acetate BS (pH 3.5) and a quantity of water to produce 25 ml, carry out the limit test for heavy metals (Appendix VIII H, method 1); not more than 0.0002%.

Arsenic Dissolve 5.0 g in 23 ml of water, add 5 ml of hydrochloric acid, carry out the limit test for arsenic (Appendix VIII J, method 1), complies with the test (0.00004%).

Assay Dissolve about 0.12 g, accurately weighed, in 50 ml of water, add 5 ml of dextrin solution (1→50) and 5-8 drops of fluorescein IS, titrate with silver nitrate (0.1 mol/L) VS. Each ml of silver nitrate (0.1 mol/L) VS is equivalent to 5.844 mg of NaCl.

Category Electrolyte supplement.

Storage Preserve in tightly closed containers.

Preparation (1) Sodium Chloride Injection
(2) Sodium Chloride Physiological Injection

(3) Concentrated Sodium Chloride Injection

Sodium Chloride Injection

Sodium Chloride Injection is a sterile and isotonic solution of Sodium Chloride in Water for Injection. It contains not less than 0.850% and not more than 0.950% (g/ml) of NaCl.

Description A clear, colourless liquid; taste, slightly salty.

Identification Yields the reactions characteristic of sodium salts and chlorides (Appendix III).

pH value 4.5-7.0 (Appendix VI H).

Heavy metals Evaporate 50 ml to about 20 ml and cool, add 2 ml of acetate BS (pH 3.5) and a quantity of water to produce 25 ml. Carry out the limit test for heavy metals (Appendix VIII H, method 1); not more than 0.00003%.

Bacterial endotoxin Carry out the test for bacterial endotoxin (Appendix XI E); less than 0.5 EU per ml.

Other requirements Complies with the general requirements for injections (Appendix I B).

Assay To 10 ml, accurately measured, add 40 ml of water, 5 ml of dextrin solution (1 → 50) and 5-8 drops of fluorescein IS and titrate with silver nitrate (0.1 mol/L) VS. Each ml of silver nitrate (0.1 mol/L) VS is equivalent to 5.844 mg of NaCl.

Category As described under Sodium Chloride.

Strength

(1) 2 ml : 18 mg	(2) 5 ml : 45 mg
(3) 10 ml : 90 mg	(4) 20 ml : 180 mg
(5) 50 ml : 0.45 g	(6) 100 ml : 0.9 g
(7) 200 ml : 1.8 g	(8) 250 ml : 2.25 g
(9) 300 ml : 2.7 g	(10) 500 ml : 4.5 g
(11) 1000 ml : 9 g	

Storage Preserve in well closed containers.

Concentrated Sodium Chloride Injection

Concentrated Sodium Chloride Injection is a sterile and hypertonic solution of Sodium Chloride in Water for Injection. It contains not less than 9.50% and not more than 10.50% of NaCl (g/ml).

Description A clear, colourless liquid; taste, saline.

Identification Yields the reactions characteristic of sodium salts and chlorides (Appendix III).

pH value 4.5-7.0 (Appendix VI H).

Bacterial endotoxin Carry out the test for bacterial endotoxin (Appendix XI E); less than 0.05 EU per ml.

Other requirements Complies with the general requirements for injections (Appendix I B).

Assay Transfer 10 ml, accurately measured, into a 100 ml volumetric flask, dilute with water to volume and mix well. Measure accurately 10 ml, add 40 ml of water, 5 ml of dextrin solution (1 → 50) and 5-8 drops of fluorescein IS, then titrate with silver nitrate (0.1 mol/L) VS. Each ml of silver nitrate (0.1 mol/L) VS is equivalent to 5.844 mg of NaCl.

Category As described under Sodium Chloride.

Strength 10 ml : 1 g

Storage Preserve in well closed containers.

Sodium Chloride Physiological Solution

Sodium Chloride Physiological Solution is a sterile solution of Sodium Chloride in Water. It contains not less than 0.85% and not more than 0.95% (g/ml) of sodium chloride (NaCl).

Description A clear, colourless liquid; taste, slightly salty.

Identification Yields the reactions characteristic of sodium salts and chlorides (Appendix III).

pH value 4.5-7.0 (Appendix VI H).

Other requirements Complies with the general requirements for lotions (Appendix I S).

Assay To 10 ml, accurately measured, add 40 ml of water, 5 ml of dextrin solution (1 → 50) and 5-8 drops of fluorescein IS and titrate with silver nitrate (0.1 mol/L) VS. Each ml of silver nitrate (0.1 mol/L) VS is equivalent to 5.844 mg of NaCl.

Category Irrigation.

Storage Preserve in tightly closed containers.

Compound Sodium Chloride Injection

Compound Sodium Chloride Injection is a sterile mixture of Sodium Chloride, Potassium Chloride and Calcium Chloride in Water for Injection. It contains 0.52%-0.58% (g/ml) of total chlorides (Cl); 0.028%-0.032% (g/ml) of potassium chloride (KCl) and 0.031%-0.035% (g/ml) of calcium chloride ($\text{CaCl}_2 \cdot 2\text{H}_2\text{O}$).

Formula	Sodium Chloride	8.5 g
	Potassium Chloride	0.30 g
	Calcium Chloride	0.33 g
	Water for Injection	a sufficient quantity
	To make	1000 ml

Description A clear, colourless liquid; taste, saline.

Identification Yields the reactions characteristic of sodium, potassium, calcium salts and chlorides (Appendix III).

pH value 4.5-7.5 (Appendix VI H).

Heavy metals Evaporate 50 ml of the injection to about 20 ml, cool, add 2 ml of acetate BS (pH 3.5) and a sufficient quantity of water to produce 25 ml. Carry out the limit test for heavy metals (Appendix VIII H, method 1); not more than 0.00003%.

Arsenic To 20 ml of the injection add 3 ml of water and 5 ml of hydrochloric acid, carry out the limit test for arsenic (Appendix VIII J); not more than 0.00001%.

Bacterial endotoxin Carry out the test for bacterial endotoxin (Appendix XI E); less than 0.5 EU per ml.

Other requirements Complies with the general requirements for injections (Appendix I B).

Assay Total chlorides To 10 ml of the injection, accurately measured, add 40 ml of water, 5 ml of 2% dextrin solution and 5-8 drops of fluorescein IS, titrate with silver nitrate (0.1 mol/L) VS. Each ml of silver nitrate (0.1 mol/L) VS is equivalent to 3.545 mg of Cl.

Potassium Chloride To 60 ml of sodium tetraphenylborate solution (0.02 mol/L) VS in a beaker add 1 ml of glacial acetic acid and 25 ml of water. Add accurately 100 ml of the injection, heat in a water bath at 50-55°C for 30 minutes, cool and allow to stand in an ice bath for 30 minutes. Filter with a tared No. 4 sintered glass crucible previously dried to constant weight at 105°C, wash the precipitate with 20 ml of clear saturated potassium tetraphenylborate solution in 4 portions, finally wash it with a small amount of water. dry at 105°C to constant weight and weigh accurately. Multiply the weight of precipitate by 0.2081, the product represents the weight of KCl in the sample being examined.

Calcium chloride To a 200 ml conical flask add 100 ml of the injection, accurately measured. To 15 ml of ammonia-ammonium chloride BS (pH 10.0) add a few drops of magnesium sulfate TS and a small amount of eriochrome black T indicator mixture, titrate with disodium edetate (0.05 mol/L) VS until a blue colour is produced. Pour the titrated solution into the conical flask mentioned above, titrate again with disodium edetate (0.05 mol/L) VS until the blue colour is restored. Each ml of disodium edetate (0.05 mol/L) VS is equivalent to 7.351 mg of $\text{CaCl}_2 \cdot 2\text{H}_2\text{O}$.

Category Electrolyte replenisher.

Strength (1) 100 ml (2) 500 ml (3) 1000 ml

Storage Preserve in well closed containers, protected from light

Sodium Chromate [^{51}Cr] Injection

Sodium Chromate [^{51}Cr] Injection is a sterile solution of Sodium Chromate [^{51}Cr] made isotonic by the addition of sodium chloride. It contains not less than 90.0% and not more than 110.0% of the labelled amount of radioactive concentration of chromium-51 at the date and hour stated on the label.

Description A clear, pale yellow liquid.

Identification (1) Carry out the γ -ray spectrum method (Appendix XIII), using suitable amount of sample, the prominent photon has an energy of 0.320 MeV. (2) The principal spot obtained in the determination of Radiochemical purity has a prominent radioactive peak with R_f value of about 0.8.

pH value 7.0-8.0 (Appendix VI H).

Chromium Dilute 0.2 ml of the injection, accurately measured, with 0.05 mol/L sodium hydroxide solution to 4.0 ml, mix well and measure the absorbance at 370 nm (Appendix IV A), taking 299 as the value of A (1%, 1 cm) for sodium chromate [^{51}Cr]. Calculate the content of Cr, not more than 50 μg per ml.

Bacterial endotoxin Carry out the test for bacterial endotoxin (Appendix XI E), using 1 vial, it contains less than 40 EU per ml.

Sterility Complies with the test for sterility (Appendix XI H).

Radiochemical purity Carry out the determination of radiochemical purity (Appendix XIII, method 1), using a mixture of water-ethanol-concentrate ammonia solution (5:2:1) as the mobile phase. Not less than 95% of the total radioactivity is found in the spot corresponding to sodium chromate [^{51}Cr].

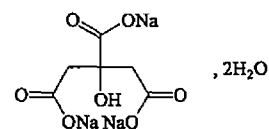
Radioactive concentration Not less than 37 MBq per ml (Appendix XIII).

Category Diagnostic.

Strength (1) 37 MBq (2) 185 MBq

Storage Preserve in well closed lead containers, the intensity of radiation on the surface of the container complies with relevant regulation.

Sodium Citrate



$\text{C}_6\text{H}_5\text{Na}_3\text{O}_7 \cdot 2\text{H}_2\text{O}$ 294.10

[6132-04-3]

Sodium Citrate is 2-hydroxypropane-1,2,3-tricarboxylic acid trisodium salt dihydrate. It contains not less than 99.0% of $\text{C}_6\text{H}_5\text{Na}_3\text{O}_7$, calculated on the dried basis.

Description Colourless crystals or a white crystalline powder; odourless; taste, saline and cool; slightly deliquescent in moist air, and efflorescent in hot air. Freely soluble in water, practically insoluble in ethanol.

Identification Yields the reactions characteristic of sodium salts and citrates (Appendix III).

Alkalinity Dissolve 1.0 g in 20 ml of water, add 1 drop of phenolphthalein IS. Not more than 0.10 ml of sulfuric acid (0.05 mol/L) VS is required to change the colour of the solution.

Clarity of solution A solution of 2.5 g in 10 ml of water is clear.

Chloride Carry out the limit test for chlorides (Appendix VII A), using 0.60 g. Any opalescence produced is not more pronounced than that of a reference solution using 6.0 ml of sodium chloride standard solution (0.01%).

Sulfate Carry out the limit test for sulfates (Appendix VII B), using 0.50 g. Any opalescence produced is not more pronounced than that of a reference solution using 2.5 ml of potassium sulfate standard solution (0.05%).

Tartrate Dissolve 1 g in 2 ml of water in a test tube, add 1 ml each of potassium acetate TS and acetic acid. Rub the inner wall of the test tube with a glass rod, no crystalline precipitate is formed.

Readily carbonizable substances Heat 0.40 g with 5 ml of sulfuric acid (94.5%-95.5%) for 1 hour at $90^\circ\text{C} \pm 1^\circ\text{C}$, cool immediately. Carry out the limit test for readily carbonizable substances (Appendix VII O). Any colour produced is not more intense than reference solution YG_8 or Y_8 (for parenteral administration), and YG_{10} or Y_{10} (for oral administration).

Loss on drying When dried to constant weight at 180°C , loses 10.0%-13.0% of its weight (Appendix VII L).

Calcium salts or oxalate Dissolve 2.0 g in 20 ml of freshly boiled and cooled water, add 0.4 ml of ammonia TS and 2 ml of ammonium oxalate TS, mix well, allow to stand for 1 hour. Any opalescence produced is not more pronounced than that of a reference solution using 1.0 ml of calcium standard solution (dissolve 0.125 g of calcium carbonate, accurately weighed, in a 500 ml volumetric flask with a mixture of 5 ml of water and 0.5 ml of hydrochloric acid, dilute to volume with water and mix well. Each ml is equivalent to 0.10 mg of Ca) (0.005%).

If no opalescence is produced in above test, dissolve 1.0 g in a mixture of 1 ml of water and 3 ml of dilute hydrochloric acid, add 4 ml of 90% ethanol and 4 drops of calcium chloride TS, allow to stand for 1 hour. No opalescence is produced.

Iron Carry out the limit test for iron (Appendix VIII G) by extract 1.0 g with *n*-butanol. Any opalescence produced is not more pronounced than that of a reference solution prepared in the same manner, using 1.0 ml of iron standard solution (0.001%).

Heavy metals Dissolve 2.0 g in 10 ml of water, add 10 ml of dilute acetic acid and a sufficient quantity of water to produce 25 ml. Carry out the limit test for heavy metals (Appendix VIII H, method 1); not more than 0.0005%.

Arsenic Dissolve 2.0 g in 23 ml of water, add 5 ml of hydrochloric acid. Complies with the limit test for arsenic (Appendix VIII J, method 1) (0.0001%).

Assay Heat and dissolve about 80 mg, accurately weighed, in 5 ml of glacial acetic acid, allow to cool, add 10 ml of acetic anhydride and 1 drop of crystal violet IS and titrate with perchloric acid (0.1 mol/L) VS until the colour changes to bluish-green. Perform a blank determination and make any necessary correction. Each ml of perchloric acid (0.1 mol/L) VS is equivalent to 8.602 mg of $C_{23}H_{14}Na_2O_{11}$.

Category Anticoagulant.

Storage Preserve in tightly closed containers.

Preparation Sodium Citrate Injection for Transfusion

Sodium Citrate Injection for Transfusion

Sodium Citrate Injection for Transfusion is a sterile solution of Sodium Citrate in Water for Injection. It contains not less than 2.35% and not more than 2.65% of $C_6H_5Na_3O_7 \cdot 2H_2O$.

Description A clear, colourless liquid.

Identification Yields the reactions characteristic of sodium salts and citrates (Appendix III).

pH value 6.5-8.5 (Appendix VI H).

Bacterial endotoxin Carry out the test for bacterial endotoxin (Appendix XI E); less than 0.25 EU per mg of sodium citrate.

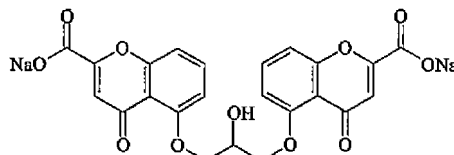
Other requirements Complies with the general requirements for injections (Appendix I B).

Assay Evaporate 3 ml, accurately measured, on a water bath to dryness, dry at 105°C for 30 minutes and cool. Carry out the Assay described under Sodium Citrate, beginning at the words "in 5 ml of glacial acetic acid...". Calculate the content of $C_6H_5Na_3O_7 \cdot 2H_2O$. Each ml of perchloric acid (0.1 mol/L) VS is equivalent to 9.803 mg of $C_6H_5Na_3O_7 \cdot 2H_2O$.

Category As described under Sodium Citrate.

Storage Preserve in well closed containers.

Sodium Cromoglicate



$C_{23}H_{14}Na_2O_{11}$ 512.34

[15826-37-6]

Sodium Cromoglicate is 5,5'-[(2-hydroxy-1,3-propanediyl) bis (oxy)] bis [4-oxo-4H-1-benzopyran-2-carboxylic acid] disodium salt. It contains not less than 98.0% of $C_{23}H_{14}Na_2O_{11}$, calculated on the dried basis.

Description A white crystalline powder; odourless; hygroscopic; discoloured on exposure to light. Soluble in water; insoluble in ethanol or chloroform.

Identification (1) To 0.1 g add 2 ml of water and 2 ml of sodium hydroxide TS, boil for 1 minute, a yellow solution is obtained; add a few drops of diazotized sulfanilic acid TS, the colour of the solution changes blood red.

(2) The light absorption of a solution of 10 µg per ml in phosphate BS (pH 7.4) exhibits maxima at 238 nm and 326 nm (Appendix IV A).

(3) The infrared absorption spectrum is (Appendix IV C), concordant with the reference spectrum of sodium cromoglicate (Appendix XVI).

(4) The aqueous solution yields the reactions characteristic of sodium salts (Appendix III).

Acidity and alkalinity Dissolve 0.10 g in 10 ml of water, add 1 drop of bromothymol blue IS; if a yellow colour is produced, add 0.15 ml of sodium hydroxide (0.01 mol/L) VS the colour changes to blue; if a blue colour is produced, add 0.15 ml of hydrochloric acid (0.01 mol/L) VS, the colour changes to yellow.

Oxalate To 0.10 g and 1 ml of oxalic acid reference solution (dissolve 25 mg, accurately weighed, of dehydrated oxalic acid in a 100 ml volumetric flask in water and dilute to volume and mix well), in two 50 ml volumetric flasks separately add 20 ml of water and 5.0 ml of ferric salicylate TS, dilute with water to volume and mix well; measure the absorbances of the resulting solutions at 480 nm. The absorbance of the test solution is not greater than that of the oxalate reference solution (0.25%).

Loss on drying When dried to constant weight at 120°C, loses not more than 10.0% of its weight (Appendix VII L).

Heavy metals Carry out the limit test for heavy metals (Appendix VIII H, method 2), using 1.0 g; not more than 0.001%.

Assay Dissolve 0.18 g, accurately weighed, in a mixture of 20 ml of propylene-glycol and 5 ml of isopropanol by heating and cool. Add 20 ml of dioxane and a few drops of methyl orange-xylene cyanol blue FF IS, titrate with perchloric acid in dioxane (0.1 mol/L) VS until the solution becomes bluish-grey. Each ml of perchloric acid in dioxane (0.1 mol/L) VS is equivalent to 25.62 mg of $C_{23}H_{14}Na_2O_{11}$.

Category Anti-allergic agent.

Storage Preserve in tightly closed containers, protected

from light.

Preparation (1) Sodium Cromoglicate Aerosol
(2) Sodium Cromoglicate Eye Drops

Sodium Cromoglicate Aerosol

Sodium Cromoglicate Aerosol contains not less than 85.0% and not more than 120.0% of the labelled amount of sodium cromoglicate ($C_{23}H_{14}Na_2O_{11}$). The labelled concentration of sodium cromoglicate aerosol is not less than 80.0% (g/g) and not more than 130.0% (g/g).

Description A colourless to pale yellow suspension in pressurized container, spray out as foggy particles on release of the delivery valve.

Identification (1) Mix each 2 ml of water and sodium hydroxide TS in a test tube, spray the solution for several times with sodium cromoglicate aerosol, mix well, boil for 1 minute, a yellow colour is produced; add a few drops of diazotized sulfanilic acid TS, the colour of the solution changes to red.

(2) The light absorption of the solution obtained in the Assay exhibits a maximum at 326 nm (Appendix IV A).

Other requirements Complies with the general requirements of aerosols and sprays (Appendix I L) except that the dose of principal drug substance in each spray is 80%-120% of the labelled amount.

Assay Allow the content of one container to precipitate on standing, accurately weighed, punch a small hole on the aluminium cover, until the propellant expels. Remove the cover, place the container and the cover in a beaker, add 150 ml of water, heat to dissolve sodium cromoglicate. Transfer the solution to a 250 ml volumetric flask, wash the container and cover with water in divided portions, combine the washings into the volumetric flask, cool, dilute with water to volume and mix well. Measure accurately 10 ml to a 100 ml volumetric flask, dilute with phosphate BS (pH 7.4) to volume and mix well. Measure accurately 10 ml to another 100 ml volumetric flask, dilute with phosphate BS (pH 7.4) to volume and mix well. Measure the absorbance of the resulting solution at 326 nm and make necessary correction using phosphate BS (pH 7.4) as blank (Appendix IV A). Weigh accurately 0.7 g of sodium cromoglicate CRS in a 250 ml volumetric flask, dissolve it in water, dilute to volume and mix well. Measure accurately 10 ml to a 100 ml volumetric flask, dilute with phosphate BS (pH 7.4) to volume, mix well. Measure accurately 10 ml to another 100 ml volumetric flask, dilute with phosphate BS (pH 7.4) to volume. Measure the absorbance in the same manner, calculate the content of sodium cromoglicate in each container. Dry and weigh accurately the empty container, valve and cover, calculate the weight of content and the concentration of sodium cromoglicate in the aerosol.

Category As described under Sodium Cromoglicate.

Strength (1) The total weight of content in each container is 14 g which contains 0.7 g of sodium cromoglicate, and 3.5 mg of sodium cromoglicate in each spray.
(2) The total weight of content in each container is 19.97 g which contains 0.7 g of sodium cromoglicate, and 5 mg of sodium cromoglicate in each spray.

Storage Preserve in tightly closed containers, stored in a

cool place.

Sodium Cromoglicate Eye Drops

Sodium Cromoglicate Eye Drops contain not less than 90.0% and not more than 110.0% of the labelled amount of sodium cromoglicate ($C_{23}H_{14}Na_2O_{11}$).

Description A clear, colourless or almost colourless liquid.

Identification (1) To 5 ml add 2 ml of sodium hydroxide TS, boil for 1 minute, a yellow colour is produced. Add a few drops of diazotized sulfanilic acid TS, the solution becomes blood red.

(2) The light absorption of the solution obtained in the Assay exhibits a maximum at 326 nm (Appendix IV A).

pH value 4.0-7.0 (Appendix VI H).

Other requirements Comply with the general requirements for eye preparations (Appendix I G).

Assay Place 2 ml of the eye drops, accurately measured, in a 100 ml volumetric flask, dilute with phosphate BS (pH 5.8) to volume and mix well. Transfer 5 ml of the solution, accurately measured, into another 100 ml volumetric flask, dilute with phosphate BS (pH 5.8) to volume and mix well. Measure the absorbance of the solution at 326 nm (Appendix IV A). Calculate the content of $C_{23}H_{14}Na_2O_{11}$, taking 164 as the value of A (1%, 1 cm).

Category As described under Sodium Cromoglicate.

Strength 8 ml + 0.16 g

Storage Preserve in tightly closed containers, protected from light.

Sodium Diatrizoate Injection

Sodium Diatrizoate Injection is a sterile solution of Diatrizoic Acid in Water for Injection neutralized with sodium hydroxide. It contains not less than 95.0% and not more than 105.0% of the labelled amount of sodium diatrizoate ($C_{11}H_8I_3N_2NaO_4$).

Description A clear, colourless to pale yellow liquid.

Identification (1) Evaporate about 1 ml to dryness, heat the residue gently; violet iodine vapour is evolved.

(2) Complies with test (2) for Identification described under Diatrizoic Acid.

(3) Yields the reactions characteristic of sodium salts (Appendix III).

pH value 6.5-8.0 (Appendix VI H).

Colour Not more intensely coloured than reference solution Y₃ (Appendix IX A, method 1).

Free iodine To a quantity equivalent to about 1.0 g of sodium diatrizoate add water to produce 10 ml, the resulting solution complies with the test for Free iodine described under Diatrizoic Acid.

Iodide To a quantity equivalent to about 0.8 g of sodium diatrizoate add water to produce 10 ml. Add dropwise 3 ml of dilute nitric acid, stir for a few minutes, a precipitate is produced. Filter, wash the precipitate with 5 ml of water, combine the washings with the filtrate. Add 1 ml of chloroform and 1 ml of concentrated hydrogen peroxide solution, mix well and allow to stand. Any colour produced

in the chloroform layer is not more intense than that of a reference solution prepared in the same manner using 4.0 ml of a 0.0013% solution of potassium iodide.

Pyrogens Complies with the test for pyrogens (Appendix XI D), inject 3 ml per kg of rabbit's weight slowly.

Other requirements Complies with the general requirements for injections (Appendix I B).

Assay Transfer accurately a quantity equivalent to about 5 g of sodium diatrizoate to a 100 ml volumetric flask, add water to volume, mix well. Measure accurately 10 ml, carry out the Assay described under Diatrizoic Acid, beginning at the words "add 30 ml of sodium hydroxide TS and 1.0 g of powdered zinc...". Each ml of silver nitrate (0.1 mol/L) VS is equivalent to 21.20 mg of $C_{11}H_8I_3N_2NaO_4$.

Category Diagnostic aid.

Strength (1) 1 ml : 0.3 g (2) 20 ml : 10 g

Storage Preserve in well closed containers, protected from light.

Sodium Dihydrogen Phosphate

$NaH_2PO_4 \cdot H_2O$ 137.99 [10049-21-5]

Sodium Dihydrogen Phosphate contains not less 98.0% of NaH_2PO_4 , calculated on the dried basis.

Description Colourless crystals or a white crystalline powder; odourless; taste, salty and sour; slightly hygroscopic. Freely soluble in water; practically insoluble in ethanol.

Identification (1) The aqueous solution effervesces on addition of sodium carbonate.
(2) The aqueous solution yields the reactions characteristic of sodium salts and phosphates (Appendix III).

Acidity Dissolve 2.0 g in 40 ml of water, pH 4.1-4.5 (Appendix VI H).

Chloride Carry out the limit test for chlorides (Appendix VIII A), using 0.50 g. Any opalescence produced is not more pronounced than that of a reference solution using 5.0 ml of sodium chloride standard solution (0.01%).

Sulfate Carry out the limit test for sulfates (Appendix VII B), using 1.0 g. Any opalescence produced is not more pronounced than that of a reference solution using 5.0 ml of potassium sulfate standard solution (0.05%).

Loss on drying When dried at 60°C for 2 hours and then to constant weight at 105°C, loses not more than 15.0% and not less than 10.0% of its weight (Appendix VIII L).

Aluminum Dissolve 0.50 g in a quantity of water, add 5 ml of acetic acid-ammonium acetate BS (pH 4.5) and sufficient water to produce 25 ml, then add 1 ml of 0.1% ammonium aurintricarboxylate solution, mix well. Any red colour produced is not more intense than that of a reference solution using 5.0 ml of aluminium standard solution [weigh accurately 1.76 g of aluminium potassium sulfate ($AlK(SO_4)_2 \cdot 12H_2O$) into a 1000 ml volumetric flask, add water to dissolve it and dilute to volume, mix well. Measure accurately 10 ml of the resulting solution into a 100 ml volumetric flask prior to use, dilute with water to volume, mix well. Each ml of the solution is equivalent to 10 µg of Al] (0.01%).

Calcium Dissolve 0.50 g in a quantity of water, add 1 ml of ammonium oxalate TS, allow to stand for 1 minute. Add 2 ml of dilute acetic acid, 5 ml of ethanol and 25 ml of water, mix well. Any opalescence produced is not more

pronounced than that of a reference solution using 5.0 ml of calcium standard solution (weigh accurately 0.125 g of calcium carbonate, previously dried to constant weight at 105°C, into a 500 ml volumetric flask, dissolve in 5 ml of water and 0.5 ml of hydrochloric acid, dilute with water to volume and mix well. Transfer accurately 10 ml of resulting solution to a 100 ml volumetric flask before use, dilute with water to volume, mix well. Each ml of the solution is equivalent to 10 µg of Ca) (0.01%).

Heavy metals Dissolve 1.0 g in 20 ml of water, add 2 ml of acetate BS (pH 3.5) and sufficient water to produce 25 ml. Carry out the limit test for heavy metals (Appendix VIII H, method 1): not more than 0.001%.

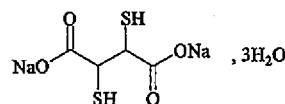
Arsenic Dissolve 0.4 g in 23 ml of water, add 5 ml of hydrochloric acid. Carry out the limit test for arsenic (Appendix VIII J, method 1): not more than 0.0005%.

Assay Dissolve about 2.5 g, accurately weighed, in 10 ml of water, add 20 ml of saturated sodium chloride solution and 2-3 drops of phenolphthalein IS. Titrate with sodium hydroxide (1 mol/L) VS. Each ml of sodium hydroxide (1 mol/L) VS is equivalent to 120.0 mg of NaH_2PO_4 .

Category Buffering agent, phosphorus replenisher.

Storage Preserve in tightly closed containers.

Sodium Dimercaptosuccinate



$C_4H_4Na_2O_4S_2 \cdot 3H_2O$ 280.23

Sodium Dimercaptosuccinate is 2,3-dimercaptosuccinic acid, disodium salt, trihydrate. It contains not less than 95.0% of $C_4H_4Na_2O_4S_2$, calculated on the dried basis.

Description A white to pale yellow powder; odour, characteristic, alliaceous. Freely soluble in water; insoluble in ethanol, chloroform or ether.

Identification (1) Dissolve about 0.2 g in 2 ml of water, make alkaline with sodium hydroxide TS and add dropwise sodium nitroprusside TS; a violet-red colour is produced.
(2) Dissolve about 0.2 g in 2 ml of water, add 1 ml of lead acetate TS; a pale yellow precipitate is produced.
(3) The aqueous solution yields the reactions characteristic of sodium salts (Appendix III).

Acidity or alkalinity Dissolve 1.0 g in 10 ml of water, pH 6.0-7.5 (Appendix VI H).

Colour of solution A solution of 1.0 g in 10 ml of water is colourless. Any colour produced is not more intense than that of reference solution BR₄ (Appendix IX A, method 1).

Loss on drying When dried in vacuum over phosphorous pentoxide to constant weight at 60°C, loses not less than 18.0% and not more than 24.0% of its weight (Appendix VIII L).

Sterility A solution of 1.0 g in 10 ml of sterile water complies with the test for sterility (Appendix XI H).

Assay Dissolve about 0.1 g, dried previously to constant weight and accurately weighed, in 30 ml of water in a 100 ml volumetric flask, add 2 ml of dilute acetic acid and 50 ml of

silver nitrate (0.1 mol/L) VS accurately measured. Shake vigorously, heat in a water bath for 2-3 minutes, cool, dilute with water to volume and mix well. Filter, measure accurately 50 ml of the successive filtrate to a conical flask with stopper. Add 2 ml of nitric acid and 2 ml of ferric ammonium sulfate IS, titrate with ammonium thiocyanate (0.1 mol/L) VS. Perform a blank determination and make any necessary correction. Each ml of silver nitrate (0.1 mol/L) VS is equivalent to 5.656 mg of $C_4H_4Na_2O_4S_2$.

Category Antidote.

Storage Preserve in hermetically sealed containers, stored in a dark and cool place.

Preparation Sodium Dimercaptosuccinate for Injection

Sodium Dimercaptosuccinate for Injection

Sodium Dimercaptosuccinate for Injection is a sterile powder of Sodium Dimercaptosuccinate. It contains not less than 95.0% and not more than 105.0% of the labelled amount of sodium dimercaptosuccinate ($C_4H_4Na_2O_4S_2 \cdot 3H_2O$), calculated on the basis of average content in each container.

Description A white to pale yellow powder; odour, characteristic, alliaceous.

Identification Complies with the tests for Identification as described under Sodium Dimercaptosuccinate.

Colour of solution A solution of the content of container in 5 ml of water (0.5 g) or 10 ml of water (1 g) is colourless; any colour produced is not more intense than that of reference solution RB₁ (Appendix IX A, method 1).

Sterility Add separately a quantity of sterile water to two containers to produce solutions of 0.1 g per ml, the solutions comply with the test for sterility (Appendix XI H).

Acidity or alkalinity, Loss on drying Complies with the respective test as described under Sodium Dimercaptosuccinate.

Other requirements Complies with the general requirements for injections (Appendix I B).

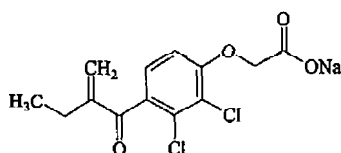
Assay Weigh accurately 0.1 g of the mixed contents obtained in the test for weight variation of content, carry out the Assay as described under Sodium Dimercaptosuccinate. Each ml of silver nitrate (0.1 mol/L) VS is equivalent to 7.006 mg of $C_4H_4Na_2O_4S_2 \cdot 3H_2O$.

Category As described under Sodium Dimercaptosuccinate.

Strength (1) 0.5 g (2) 1 g

Storage Preserve in well closed containers, stored in a dark and cool place.

Sodium Etacrylate



$C_{13}H_{11}Cl_2NaO_4$ 325.12

Sodium Etacrylate is [2,3-dichloro-4-(2-methylene-1-oxobutyl) phenoxy]-acetic acid, sodium salt. It contains not less than 98.0% of $C_{13}H_{11}Cl_2NaO_4$, calculated on the dried basis.

Description A white powder; odourless; taste, bitter and astringent.

Soluble in water; slightly soluble in ethanol.

Identification (1) Complies with tests (1) and (4) for Identification described under Etacrynic Acid.

(2) The infrared absorption spectrum (Appendix IV C) is concordant with the reference spectrum of sodium etacrylate (Appendix XVI).

(3) The aqueous solution yields the reactions characteristic of sodium (Appendix III).

Acidity Dissolve 25 mg in 25 ml of water, pH 5.5-7.0 (Appendix VI H).

Loss on drying When dried in vacuum at 60°C over phosphorus pentoxide to constant weight, loses not more than 4.0% of its weight (Appendix VIII L).

Heavy metals Carry out the limit test for heavy metals (Appendix VIII H, method 1), using 1 g; not more than 0.002%.

Sterility Dissolve 0.1 g in 10 ml of sterile water respectively, the solutions comply with the test for sterility (Appendix XI H).

Assay Carry out the Assay described under Etacrynic Acid, using about 0.15 g, accurately weighed. Each ml of bromine (0.05 mol/L) VS is equivalent to 16.26 mg of $C_{13}H_{11}Cl_2NaO_4$.

Category Diuretic.

Storage Preserve in hermetically closed containers, protected from light.

Preparation Sodium Etacrylate for Injection

Sodium Etacrylate for Injection

Sodium Etacrylate for Injection is a sterile powder of Sodium Etacrylate. It contains not less than 90.0% and not more than 110.0% of the labelled amount of sodium etacrylate ($C_{13}H_{11}Cl_2NaO_4$), calculated on the basis of average content.

Description A white powder; odourless; taste, bitter and astringent.

Identification Complies with the tests for Identification described under Sodium Etacrylate.

Acidity Dissolve 25 mg in 25 ml of water, pH 5.5-7.0 (Appendix VI H).

Loss on drying When dried in vacuum at 60°C over phosphorus pentoxide to constant weight, loses not more than 5.0% of its weight (Appendix VIII L).

Sterility Dissolve the contents of containers in sterile water to produce solutions of 10 mg per ml, the resulting solutions comply with the related requirements (Appendix XI H).

Other requirements Complies with the general requirements for injections (Appendix I B).

Assay Carry out the assay as described under Etacrynic Acid, using about 0.15 g, accurately weighed, of the mixed contents obtained in the test for weight variation of contents. Each ml of bromine (0.05 mol/L) VS is

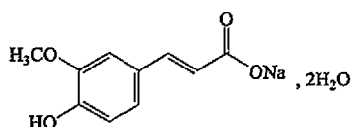
equivalent to 16.26 mg of $C_{13}H_{11}Cl_2NaO_4$.

Category As described under Sodium Etacrylate.

Strength 25 mg

Storage Preserve in well closed containers, protected from light.

Sodium Ferulate



$C_{10}H_9NaO_4 \cdot 2H_2O$ 252.20

Sodium Ferulate is sodium 3-methoxy-4-hydroxy cinnamate dihydrate. It contains not less than 98.5% (for oral administration) or 99.0% (for injection) of $C_{10}H_9NaO_4$, calculated on anhydrous basis.

Description White or almost white crystals or crystalline powder, odourless. Soluble in water; very slightly soluble in ethanol; insoluble in trichloromethane or ether.

Specific absorbance Protected from light throughout the procedure. Measure the absorbance of a solution of 10 μ g per ml in water at 310 nm (Appendix IV A), the value of A (1%, 1 cm) is 690-732.

Identification (1) The light absorption of a solution of 10 μ g per ml in water exhibits two maxima at 287 nm and 310 nm, and a minima at 254 nm (Appendix IV A).

(2) The infrared absorption spectrum (Appendix IV C) is concordant with the reference spectrum of sodium ferulate (Appendix XVI).

(3) The aqueous solution yields the reactions characteristic of sodium salts (Appendix III).

Acidity or alkalinity An aqueous solution of 50 mg per ml, pH 6.0-7.5 (Appendix VI H).

Clarity and colour of solution An aqueous solution of 20 mg per ml is clear and colourless; any colour produced is not more intense than that of reference solution Y2 or YG₂ (Appendix IX A, method 1) (for injection).

Related substances Protected from light throughout the procedure. Carry out the method for high performance liquid chromatography (Appendix V D), using a column packed with octadecylsilane bonded silica gel and a mixture of water-methanol-acetic acid (69 : 30 : 1.5) as the mobile phase. Detection wavelength is 322 nm and the number of theoretical plates of the column is not less than 2000, calculated with reference to the peak of sodium ferulate. Dissolve a quantity of the substance being examined in mobile phase to produce a solution of 0.7 mg per ml as test solution, transfer accurately 1 ml of the test solution into a 100 ml volumetric flask, dilute with mobile phase, shake thoroughly as reference solution. Inject 10 μ l of the reference solution into the column and adjust the attenuation so that the principal peak height in the chromatogram is 10% of full scale of the chart. Inject separately 10 μ l each of the test solution and the reference solution into the column, and record the chromatogram for 2.5 times of the retention time of the principal peak. The sum of the areas of all impurity peaks in the chromatogram obtained with the test solution is not greater than that of the principal peak in the chromatogram

obtained with the reference solution.

Water 13.0%-15.5% (Appendix VIII M, method 1, A).

Pyrogens Complies with the test for pyrogens (Appendix XI D), using 1 ml of a solution of 5 mg per ml in Sterile Water for Injection per kg of rabbit's weight (for injection).

Sterility Complies with the test for sterility (Appendix XI H). Using a solution of 20 mg per ml in Sterile Water for Injection (for injection).

Assay Protected from light throughout the procedure. Dissolve about 0.15 g, accurately weighed, in 20 ml of glacial acetic acid, add 3 ml of acetic anhydride and 1 drop of crystal violet IS, titrate with perchloric acid (0.1 mol/L) VS until the blue color changes to pink. Perform blank determination and make any necessary correction. Each ml of perchloric acid (0.1 mol/L) VS is equivalent to 25.62 mg of $C_{10}H_9NaO_4$.

Category Anticoagulant.

Storage Preserve in tightly closed containers, protected from light.

Preparation (1) Sodium Ferulate for Injection
(2) Sodium Ferulate Tablets

Sodium Ferulate for Injection

Sodium Ferulate for Injection is a sterile powder of Sodium Ferulate. It contains not less than 90.0% and not more than 110.0% of the labelled amount of sodium ferulate ($C_{10}H_9NaO_4 \cdot 2H_2O$), calculated with reference to the average weight of contents.

Description White or almost white crystals or a crystalline powder; odourless.

Identification Complies with the test (1) and (3) for Identification described under Sodium Ferulate.

Acidity or alkalinity An aqueous solution of 50 mg per ml, pH 6.0-7.5 (Appendix VI H).

Clarity and colour of solution An aqueous solution of 20 mg per ml is clear and colourless; any opalescence produced is not more pronounced than that of reference suspension I (Appendix IX B), any colour produced is not more intense than that of reference solution Y3 or YG3 (Appendix IX A, method 1).

Water 13.0%-16.0% (Appendix VIII M, method 1, A).

Pyrogens Complies with the test for pyrogens (Appendix XI D), using 3 ml of a solution of 5 mg per ml in Sterile Water for Injection per kg of rabbit's weight.

Sterility Complies with the test for sterility (Appendix XI H). Using a solution of 20 mg per ml in Sterile Water for Injection.

Other requirements Complies with the general requirements for injections (Appendix I B).

Assay Protected from light throughout the procedure. To about 0.15 g of the mixed contents obtained under the test for Weight variation, accurately weighed. Carry out the Assay described under Sodium Ferulate beginning at the words "in 20 ml of glacial acetic acid". Each ml of perchloric acid (0.1 mol/L) VS is equivalent to 25.22 mg of $C_{10}H_9NaO_4 \cdot 2H_2O$.

Category As described under Sodium Ferulate.

Strength 0.1 g

Storage Preserve in tightly closed containers, protected from light.

Sodium Ferulate Tablets

Sodium Ferulate Tablets contain not less than 90.0% and not more than 110.0% of the labelled amount of sodium ferulate ($C_{10}H_9NaO_4 \cdot 2H_2O$).

Description White or almost white tablets.

Identification (1) The solution obtained in Assay complies with the test (1) for Identification described under Sodium Ferulate.

(2) Comply with the test (3) for Identification described under Sodium Ferulate.

Dissolution Protected from light throughout the procedure. Carry out the dissolution test (Appendix X C, method 1), using 900 ml of water as the dissolution medium, adjust the rotational speed of the basket to 50 rpm. Withdraw the solution at exactly 30 minutes and filter. Dilute a quantity of the successive filtrate, accurately measured, with water to produce a solution of about 10 μ g per ml. Measure the absorbance of the solution at 310 nm (Appendix IV A). Calculate the dissolution of $C_{10}H_9NaO_4 \cdot 2H_2O$ from each tablet, taking 712 as the value of A (1%, 1 cm), and multiply the result by 1.167. Not less than 80% of the labelled amount is dissolved.

Other requirements Comply with the general requirements for tablets (Appendix I A).

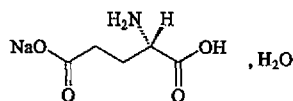
Assay Protected from light throughout the procedure. Weigh accurately and powder 20 tablets. Weigh accurately a quantity of the powder, equivalent to about 50 mg of sodium ferulate, into a 250 ml volumetric flask, add a quantity of water to dissolve sodium ferulate, and dilute with water to volume, shake thoroughly and filter, measure accurately 5 ml of the successive filtrate into a 100 ml volumetric flask, dilute to volume with water and shake thoroughly. Measure the absorbance of the resulting solution at 310 nm (Appendix IV A). Calculate the content of $C_{10}H_9NaO_4 \cdot 2H_2O$, taking 712 as the value of A (1%, 1 cm), and multiply the result by 1.167.

Category As described under Sodium Ferulate.

Strength 50 mg

Storage Preserve in tightly closed containers, protected from light.

Sodium Glutamate



$C_5H_8NNaO_4 \cdot H_2O$ 187.13

Sodium Glutamate is *L*-2-aminopentane-1,5-dioic acid monosodium monohydrate. It contains not less than 99.0% and not more than 100.5% of $C_5H_8NNaO_4 \cdot H_2O$, calculated on the dried basis.

Description White crystals or a crystalline powder. Freely soluble in water, slightly soluble in ethanol.

Specific optical rotation $+24.8^\circ$ to $+25.3^\circ$, in a solution of about 0.1 g per ml in 2 mol/L hydrochloric acid solution (Appendix VI E).

Identification (1) Dissolve about 5 mg in 1 ml of water; add several drops of ninhydrin TS and heat, the solution exhibits a blue to violet-blue colour.

(2) The infrared absorption spectrum (Appendix IV C) is concordant with the reference spectrum of sodium glutamate (Appendix XVI).

(3) Yields the reactions characteristic of sodium salts (Appendix III).

Acidity or alkalinity Dissolve 1.0 g in 10 ml of water, pH 6.7-7.2 (Appendix VI H).

Transmittance of solution Dissolve 1.0 g in 10 ml of water, the transmittance at 430 nm is not less than 98.0% (Appendix IV A).

Chloride Carry out the limit test for chloride (Appendix VII A), using 0.10 g. Any opalescence produced is not more pronounced than that of a reference solution using 5.0 ml of sodium chloride standard solution (0.05%).

Sulfate Carry out the limit test for sulfate (Appendix VII B), using 0.5 g. Any opalescence produced is not more pronounced than that of a reference solution using 1.5 ml of potassium sulfate standard solution (0.03%).

Ammonium Carry out the limit test for ammonium (Appendix VIII K), using 0.10 g. Any colour produced is not more intense than that of a reference solution using 2.0 ml of ammonium chloride standard solution (0.02%).

Other amino acids Carry out the method for thin-layer chromatography (Appendix V B), using silica gel G as the coating substance and *n*-butanol-water-glacial acetic acid (2 : 1 : 1) as the mobile phase. Apply separately to the plate 5 μ l of each of two solutions in water containing (1) 20 mg per ml, (2) 0.1 mg per ml of the substance being examined. After developing and removal of the plate, dry in air, spray with ninhydrin acetone solution (1 \rightarrow 50), heat at 80°C until the colour is produced and examine immediately. Any spot, other than the principal spot in the chromatogram, obtained with solution (1) is not more intense than the principal spot obtained with solution (2) (0.5%).

Loss on drying When dried at 97°C to 99°C for 5 hours, loses not more than 0.1% of its weight (Appendix VIII L).

Iron Carry out the limit test for iron (Appendix VIII G), using 1.0 g. Any colour produced is not more intense than that of a reference solution using 1.0 ml of iron standard solution (0.001%).

Heavy metals Dissolve 1.0 g in 23 ml of water, add 2 ml of acetate BS (pH 3.5). Carry out the limit test for heavy metals (Appendix VIII H, method 1); not more than 0.001%.

Arsenic Dissolve 2.0 g in 23 ml of water, add 5 ml of hydrochloric acid, carry out the limit test for arsenic (Appendix VIII J, method 1); not more than 0.0001%.

Pyrogens Complies with the test for pyrogens (Appendix XI D), using 10 ml of a solution of 20 mg per ml in Sodium Chloride Injection, per kg of the rabbit's weight.

Assay Dissolve about 80 mg, accurately weighed, in 3 ml of dehydrated formic acid, add 30 ml of glacial acetic acid. Carry out the method for potentiometric titration (Appendix VII A), titrate with perchloric acid (0.1 mol/L) VS. Perform a blank determination and make any necessary correction. Each ml of perchloric acid (0.1 mol/L) VS is equivalent to 9.357 mg of $C_5H_8NNaO_4 \cdot H_2O$.

Category Amino acid.

Storage Preserve in tightly closed containers, protected from light.

Preparation Sodium Glutamate Injection

Sodium Glutamate Injection

Sodium Glutamate Injection is a sterile aqueous solution of glutamic acid with a quantity of sodium hydroxide. It contains not less than 95.0% and not more than 105.0% of the labelled amount of sodium glutamate ($C_5H_8NNaO_4$).

Description A clear, colourless or almost colourless liquid.

Identification (1) Dilute 1 drop with 2 ml of water, add about 2 mg of ninhydrin and heat, the solution exhibits a blue to violet-blue colour.

(2) Yields the reactions characteristic of sodium salts (Appendix III).

pH value 7.5-8.5 (Appendix VI H).

Bacterial endotoxin Carry out the test for bacterial endotoxin (Appendix XI E); less than 0.025 EU per mg of sodium glutamate.

Other requirements Complies with the general requirements for injections (Appendix I B).

Assay Measure accurately 15 ml to a 50 ml volumetric flask, add 10 ml of hydrochloric acid, dilute with water to volume and mix well. Carry out the determination of optical rotation (Appendix VI E) and multiply by 5.986 to obtain the amount (g) of $C_5H_8NNaO_4$ in 100 ml.

Category As described under Glutamic Acid.

Strength 20 ml : 5.75 g

Storage Preserve in well closed containers, protected from light.

Sodium Glycerophosphate

[1334-74-3]

Sodium Glycerophosphate is a mixture of α -Sodium Glycerophosphate and β -Sodium Glycerophosphate. It contains not less than 67.0% and not more than 71.0% of $C_3H_7Na_2O_6P$.

Description Colourless crystals or a white crystalline powder; odourless; taste, salty. Freely soluble in water; insoluble in ethanol or acetone.

Identification (1) Heat a mixture of about 0.1 g and 0.5 g of potassium hydrogen sulfate in a test tube, pungent vapours of acrolein are evolved.

(2) The aqueous solution yields the reactions characteristic of sodium salts (Appendix III).

(3) To about 0.1 g add 5 ml of dilute nitric acid, heat to boil about 1 minute, cool, the solution yields the reactions characteristic of phosphates (Appendix III).

Alkalinity Dissolve 1.0 g in 30 ml of water, add 1.0 ml of hydrochloric acid (0.1 mol/L) VS and 4 drops of phenolphthalein IS, the solution is colourless.

Clarity and colour of solution Dissolve 1.0 g in 10 ml of water, the solution is clear and colourless. Any opalescence produced is not more pronounced than that of reference

suspension 2 (Appendix IX B). Any colour produced is not more intense than that of reference solution Y_1 (Appendix IX A, method 1).

Free glycerol and ethanol-soluble substances To 1.0 g add 25 ml of dehydrated ethanol, stir for 10 minutes and filter. Wash the residue with 5 ml ethanol, evaporate the combined filtrate and washings on a water bath to dryness and dry for 1 hour, the weight of residue is not more than 10 mg.

Chloride Dissolve 0.25 g in 15 ml of water, carry out the limit test for chloride (Appendix VIII A). Any opalescence produced is not more pronounced than that of a reference using 5.0 ml of sodium chloride standard solution (0.02%).

Sulfate Dissolve 0.60 g in 15 ml of water. Carry out the limit test for sulphate (Appendix VIII B). Any opalescence produced is not more pronounced than that of a reference using 3.0 ml of potassium sulfate standard solution (0.5%).

Free Phosphate Dissolve 0.10 g in 10 ml of water. Dilute 1.0 ml with water to 100 ml, add 4 ml of ammonium molybdate solution (to 2.5 g of ammonium molybdate, add 20 ml of water, heat to dissolve; to 28 ml of sulfuric acid dilute with 50 ml of water, cool; combine two solutions and dilute with water to 100 ml), mix well, add 0.1 ml of stannous chloride solution (dissolve 3.3 g of stannous chloride in 1 ml of hydrochloric acid, dilute with water to 10 ml, measure 1 ml, add 9 ml of 2 mol/L hydrochloric acid solution), mix well, allow to stand 10 minutes. Any colour produced is not more intense than that of 2.0 ml of phosphate standard solution (dissolve potassium dihydrogen phosphate 0.716 g in water and dilute with water to 1000 ml, measure 1.00 ml dilute with water to 100 ml), add 98 ml of water, proceed in the same manner (0.1%).

Loss on drying When dried to constant weight at 105°C, loses 29.0%-33.5% of its weight (Appendix VIII L).

Iron Dissolve 0.50 g in 10 ml of water. Carry out the limit test for iron (Appendix VIII G). Any colour produced is not more intense than that of a reference using 2.0 ml of iron standard solution (0.004%).

Heavy metals Dissolve 1.0 g in 23 ml of water, add 2 ml of acetate BS (pH 3.5). Carry out the limit test for heavy metals (Appendix VIII H, method 1); not more than 0.002%.

Arsenic Dissolve 0.40 g in 25 ml of water. Carry out the limit test for arsenic (Appendix VIII J); not more than 0.0005%.

Assay Dissolve 0.20 g, accurately weighed, in 30 ml of water, carry out the method for potentiometric titration (Appendix VII A), titrate with sulfuric acid (0.05 mol/L) VS. Each ml of sulfuric acid (0.05 mol/L) VS is equivalent to 21.6 mg of $C_3H_7Na_2O_6P$.

Category Phosphorus replenisher.

Storage Preserve in tightly closed containers.

Sodium Glycerophosphate Injection

Sodium Glycerophosphate Injection is a sterile solution of Sodium Glycerophosphate in Water for Injection. It contains 28.80-33.14 mg of phosphorus (P) per ml and 43.68-48.28 mg of sodium (Na) per ml.

Description A clear, colourless or almost colourless liquid.

Identification (1) Measure 1 ml, add 10 ml of water, 10 ml of diluted nitric acid solution and 5 ml of ammonium molybdate TS, heat for a moment and cool, a yellow precipitate is produced which dissolves in ammonia TS.

(2) Heat a mixture of about 5 ml and a quantity of potassium hydrogen sulfate in a test tube, pungent vapours of acrolein are evolved.

(3) Carry out the method as described under Assay of sodium, the absorption exhibits a maximum at 589 nm.

pH value 7.2-7.6 (Appendix VI H).

Free phosphate *Reference solution* Carry out the method as described under Assay of phosphorus.

Procedure Dilute 1.0 ml to 30 ml with water and mix well as the test solution. Carry out the method as described under Assay of phosphorus, beginning at the words "Measure accurately 5 ml of the reference solution and the test solution". The absorption of the test solution is not greater than that of the reference solution (<0.03 mmol/L).

Bacterial endotoxin Dilute the content of a quantity with water-BET to 40 times of its original volume. Carry out the test for bacterial endotoxin (Appendix XI E): less than 0.4 EU per ml of diluted solution.

Other requirements Complies with the general requirements for injections (Appendix I B).

Assay *Sodium* Measure accurately 2 ml in a 200 ml volumetric flask, dilute to volume with water and mix well. Measure accurately 10 ml of the resulting solution in a 50 ml volumetric flask, dilute to volume with water and mix well. Measure accurately 2 ml to a 100 ml volumetric flask, add 4.0 ml of cesium chloride solution (Dissolve 63.34 g of cesium chloride in water and dilute to 1000 ml.), dilute to volume with water and mix well as the test solution. Weigh 1.2711 g of sodium chloride previously dried to constant weight at 130°C in a 500 ml volumetric flask. Dissolve in water, dilute to volume to produce a solution of 1 mg (Na) per ml and mix well. Measure accurately 10 ml to a 50 ml volumetric flask, dilute to volume with water. Transfer 0.00 ml, 0.05 ml, 1.00 ml, 1.50 ml of the resulting solution, add 4.0 ml of cesium chloride solution, to 100 ml volumetric flasks, respectively. Dilute to volume with water and mix well as the reference solution. Carry out the method for atomic absorption spectrophotometry (Appendix IV D, method 1), measure the absorbance of the solutions at 589 nm. Calculate the content of Na.

Phosphorus Measure accurately 5 ml in a 50 ml volumetric flask, dilute to volume with water and mix well. Measure accurately 1 ml of the resulting solution in a crucible and add 1 g of zinc oxide. Heat gently until it is charred, ignite at 600°C for 1 hour and cool to room-temperature. Add 5 ml of water and 5 ml of hydrochloric acid, heat to dissolve the residue. Transfer the resulting solution to a 100 ml volumetric flask, dilute to volume with water and mix well as the test solution. Weigh 136.09 mg of potassium dihydrogen phosphate previously dried to constant weight at 105°C in a 100 ml volumetric flask, dilute to volume with water and mix well. Measure accurately 10 ml to a 100 ml volumetric flask, dilute to volume with water and mix well as the reference solution. Measure accurately 5 ml of the reference solution and the test solution, to 25 ml volumetric flasks, respectively add 1 ml of ammonium molybdate solution [Weigh 5 g of ammonium molybdate, dissolve with 5% (g/ml) sulfuric acid solution and dilute to 100 ml.] and 1 ml of freshly prepared 0.5% hydroquinone solution [Weigh 0.5 g of hydroquinone, dissolve with 0.25% (g/ml) sulfuric acid solution and dilute to 100 ml, freshly prepared before use.] and 3 ml of 50% sodium acetate solution, dilute to volume with water and mix well. Measure the

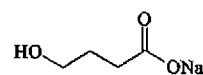
absorbance at 720 nm (Appendix IV A). Calculate the content of P.

Category Phosphorus replenisher.

Strength 10 ml : 2.16 g

Storage Preserve in tightly closed containers, stored at a temperature below 25°C and not frosted.

Sodium Hydroxybutyrate



$C_4H_7NaO_3$ 126.09

Sodium Hydroxybutyrate is the sodium salt of 4-hydroxybutyric acid. It contains not less than 99.0% of $C_4H_7NaO_3$, calculated on the dried basis.

Description A white crystalline powder; odour, faint; taste, salty; hygroscopic.

Very soluble in water; soluble in ethanol; insoluble in ether or chloroform.

Identification (1) Dissolve 0.1 g in 1 ml of water, add 3-5 drops of ferric chloride TS; a red colour is produced.

(2) Dissolve 0.1 g in 1 ml of water, add 1 ml of ammonium ceric nitrate TS, an orange-red colour is produced.

(3) The infrared absorption spectrum (Appendix IV C) is concordant with the reference spectrum of sodium hydroxybutyrate (Appendix XVI).

(4) The aqueous solution yields the reactions characteristic of sodium salts (Appendix III).

Alkalinity Dissolve 2.0 g in 10 ml of water, pH 7.5-9.0 (Appendix VI H).

Clarity and colour of solution A solution of 2.0 g in 10 ml of water is clear and colourless; any opalescence produced is not more pronounced than that of reference suspension 2 (Appendix IX B); any colour produced is not more intense than that of reference solution Y_2 (Appendix IX A, method 1).

Chloride Carry out the limit test for chlorides (Appendix VIII A), using 0.50 g. Any opalescence produced is not more pronounced than that of a reference solution using 7.0 ml of sodium chloride standard solution (0.014%).

Sulfate Carry out the limit test for sulfates (Appendix VIII B), using 1.0 g. Any opalescence produced is not more pronounced than that of a reference solution using 2.0 ml of potassium sulfate standard solution (0.020%).

Loss on drying When dried to constant weight at 105°C, loses not more than 1.5% of its weight (Appendix VIII L).

Heavy metals Carry out the limit test for heavy metals (Appendix VIII H, method 3), using 0.50 g, not more than 0.002%.

Assay Dissolve about 0.1 g, accurately weighed, in 10 ml of glacial acetic acid, add 2 ml of acetic anhydride and 1 drop of crystal violet IS, titrate with perchloric acid (0.1 mol/L) VS, until the colour changes to bluish-green. Perform a blank determination and make any necessary correction. Each ml of perchloric acid (0.1 mol/L) VS is equivalent to 12.61 mg of $C_4H_7NaO_3$.

Category General anesthetic by intravenous injection.

Storage Preserve in tightly closed containers, protected from

light.

Preparation Sodium Hydroxybutyrate Injection.

Sodium Hydroxybutyrate Injection

Sodium Hydroxybutyrate Injection is a sterile solution of Sodium Hydroxybutyrate in Water for Injection. It contains not less than 95.0% and not more than 105.0% of the labelled amount of sodium hydroxybutyrate ($\text{C}_4\text{H}_7\text{NaO}_3$).

Description A clear, colourless or almost colourless liquid.

Identification Complies with the test (1), (2) and (4) for Identification described under Sodium Hydroxybutyrate.

pH value 7.5-9.0 (Appendix IV H).

Bacterial endotoxin Carry out the test for bacterial endotoxin (Appendix XI E); not more than 0.017 EU per mg of sodium hydroxybutyrate.

Other requirements Complies with the general requirements for injections (Appendix I B).

Assay Measure accurately 5 ml to a 50 ml volumetric flask, dilute with water to volume and mix well. Evaporate 5 ml, measured accurately, to dryness on a water bath and dry it at 105°C. Carry out the Assay described under Sodium Hydroxybutyrate beginning at the words "in 10 ml of glacial acetic acid..." Each ml of perchloric acid (0.1 mol/L) VS is equivalent to 12.61 mg of $\text{C}_4\text{H}_7\text{NaO}_3$.

Category As described under Sodium Hydroxybutyrate.

Strength 10 ml : 2.5 g

Storage Preserve in well closed containers, protected from light.

Sodium Iodide

NaI 149.89 [7681-82-5]

Sodium Iodide contains not less than 99.0% of NaI, calculated on the dried basis.

Description Colourless crystals, or a white crystalline powder; odourless; taste, saline and slightly bitter; hygroscopic; easily changes to brown colour in damp atmosphere. Very soluble in water; soluble in ethanol.

Identification Yields the reactions characteristic of sodium salts and iodides (Appendix III).

Alkalinity Dissolve 1.0 g in 10 ml of water, add 1 drop of phenolphthalein IS and 0.10 ml of sulfuric acid (0.05 mol/L) VS, no red colour is produced.

Clarity and colour of solution A solution of 1.0 g in 10 ml of water is clear and colourless; any colour produced is not more intense than that of reference solution Y_1 (Appendix IX A, method 1).

Chloride Dissolve 0.25 g in 100 ml of water, add 1 ml of concentrated hydrogen peroxide solution and 1 ml of phosphoric acid, boil until the solution becomes colourless and cool. Add again 0.5 ml of concentrated hydrogen peroxide solution, boil and then cool. Transfer it to a 250 ml volumetric flask, dilute with water to volume and mix well. Carry out the limit test for chlorides, (Appendix VIII A), using 5.0 ml of the solution. Any opalescence produced

is not more pronounced than that of a reference solution using 2.5 ml of sodium chloride standard solution (0.5%).

Sulfate Carry out the limit test for sulfates (Appendix VIII B) using 0.50 g. Any opalescence produced is not more pronounced than that of a reference solution using 2.0 ml of potassium sulfate standard solution (0.04%).

Iodate Dissolve 0.50 g in 10 ml of freshly boiled and cooled water, add 2 drops of dilute sulfuric acid and 0.2 ml of starch IS, allow to stand in the dark, no blue colour is produced within 2 minutes.

Loss on drying When dried at 105°C for 4 hours, loses not more than 3.0% of its weight (Appendix VIII L).

Potassium Dissolve 1.0 g in a quantity of water in a 100 ml volumetric flask, dilute with water to volume and mix well. Measure accurately 4.0 ml of the solution, add 1.0 ml of dilute acetic acid and mix well. Add 5.0 ml of sodium tetraphenylborate solution (1→30), shake immediately and allow to stand for 10 minutes. Any opalescence produced is not more pronounced than that of a reference solution prepared in a similar manner using 4.0 ml of potassium chloride standard solution (dissolve 9.5 mg of potassium chloride in a quantity of water and dilute with water to 1000 ml) (0.05%).

Barium Dissolve 1.0 g in 20 ml of water, filter, divide the filtrate into two equal portions. Add 1 ml of dilute sulfuric acid to one portion and add 1 ml of water to the other portion. The two portions should be similar in clarity within 15 minutes.

Heavy metals Dissolve 2.0 g in 23 ml of water, add 2 ml of acetate BS (pH 3.5) carry out the limit test for heavy metals (Appendix VIII H, method 1); not more than 0.001%.

Assay Dissolve about 0.3 g, accurately weighed, in 10 ml of water, add 35 ml of hydrochloric acid. Titrate with potassium iodate (0.05 mol/L) VS until a yellow colour is produced; add 5 ml of chloroform, continue the titration and shake thoroughly until the colour disappears in the chloroform layer. Each ml of potassium iodate (0.05 mol/L) VS is equivalent to 14.99 mg of NaI.

Category Iodine replenisher.

Storage Preserve in tightly closed containers, protected from light.

Sodium Iodide [^{131}I] Capsules

Sodium Iodide [^{131}I] Capsules are capsules containing Sodium Iodide [^{131}I]. Iodine [^{131}I] is prepared by neutron irradiation in the chemical form of sodium iodide which may contain trace amount of natural iodine.

It contains not less than 90.0% and not more than 110.0% of the labelled amount of radioactive concentration of Iodine-131 at the date and hour stated on the label.

Suitable amount of stabilizer may be added to the preparation.

Identification Dissolve the suitable content in water. It is used for the following tests.

(1) Carry out the γ -spectrum method (Appendix XIII) with suitable amount of the solution, the prominent photon has an energy of 0.365 MeV.

(2) The principal spot obtained in the determination of

Radiochemical purity has a prominent peak with R_f value of about 0.8.

Content uniformity Take 20 capsules at random. measure the radioactive count of each capsule with a suitable instrument under the same geometric conditions for the measurement and calculate the average radioactivity. Compare the radioactivity count of each capsule with the average value, not less than the values of 19 capsules are found to within the range of 96.5%-103.5% of the average value.

Disintegration Take 6 capsules at random, carry out the test for disintegration (Appendix X A, for capsules).

Radiochemical purity Carry out the determination of radiochemical purity (Appendix XIII, method 1), using 75% methanol as the mobile phase. Not less than 95% of the total radioactivity is found in the spot corresponding to Sodium Iodide [^{131}I].

Radioactivity Comply with the requirements for radioactivity (Appendix XIII, Measurement of radioactivity concentration).

Category Diagnostic.

Strength 333 kBq

Storage Preserve in tightly closed lead containers. The intensity of radiation on the surface of the container complies with relevant regulation.

Sodium Iodide [^{131}I] Oral Solution

Sodium Iodide [^{131}I] Oral Solution is an aqueous solution of Sodium Iodide [^{131}I]. It contains not less than 90.0% and not more than 110.0% of the labelled amount of radioactive concentration of Iodine-131 at the date and hour stated on the label. Sodium sulfite is added as a stabilizer.

Description A clear, colourless liquid.

Identification (1) Carry out the γ -ray spectrum method (Appendix XIII) using suitable amount of sample, the prominent photon has an energy of 0.365 MeV. (2) The principal spot obtained in the determination of radiochemical purity has a prominent radioactive peak with R_f value of about 0.8.

pH value 7.0-9.0 (Appendix VI H).

Radiochemical purity Carry out the determination of radiochemical purity (Appendix XIII, method 1), using 75% methanol as the mobile phase. Not less than 95% of the total radioactivity is found in the spot corresponding to Sodium Iodide [^{131}I].

Radioactive concentration Not less than 185 MBq per ml (Appendix XIII).

Category Radiopharmaceutical.

Strength (1) 925 MBq (2) 1850 MBq
(3) 3700 MBq (4) 7400 MBq

Storage Preserve in tightly closed lead containers. The intensity of radiation on the surface of the container complies with relevant regulation.

Sodium Iodohippurate [^{131}I] Injection

Sodium Iodohippurate [^{131}I] Injection is a sterile solution of Sodium Iodohippurate [^{131}I]. It

contains not less than 90.0% and not more than 110.0% of the labelled amount of radioactive concentration of Iodine-131 at the date and hour stated on the label.

Description A clear, pale brown liquid.

Identification (1) Carry out the γ -ray spectrum method (Appendix XIII), the prominent photon has an energy of 0.36 MeV.

(2) The principal spot obtained in the determination of Radiochemical purity has a prominent radioactive peak with R_f value of about 0.5.

pH value 5.0-6.0 (method of exchange) or 6.0-8.5 (method of melting) (Appendix VI H).

Bacterial endotoxin Dilute the content of 1 vial with water-BET to 10 times of its original volume. Carry out the test for bacterial endotoxin (Appendix XI E); less than 15 EU per ml.

Sterility Complies with the test for sterility (Appendix XI H).

Radiochemical purity Carry out the determination of radiochemical purity (Appendix XIII, method 1), using a mixture of benzene-glacial acetic acid-water (4 : 4 : 1) as the mobile phase. Not less than 95% of the radiochemical purity is found in the spot corresponding to Sodium Iodohippurate [^{131}I], not more than 2% of the total radioactivity is found in the spot corresponding to Iodohippuric acid [^{131}I] (R_f value 0.9-1.0).

Radioactive concentration Not less than 37 MBq per ml (Appendix XIII).

Category Diagnostic.

Strength (1) 37 MBq (2) 111 MBq
(3) 185 MBq (4) 370 MBq

Storage Preserve in well closed lead containers. The intensity of radiation on the surface of the container complies with relevant regulation.

Sodium Lactate Injection

Sodium Lactate Injection is a sterile solution of Sodium Lactate in Water for Injection. It contains not less than 95.0% and not more than 110.0% of the labelled amount of sodium lactate ($\text{C}_3\text{H}_5\text{NaO}_3$).

Description A clear, colourless liquid.

Identification Yield the reactions characteristic of sodium salts and lactates (Appendix III).

pH value 6.0-7.5 (Appendix VI H).

Pyrogens Dilute with sterile water for injection to produce a solution containing 25 mg of $\text{C}_3\text{H}_5\text{NaO}_3$ per ml. Complies with the test for pyrogens (Appendix XI D), using 10 ml per kg of the rabbit's weight.

Other requirements Complies with the general requirements for injections (Appendix I B).

Assay Measure accurately 1 ml to a conical flask, dry at 105°C for 1 hour. Carry out the Assay described under Sodium Lactate Solution, beginning at the words "Add 15 ml of glacial acetic acid and...". Each ml of perchloric acid (0.1 mol/L) VS is equivalent to 11.21 mg of $\text{C}_3\text{H}_5\text{NaO}_3$.

Category As described under Sodium Lactate Solution.

Strength (1) 20 ml : 2.24 g (2) 50 ml : 5.60 g

Storage Preserve in well closed containers, protected from light.

Sodium Lactate Solution

Sodium Lactate Solution contains not less than 40.0% (g/g) of Sodium Lactate ($C_3H_5NaO_3$).

Description A clear, colourless or almost colourless, viscous liquid.

Miscible with water, ethanol or glycerol.

Identification Yields the reactions characteristic of sodium salts and lactates (Appendix III).

Acidity or alkalinity Prepare a solution of 0.112 g per ml in water, heat for 30 minutes in a water bath, allow to cool. pH 6.5-7.5 (Appendix VI H).

Chloride Carry out the limit test for chlorides (Appendix VII A), using 1.0 g. Any opalescence produced is not more pronounced than that of a reference solution using 5.0 ml of sodium chloride standard solution (0.005%).

Sulfate Carry out the limit test for sulfates (Appendix VII B), using 2.0 g. Any opalescence produced is not more pronounced than that of a reference solution using 2.0 ml of potassium sulfate standard solution (0.010%).

Citrate, oxalate, phosphate or tartrate To 1.0 g add a quantity of water to produce 5 ml, mix well, add 1 ml calcium chloride TS, heat for 5 minutes in a water bath, no opalescence is produced.

Reducing sugar Mix 0.5 g with 10 ml of water, add 6 ml of alkaline cupric tartrate TS and boil for 2 minutes, no red precipitate is produced.

Heavy metals Transfer 2.0 g to a quartz crucible (or platinum crucible). Carry out the limit test for heavy metals (Appendix VIII H, method 2); not more than 0.001%.

Arsenic To 1.0 g add 5 ml of hydrochloric acid and 23 ml of water. Carry out the limit test for arsenic (Appendix VIII J, method 1); not more than 0.0002%.

Assay To about 0.2 g, accurately weighed, in a conical flask, dried for an hour at 105°C, add 15 ml of glacial acetic acid and 2 ml of acetic anhydride and heat to dissolve it. Allow the solution to cool, add 1 drop of crystal violet IS, titrate with perchloric acid (0.1 mol/L) VS until the colour changes to bluish-green. Perform a blank determination and make any necessary correction. Each ml of perchloric acid (0.1 mol/L) VS is equivalent to 11.21 mg of $C_3H_5NaO_3$.

Category Alkaline sodium salt.

Storage Preserve in tightly closed containers, protected from light.

Preparation (1) Sodium Lactate Injection
(2) Sodium Lactate Ringer's Injection

Sodium Lactate Ringer's Injection

Sodium Lactate Ringer's Injection is a sterile mixture of Sodium Lactate, Sodium Chloride, Potassium Chloride and Calcium Chloride in Water for Injection. It contains not less than 93.0% and not more than 107.0% of the labelled amount of

Sodium Lactate ($C_3H_5NaO_3$). It contains not less than 95.0% and not more than 105.0% of the labelled amount of Sodium Chloride (NaCl), Potassium Chloride (KCl) and Calcium Chloride ($CaCl_2 \cdot 2H_2O$) separately.

Formula	Sodium Lactate	3.10 g
	Sodium Chloride	6.00 g
	Potassium Chloride	0.30 g
	Calcium Chloride ($CaCl_2 \cdot 2H_2O$)	0.20 g
	Water for Injection	a sufficient quantity
	To make	1000 ml

Description A clear, colourless liquid.

Identification Yields the reactions characteristic of sodium salt, potassium salt, calcium salt (2), lactate and chloride (Appendix III).

pH value 6.0-7.5 (Appendix VI H).

Heavy metals Evaporate 100 ml of the injection on a water bath to about 20 ml, cool, add 2 ml of acetate BS (pH 3.5) and a quantity of water to produce 25 ml. Carry out the limit test for heavy metals (Appendix VIII H, method 1); not more than 0.00003%.

Arsenic To 25 ml of the injection add 5 ml of hydrochloric acid, carry out the limit test for arsenic (Appendix VIII J, method 1); not more than 0.000008%.

Bacterial endotoxin Carry out the test for bacterial endotoxin (Appendix XI E); less than 0.5 EU per ml.

Other requirements Complies with the general requirements for injections (Appendix I B).

Assay Potassium chloride Reference Solution Dissolve a quantity of potassium chloride dried at 130°C for 2 hours, accurately weighed, in water to produce a solution of 15 µg of potassium chloride per ml.

Test solution Measure accurately 10 ml of the injection to a 100 ml volumetric flask, dilute with water to volume, mix well; measure accurately 10 ml of the solution to a 100 ml volumetric flask, dilute with water to volume, mix well.

Procedure Measure accurately 15.0 ml, 20.0 ml and 25.0 ml of the reference solution to three 100 ml volumetric flasks, add respectively to each flask 1.0 ml, accurately measured, of the following solution [dissolve 0.31 g of sodium lactate, 0.60 g of sodium chloride, 0.02 g of calcium chloride ($CaCl_2 \cdot 2H_2O$) in water and dilute to 100 ml], dilute with water to volume, mix well. Carry out the method of atomic absorbance spectrophotometry (Appendix IV D Assay procedure, method 1), measure the absorbance of the resulting solutions and test solution at 767 nm. Calculate the content of KCl.

Sodium chloride Reference solution Dissolve a quantity of sodium chloride dried at 110°C for 2 hours, accurately weighed, in water to produce a solution of 20 µg per ml.

Test solution Measure accurately 2 ml of the injection to a 100 ml volumetric flask, dilute to volume with water, mix well. Measure accurately 2 ml into another 100 ml volumetric flask, dilute to volume with water.

Procedure Measure accurately 10.0 ml, 15.0 ml and 20.0 ml of the reference solution to three 100 ml volumetric flasks, dilute to volume with water, mix well. Carry out the method of atomic absorbance spectrophotometry (Appendix IV D Assay procedure, method 1), measure the absorbance of the resulting solutions and the test solution at 589 nm. Calculate the content of NaCl as follows:

$$NaCl\% = (W - 1.6165 \times \text{the labelled amount of})$$

sodium lactate) $\div 6 \times 100\%$

Where W is the total content of sodium chloride tested in 1 ml of the injection (mg).

Calcium chloride Reference solution Dissolve about 0.3125 g of calcium carbonate dried at 110°C for 2 hours, accurately weighed, in a 500 ml volumetric flask with 25 ml of 1 mol/L of hydrochloric acid, and dilute with water to volume.

Lanthanum solution Dissolve 6.6 g of Lanthanum Oxide in 10 ml of hydrochloric acid, dilute to 100 ml with water.

Test solution Measure accurately 10 ml of the injection to a 50 ml volumetric flask, add 2 ml of lanthanum solution, dilute to volume with water.

Procedure Measure accurately 1 ml, 2 ml and 3 ml of the reference solution to three 50 ml volumetric flasks, add respectively to each flask 10 ml, accurately measured, of the following solution [dissolve 0.31 g of sodium lactate, 0.60 g of sodium chloride, 0.03 g of potassium chloride in water and dilute to 100 ml], and 2 ml of lanthanum solution, dilute to volume with water, mix well. Carry out the method of atomic absorbance spectrophotometry (Appendix IV D Assay procedure, method 1), measure the absorbance of the resulting solutions and the test solution at 422.7 nm. Calculate the content of $\text{CaCl}_2 \cdot 2\text{H}_2\text{O}$.

Sodium lactate Measure accurately 10 ml of the injection to a conical flask with stopper, add accurately measured 25 ml of potassium dichromate (0.01667 mol/L) VS and 15 ml of sulfuric acid solution (1 \rightarrow 2), heat for about 20 minutes on a water bath. Cool, add 2.5 g of potassium iodide, cover the stopper, allow to stand in dark place for 10 minutes. Add 10 ml of water, titrate with sodium thiosulfate (0.1 mol/L) VS towards the end of titration. Add 1 ml of starch IS, continue to titrate until blue colour disappears and a bright green colour is produced. Perform a blank determination and make any necessary correction. Each ml of potassium dichromate (0.01667 mol/L) VS is equivalent to 2.802 mg of $\text{C}_3\text{H}_5\text{NaO}_3$.

Category Body fluid, electrolyte, regulator of acid-base balance.

Strength 500 ml

Storage Preserve in well closed containers.

Compound Sodium Lactate and Glucose Injection

Compound Sodium Lactate and Glucose Injection is a sterile mixture of Sodium Lactate ($\text{C}_3\text{H}_5\text{NaO}_3$), Sodium Chloride (NaCl), Potassium Chloride (KCl), Calcium Chloride ($\text{CaCl}_2 \cdot 2\text{H}_2\text{O}$) and Anhydrous Glucose ($\text{C}_6\text{H}_{12}\text{O}_6$) in Water for Injection. It contains not less than 93.0% and not more than 107.0% of the labelled amount of sodium lactate; not less than 95.0% and not more than 110.0% of the labelled amount of sodium chloride, potassium chloride, calcium chloride and anhydrous glucose respectively.

Formula	Sodium Lactate	3.10 g
	Sodium Chloride	6.00 g
	Potassium Chloride	0.30 g
	Calcium Chloride ($\text{CaCl}_2 \cdot 2\text{H}_2\text{O}$)	0.20 g
	Anhydrous Glucose	50.0 g

Water for Injection

a sufficient quantity

To make

1000 ml

Description A clear, colourless to pale yellow liquid.

Identification (1) Add 5 ml of the injection dropwise to hot alkaline cupric tartrate TS; a red precipitate of cuprous oxide is produced.

(2) Yields the reactions characteristic of sodium salt, potassium salt, calcium salt, lactates and chlorides (Appendix III).

pH value 3.6-6.5 (Appendix VI H).

Heavy metals Evaporate 100 ml of the injection on a water bath to dryness, heat gently until it is thoroughly charred, cool, add 2 ml of nitric acid and 5 drops of sulfuric acid. Heat gently until fumes are no longer evolved, ignite at $500-600^\circ\text{C}$ until the incineration is complete. Allow to cool, add 2 ml of hydrochloric acid, heat on a water bath for 2 minutes, add 1 drop of phenolphthalein IS and a quantity of ammonia TS until the solution becomes pale red, filter. To the filtrate add 2 ml of acetate BS (pH 3.5) and a quantity of water to produce 25 ml. Carry out the limit test for heavy metals (Appendix VII H, method 2): not more than 0.00002%.

Arsenic Evaporate 40 ml of the injection on a water bath to about 5 ml, add 5 ml of diluted sulfuric acid and 1 ml of bromine TS, and then evaporate to about 5 ml, cool, add 5 ml of hydrochloric acid and 18 ml of water, carry out the limit test for arsenic (Appendix VIII J, method 2): not more than 0.000005%.

Pyrogens Complies with the test for pyrogens (Appendix XI D), inject slowly 10 ml per kg of the rabbit's weight.

Other requirements Complies with the general requirements for injections (Appendix I B).

Assay Potassium chloride Reference solution Weigh accurately a quantity of potassium chloride dried at 130°C for 2 hours, dissolve it in water to produce a solution of 15 μg of potassium chloride per ml.

Test solution Measure accurately 10 ml of the injection to a 100 ml volumetric flask, dilute with water to volume, mix well; measure accurately 10 ml of the solution to a 100 ml volumetric flask, dilute with water to volume, mix well.

Procedure Measure accurately 15.0 ml, 20.0 ml and 25.0 ml of the reference solution to three 100 ml volumetric flasks separately, add to each volumetric flask 1.0 ml, accurately measured, of the following solution [dissolve 0.31 g of sodium lactate, 0.60 g of sodium chloride, 0.02 g of calcium chloride ($\text{CaCl}_2 \cdot 2\text{H}_2\text{O}$) and 5.00 g of anhydrous glucose with water in a 100 ml volumetric flask, and dilute to volume] dilute to volume with water, mix well. Carry out the method of atomic absorption spectrophotometry (Appendix IV D Assay procedure, method 1), measure the absorbance of the resulting solution at 767 nm. Calculate the content of KCl.

Sodium chloride Reference solution Dissolve a quantity of sodium chloride dried at 110°C for 2 hours, accurately weighed, in water to produce a solution of 20 μg per ml.

Test solution Measure accurately 2 ml of the injection to a 100 ml volumetric flask, dilute to volume with water, mix well. Measure accurately 2 ml into a 100 ml volumetric flask, dilute to volume with water.

Procedure Measure accurately 10 ml, 15 ml and 20 ml of the reference solution to three 100 ml volumetric flasks, dilute to volume with water, mix well. Carry out the method of atomic absorbance spectrophotometry (Appendix

IV D Assay procedure, method 1), measure the absorbance of the resulting solutions and the test solution at 589 nm. Calculate the content of NaCl as follows:

$$\text{NaCl}\% = (\text{W} - 1.6165 \times \text{the labelled amount of sodium lactate}) \div 6 \times 100\%$$

Where W is the total content of sodium chloride tested in 1 ml of the injection (mg).

Calcium chloride Reference solution Dissolve a quantity of calcium carbonate dried at 110°C for 2 hours, accurately weighed, in water to produce a solution of 250 µg per ml.

Lanthanum solution Dissolve 6.6 g of Lanthanum Oxide in 10 ml of hydrochloric acid, dilute to 100 ml with water.

Test solution Measure accurately 10 ml of the injection to a 50 ml volumetric flask, add 2 ml of lanthanum solution, dilute to volume with water.

Procedure Measure accurately 1 ml, 2 ml and 3 ml of the reference solution to three 50 ml volumetric flasks, add respectively to each flask 10 ml, accurately measured, of the following solution [dissolve 0.31 g of sodium lactate, 0.60 g of sodium chloride, 0.03 g of potassium chloride in water and dilute to 100 ml], and 2 ml of lanthanum solution, dilute to volume with water, mix well. Carry out the method of atomic absorbance spectrophotometry (Appendix IV D Assay procedure, method 1), measure the absorbance of the resulting solutions and the test solution at 422.7 nm. Calculate the content of $\text{CaCl}_2 \cdot 2\text{H}_2\text{O}$.

Sodium lactate Measure accurately 10 ml of the injection to a conical flask with stopper, add accurately measured 25 ml of potassium dichromate (0.01667 mol/L) VS and 15 ml of sulfuric acid solution (1→2), heat about 20 minutes on a water bath. Cool, add 2.5 g of potassium iodide, cover the stopper, allow to stand in dark place for 10 minutes. Add 10 ml of water, titrate with sodium thiosulfate (0.1 mol/L) VS towards the end of titration. Add 1 ml of starch IS, continue to titrate until blue colour disappears and a bright green colour is produced. Perform a blank determination and make any necessary correction. Each ml of potassium dichromate (0.01667 mol/L) VS is equivalent to 2.802 mg $\text{C}_3\text{H}_5\text{NaO}_3$.

Anhydrous glucose Carry out the determination of optical rotation (Appendix VI E). The observed rotation in degree multiplied by 1.8958 represents the weight (g) of $\text{C}_6\text{H}_{12}\text{O}_6$.

Category Antacid.

Strength 500 ml

Storage Preserve in well closed containers.

Sodium Morrhuate Injection

Sodium Morrhuate Injection is a sterile solution of the sodium salts of the fatty acids of Cod Liver Oil in Water for Injection. It contains not less than 93.0% and not more than 107.0% of the labelled amount of Sodium Morrhuate.

A suitable quantity of benzyl alcohol may be added.

Description A clear, yellow to brownish-yellow liquid; deteriorated on exposure to light.

Identification (1) Evaporate 5 ml of chloroform solution obtained in the test for Iodine value to 1 ml on a water bath, add 1 drop of sulfuric acid, a transient red colour is produced, and changing rapidly to brownish red.
(2) Yields the flame reactions of sodium salts (Appendix III).

Acidity or alkalinity To 5.0 ml add 5 ml of ethanol (neutral to phenolphthalein IS) and 2 drops of phenolphthalein IS. If the solution is colourless, add 0.5 ml of sodium hydroxide (0.1 mol/L) VS, a pale red colour is produced; If the colour of the solution is red, add 0.3 ml of hydrochloric acid (0.1 mol/L) VS, the colour disappears.

Iodine value Evaporate the petroleum ether extract obtained in the Assay to dryness at 60°C, dry the residue in vacuum over phosphorus pentoxide for 12 hours and weigh it accurately. Dissolve the residue in chloroform to produce a solution of 100 ml. Measure accurately 25 ml of the solution and determine the iodine value (Appendix VII H); the iodine value is not less than 130.

Other requirements Complies with the general requirements for injections (Appendix I B).

Assay Measure accurately a quantity of the injection equivalent to about 0.5 g of Sodium Morrhuate to a separator. Add 25 ml of petroleum ether. And add 25 ml of sulfuric acid (0.05 mol/L) VS, accurately measured, shake gently, and allow to separate. Withdraw the acid layer and wash the petroleum ether layer with two 10 ml portions of water, combine the washings and the acid solution. Add 1 drop of methyl orange TS, and titrate with sodium hydroxide (0.1 mol/L) VS. Each ml of sulfuric acid (0.05 mol/L) VS is equivalent to 32.40 mg of Sodium Morrhuate.

Category Sclerosing agent, hemostatic.

Strength (1) 1 ml : 0.05 g (2) 2 ml : 0.1 g
(3) 5 ml : 0.25 g (4) 10 ml : 0.5 g

Storage Preserve in well closed containers, protected from light.

Sodium Nitrite

NaNO_2 69.00

[7632-00-0]

Sodium nitrite contains not less than 99.0% of NaNO_2 , calculated on the dried basis.

Description Colourless or white to pale yellow crystals; odourless; taste, slightly saline; hygroscopic. The aqueous solution exhibits alkaline reaction. Freely soluble in water; slightly soluble in ethanol.

Identification (1) Acidify 1 ml of aqueous solution (0.3→10) with acetic acid, add a few drops of freshly prepared ferrous sulfate TS, a brown colour is produced.
(2) Heat a quantity of the above solution with dilute mineral acid, a reddish-brown fume is evolved.
(3) The aqueous solution yields the reactions characteristic of sodium salts (Appendix III).

Chloride Carry out the limit test for chlorides (Appendix VIII A), using 0.30 g. Any opalescence produced is not more pronounced than that of a reference solution using 6.0 ml of sodium chloride standard solution (0.02%).

Sulfate Carry out the limit test for sulfates (Appendix VIII B), using 1.0 g. Any opalescence produced is not more pronounced than that of a reference solution using 3.0 ml of potassium sulfate standard solution (0.03%).

Loss on drying When dried over sulfuric acid to constant weight, loses not more than 1.0% of its weight (Appendix VIII L).

Heavy metals Dissolve 2.0 g in 6 ml of dilute hydrochloric acid, evaporate to dryness on a water bath with constant

stirring to make the residue a coarse powder. Add 5 ml of water, evaporate to dryness, then add 23 ml of water and 2 ml of acetate BS (pH 3.5). Carry out the limit test for heavy metals (Appendix VIII H, method 1): not more than 0.001%.

Arsenic Dissolve 1.0 g in 0.4 ml of sulfuric acid and 1 ml of water, evaporate to dryness, heat until white fumes are evolved, cool, add 5 ml of hydrochloric acid and 23 ml of water. Carry out the limit test for arsenic (Appendix VIII J, method 1), complies with the requirement (0.0002%).

Assay Dissolve about 1 g, accurately weighed, in water in a 100 ml volumetric flask, dilute to volume and mix well. Add slowly with swirling 10 ml of the solution, accurately measured, to a conical flask containing 50.0 ml of potassium permanganate (0.02 mol/L) VS, 100 ml of water and 5 ml of sulfuric acid, keep the tip of the pipet below the surface during the addition. Stopper the flask tightly, allow to stand for 10 minutes, add 3 g of potassium iodide, stopper the flask tightly again, shake gently and allow to stand for 10 minutes. Titrate with sodium thiosulfate (0.1 mol/L) VS, adding 2 ml of starch IS towards the end of the titration and continue the titration until the blue colour disappears. Perform a blank determination and make any necessary correction. Each ml of potassium permanganate (0.02 mol/L) VS is equivalent to 3.45 mg of NaNO_2 .

Category Antidote.

Storage Preserve in tightly closed containers.

Sodium Nitroprusside

$\text{Na}_2\text{Fe}(\text{CN})_5\text{NO} \cdot 2\text{H}_2\text{O}$ 297.95 [13755-38-9]

Sodium Nitroprusside is disodium pentacyanonitrosyl ferrate (2-) dihydrate. It contains not less than 99.0% of $\text{Na}_2\text{Fe}(\text{CN})_5\text{NO}$, calculated on the dried basis.

Description Reddish-brown crystals or a powder; odourless or almost odourless. Freely soluble in water; slightly soluble in ethanol.

Identification (1) Dissolve about 50 mg in 10 ml of 2% ascorbic acid solution, add 1 ml of dilute hydrochloric acid and mix well. Add dropwise 1 ml of sodium hydroxide TS; a blue colour is produced, which disappears gradually on standing.

(2) The light absorption of a solution of 10 mg per ml in water exhibits a maximum at 394 nm (Appendix IV A).

(3) Yields the reactions characteristic of sodium salts (Appendix III).

Chloride Dissolve 1.0 g in 90 ml of water, add 10 ml of cupric sulfate TS, mix well, allow to stand for 10 minutes and then centrifuge. Carry out the limit test for chlorides (Appendix VIII A), using 25 ml of the supernatant liquid. Any opalescence produced is not more pronounced than that of a reference solution using 5.0 ml of sodium chloride standard solution and treated by adding cupric sulfate TS dropwise until the colour matches that of the test solution (0.02%).

Ferricyanide Dissolve 0.5 g in 10 ml of water, add 1 ml of ferrous sulfate TS; a reddish-brown precipitate is produced, showing no greyish-green colour.

Ferrocyanide Dissolve 1.0 g in 20 ml of water, divide the solution into two equal portions A and B. To portion B add 0.05 ml of ferric chloride TS and mix well. Compare it with portion A; no greyish-green colour is produced.

Water-insoluble substances Dissolve 10.0 g in 50 ml of water, heat on a water bath for 30 minutes, filter with a sintered glass crucible previously dried to constant weight at 105°C and wash with water until the filtrate is colourless. The residue, when dried to constant weight at 105°C, weighs not more than 1 mg.

Loss on drying When dried to constant weight at 120°C, loses not less than 11.6% and not more than 12.6% of its weight (Appendix VIII L).

Bacterial endotoxin Carry out the test for bacterial endotoxin (Appendix XI E): less than 8.3 EU per mg of Sodium Nitroprusside.

Assay Dissolve 0.12 g, accurately weighed, in 50 ml of water, carry out the method for potentiometric titration (Appendix VII A), using saturated calomel electrode with potassium nitrate salt bridge as the reference electrode, and silver electrode as the indicator electrode, titrate with silver nitrate (0.1 mol/L) VS. Each ml of silver nitrate (0.1 mol/L) VS is equivalent to 13.10 mg of $\text{Na}_2\text{Fe}(\text{CN})_5\text{NO}$.

Category Vasodilator.

Storage Preserve in tightly closed containers, protected from light.

Preparation Sodium Nitroprusside for Injection

Sodium Nitroprusside for Injection

Sodium Nitroprusside for Injection is a sterile, freeze dried preparation. It contains not less than 90.0% and not more than 110.0% of the labelled amount of sodium nitroprusside [$\text{Na}_2\text{Fe}(\text{CN})_5\text{NO} \cdot 2\text{H}_2\text{O}$], calculated with reference to the average weight of contents each container.

Description A pink crystalline powder; unstable in aqueous solution; decomposed rapidly on exposure to light.

Identification Complies with the tests for Identification described under Sodium Nitroprusside.

Acidity Dissolve the contents of 2 containers in 10 ml of water, pH 5.0-7.0 (Appendix VI H).

Cyanide Carry out the limit test for cyanides (Appendix VIII F, method 2), using the contents of 5 containers (equivalent to 0.25 g of sodium nitroprusside). The absorbance of the resulting solution is not greater than that of a reference solution prepared in the same manner, using 1.0 ml of potassium cyanide standard solution (0.0008%).

Ferricyanide, Ferrocyanide Complies with the test for Ferricyanide and Ferrocyanide described under Sodium Nitroprusside.

Loss on drying When dried to constant weight at 120°C, loses not more than 12.6% of its weight (Appendix VIII L).

Bacterial endotoxin Carry out the test for bacterial endotoxin (Appendix XI E): less than 8.3 EU per mg of Sodium Nitroprusside.

Other requirements Complies with the general requirements for injections (Appendix I B).

Assay Weigh accurately 0.12 g of the mixed contents obtained in the test for weight variation of contents. Proceed as directed in the Assay under Sodium Nitroprusside. Each ml of silver nitrate (0.1 mol/L) VS is equivalent to 14.90 mg of $\text{Na}_2\text{Fe}(\text{CN})_5\text{NO} \cdot 2\text{H}_2\text{O}$.

Category As described under Sodium Nitroprusside.

Strength 50 mg

Storage Preserve in well closed containers, protected from light.

Sodium Pertechnetate [$^{99\text{m}}\text{Tc}$] Injection

Sodium Pertechnetate [$^{99\text{m}}\text{Tc}$] Injection is a sterile isotonic solution of Sodium Pertechnetate [$^{99\text{m}}\text{Tc}$]. Technetium-99 m is a decay product of Molybdenum-99. ^{99}Mo is a radioactive isotope. [^{99}Mo] obtained by neutron irradiation of molybdenum compound is adsorbed on a column of alumina to form neutron irradiation Technetium [$^{99\text{m}}\text{Tc}$]. Prepare Molybdenum [^{99}Mo] obtained from this generator in colloidal form, then absorbed on a column to form Technetium [$^{99\text{m}}\text{Tc}$] generator, known as Colloided Molybdenum Technetium [$^{99\text{m}}\text{Tc}$] generator, Molybdenum [^{99}Mo] isolated from uranium fission products is absorbed on a column of alumina, known as Fission Technetium [$^{99\text{m}}\text{Tc}$] generator. Sodium Pertechnetate [$^{99\text{m}}\text{Tc}$] Injection is eluted from the generator with Sodium Chloride Injection under aseptic condition. It contains not less than 90.0% and not more than 110.0% of the labelled amount of Technetium-99 m radioactivity at the date and hour stated on the label.

Description A clear, colourless liquid.

Identification (1) Carry out the γ -ray spectrum method (Appendix XIII). The prominent photo has an energy of 0.140 MeV. Or half-life is not less than 5.72 hours and not more than 6.32 hours.

(2) The principal spot of prominent radioactive peak obtained in the determination of Radiochemical purity has a R_f value of 0.9-1.0.

pH value 4.0-7.0 (Appendix VI H).

Aluminium This test is applied to Technetium-99m obtained by neutron irradiation or from fission products.

To each of five 5 ml volumetric flasks containing 0 ml, 1.0 ml, 1.0 ml of aluminium standard solution (1 μg per ml) and 0.10 ml, 1.0 ml of the Injection add 1.0 ml of hydrochloric acid (0.1 mol/L) VS, 1.0 ml of 0.02% chrome azurol S solution and 1.0 ml of 0.1% cetrimonium bromide solution, 1.5 ml acetic acid-sodium acetate BS (pH 6.0) and water to volume, shake well. Allow to stand for 15-20 minutes, measure the absorbance at 620 nm (Appendix IV A), using 1 cm cells. Calculate the content of aluminium; not more than 10 μg per ml (Technetium-99 m obtained from fission products); or 20 μg per ml (Technetium-99 m obtained by neutron irradiation).

Zirconium This test is applied to Technetium-99 m obtained from colloidal Mo-99.

Preparation of reference solution Weigh accurately zirconium oxychloride ($\text{ZrOCl}_2 \cdot 8\text{H}_2\text{O}$) in suitable amount to dissolve in hydrochloric acid (0.05 mol/L) VS and dilute to a solution containing 10 μg per ml.

Procedure Place 1.0 ml, measured accurately, each of the reference solution and the solution being examined into 5 ml volumetric flask, add 0.5 ml of sulfuric acid solution 1 mol/L and 1.0 ml of 0.05% xylene orange solution and make up to volume with water, shake well and allow to stand for 10

minutes. Measure the absorbances at 535 nm (Appendix IV A), calculate the content of Zr; not more than 10 μg per ml.

Bacterial endotoxin Carry out the test for bacterial endotoxin (Appendix XI E), using a suitable amount of sample, diluted with water BET to 15 times of its original volume, less than 7.5 EU per ml.

Sterility Complies with the test for sterility (Appendix XI H).

Radionuclidic purity Carry out the determination of radionuclidic purity (Appendix XIII), with a suitable instrument. The radioactive impurities should comply with the following limit; $^{99}\text{Mo} < 0.1\%$.

Sodium Technetium [$^{99\text{m}}\text{Tc}$] Injection produced from Fission Technetium [$^{99\text{m}}\text{Tc}$] generator also comply to the following limits:

$$\begin{aligned} {}^{131}\text{I} &< 0.005\% \\ {}^{103}\text{Ru} &< 0.005\% \\ {}^{89}\text{Sr} &< 6 \times 10^{-5}\% \\ {}^{90}\text{Sr} &< 6 \times 10^{-6}\% \end{aligned}$$

$$\alpha\text{-radionuclide} < 1 \times 10^{-7}\%$$

$$\text{other } \beta, \gamma \text{ ray emitting impurities} < 0.01\%.$$

Radiochemical purity Carry out the determination of radiochemical purity (Appendix XIII, method 1), using hydrochloric acid solution (2 mol/L)-acetone [1 : 4] as the mobile phase. Not less than 98% of the total radioactivity is found in the spot corresponding to Sodium Pertechnetate [$^{99\text{m}}\text{Tc}$] (R_f value 0.9-1.0).

Radioactive concentration Not less than 51.8 MBq per ml (Appendix XIII).

Radioactivity Complies with the requirements for radioactivity (Appendix XIII, Measurement of radioactivity concentration).

Category Diagnostic.

Strength 3.7 GBq : 7.4 GBq (neutron irradiation generator)
18.5 GBq : 29.6 GBq : 37 GBq (fission and colloidal generator)

Sodium Phosphate [^{32}P] Injection

Sodium Phosphate [^{32}P] Injection is a sterile solution of ^{32}P -labelled Sodium Phosphate (predominantly $\text{Na}_2\text{H}^{32}\text{PO}_4$). It contains not less than 90.0% and not more than 110.0% of the labelled amount of radioactive concentration of phosphorus-32 at the date and hour stated on the label.

Description A clear, colourless liquid.

Identification Complies with the tests for Identification described under Sodium Phosphate [^{32}P] Oral Solution.

pH value 6.0-8.0 (Appendix VI H).

Phosphorus Carry out the corresponding test described under Sodium Phosphate [^{32}P] Oral Solution using 1 ml (no dilution), measured accurately; not more than 10 μg per ml.

Bacterial endotoxin Carry out the test for bacterial endotoxin (Appendix XI E), less than 15 EU per ml.

Sterility Complies with the test for sterility (Appendix XI H).

Radiochemical purity Carry out the determination of Radiochemical purity described under Sodium Phosphate [^{32}P] Oral Solution, using a strip of chromatographic paper

impregnated for 1-2 minutes with 2% ammonium chloride solution and dried at 100°C. Not less than 95% of the total radioactivity is found in the spot corresponding to Sodium Phosphate [^{32}P].

Radioactive concentration Not less than 185 MBq per ml (Appendix XIII).

Category Radiopharmaceutical.

Strength (1) 185 MBq (2) 370 MBq
(3) 925 MBq (4) 1850 MBq

Storage Preserve in well closed lead containers. The intensity of radiation on the surface of the container complies with relevant regulation.

Sodium Phosphate [^{32}P] Oral Solution

Sodium Phosphate [^{32}P] Oral Solution is a solution of ^{32}P -labelled Sodium Phosphate (predominantly $\text{Na}_2\text{H}^{32}\text{PO}_4$) with carrier. It contains not less than 90.0% and not more than 110.0% of the labelled amount of radioactive concentration of phosphorus-32 at the date and hour stated on the label.

Description A clear, colourless liquid.

Identification (1) Carry out the β -ray spectrum method (Appendix XIII) using suitable amount of sample, the β radiation has a maximum energy of 1.71 MeV.

(2) The principal spot obtained in the determination of Radiochemical purity has prominent radioactive peak with a R_f value of about 0.7.

pH value 6.0-8.0 (Appendix VI H).

Phosphorus Reference preparation Weigh accurately 21.95 mg of potassium dihydrogen phosphate to a 500 ml volumetric flask, dissolve it in water and dilute to volume, mix well. Each ml is equivalent to 10 μg of P.

Test preparation Dilute the solution being examined with water to about 10 μg of P per ml.

Procedure Transfer 1 ml each of the reference solution and test solution, both measure accurately, to 5 ml volumetric flasks separately, add successively 0.5 ml ammonium vanadate TS, 0.5 ml of ammonium molybdate TS and 1 ml of 70% perchloric acid solution with shaking, dilute with water to volume and mix well. Allow to stand for 30 minutes and measure the absorbance at 420 nm (Appendix IV A). Calculate the content of phosphorus (P): not more than 10 mg per ml.

Radiochemical purity Carry out the determination of radiochemical (Appendix XIII, method 1), using a mixture of acetone-water-concentrated amount solution-trichloroacetic acid (60 ml : 20 ml : 0.5 ml : 2.5 g) as the mobile phase. Not less than 98% of the total radioactivity is found in the spot corresponding to Sodium Phosphate [^{32}P].

Radioactive concentration Not less than 370 MBq per ml (Appendix XIII).

Category Radiopharmaceutical.

Strength (1) 370 MBq (2) 740 MBq
(3) 1850 MBq (4) 3700 MBq

Storage Preserve in well closed lead containers. The intensity of radiation on the surface of the container complies with relevant regulation.

Sodium Phytate and Stannous Chloride for Injection

Sodium Phytate and Stannous Chloride for Injection is a sterile, lyophilized mixture of Sodium Phytate ($\text{C}_6\text{H}_9\text{Na}_9\text{O}_{24}\text{P}_6$) and Stannous Chloride ($\text{SnCl}_2 \cdot 2\text{H}_2\text{O}$). It contains not less than 80.0% and not more than 115.0% of the labelled amount of Sodium Phytate, calculated as Phytic acid ($\text{C}_6\text{H}_{18}\text{O}_{24}\text{P}_6$).

Description A white lyophilized powder. Freely soluble in water.

Identification (1) Alkalinity the supernatant liquid obtained in the Assay (excess hydrogen sulfide removed) with dilute ammonia solution, add a few drops of calcium chloride TS, a white precipitate is produced.

(2) To the clear, digested solution obtained in the Assay add ammonium molybdate TS, a yellow colour is produced.

(3) Dissolve the content of 1 container in 0.5 ml of Sodium Chloride Injection, apply 1 drop of the solution to a strip of ammonium phosphomolybdate TP, a blue colour is produced.

Clarity and colour of solution Dissolve the content of 1 container in 6 ml of Sodium Chloride Injection, the solution is clear and colourless.

Stannous chloride To 5 containers, add 3 ml of 1 mol/L hydrochloric acid solution saturated by nitrogen to allow to dissolve. Carry out the method for potentiometric titration (Appendix VII A), titrate with potassium iodate (0.001667 mol/L) VS, under a current of nitrogen. The consumption of potassium iodate (0.001667 mol/L) VS of each container is not less than 0.07 ml. If one container fails the requirements, a further 5 containers may be tested and all must comply.

Acidity The pH value of the solution obtained in the test for Clarity and colour of solution is 3.0-6.0 (Appendix VI H).

Bacterial endotoxin Carry out the test for bacterial endotoxin (Appendix XI E), using suitable amount of the solution prepared by dissolving the content in water BET and diluted to 25 times of its volume with water BET; less than 75 EU each container.

Other requirements Complies with the general requirements for injections (Appendix I B).

Assay Dissolve the contents of 3 containers separately in 2 ml of water, accurately measured, combine the solutions and mix well. To 2 ml of the combined solution add 2 ml of 2% hydrochloric acid solution, both accurately measured, mix well and pass hydrogen sulfide into the solution until precipitation is complete. Centrifuge and decant the supernatant liquid, expel the excess hydrogen sulfide with a current of air. To 1 ml of the liquid, accurately measured, add 1 ml of sulfuric acid, digest until it is completely carbonized, cool and add hydrogen peroxide solution until it is clear and colourless. Heat for 15 minutes, allow to cool and transfer it to a 25 ml volumetric flask, dilute with water to volume and mix well. Transfer 2 ml of the solution, accurately measured, to another 25 ml volumetric flask, add 5 ml of molybdo-ascorbic acid solution (mix 9 ml of dilute sulfuric acid with 3 ml each of 2.5% ammonium molybdate solution and 10% ascorbic acid solution), dilute with water to volume and mix well. Warm for 30 minutes on a water bath at 45°C, measure the absorbance of total phosphorus

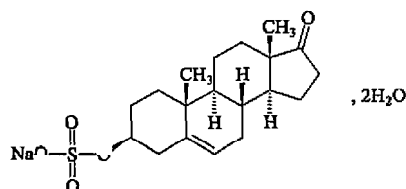
(E_1) at 660 nm (Appendix VI A). Transfer 1 ml of the liquid with hydrogen sulfide removed accurately measured, to a 25 ml volumetric flask, dilute with water to volume and mix well. Place 2 ml, accurately measured, in a 25 ml volumetric flask, add 5 ml of molybdo-ascorbic acid solution and make up to volume with water. Proceed as described above, beginning at the words "shake well,..." Measure the absorbance of inorganic phosphorus (E_1). Place 2 ml of potassium dihydrogen phosphate standard solution [corresponding to 0.05 mg of phosphorus (P) per ml], accurately measured, pass hydrogen sulfide into the solution, and then expel the excess hydrogen sulfide with a current of air. Transfer 1 ml of the liquid, accurately measured, in a 25 ml volumetric flask and add 5 ml of molybdo-ascorbic acid solution, dilute with water to volume. Proceed as described above, beginning at the words "shake well,..." measure the absorbance (E_2). Calculate the phosphorus content in the sample, multiplied by 3.548, represents the content of phytic acid ($C_6H_{18}O_{24}P_6$).

Category Used for the preparation of Technetium [^{99m}Tc] Phytate Injection.

Strength 9 mg of phytic acid and 0.12 mg of stannous chloride ($\text{SnCl}_2 \cdot 2\text{H}_2\text{O}$).

Storage Preserve in well closed containers, stored at 2–8°C in a dark place.

Sodium Prasterone Sulfate



$\text{C}_{19}\text{H}_{27}\text{NaO}_5\text{S} \cdot 2\text{H}_2\text{O}$ 426.51

Sodium Prasterone Sulfate is 3 β -hydroxy-androst-5-en-17-one sodium sulfate dihydrate. It contains not less than 97.0% and not more than 103.0% of $\text{C}_{19}\text{H}_{27}\text{NaO}_5\text{S}$, calculated on the dried basis.

Description White crystals or a crystalline powder; odourless; taste, bitter.

Soluble in ethanol, sparingly soluble in water, slightly soluble in dehydrated ethanol, practically insoluble in acetone, chloroform or ether.

Specific optical rotation +10°C to +13°C, in a solution of 40 mg per ml in methanol (Appendix VI E).

Identification (1) Dissolve about 10 mg in 1 ml of ethanol, add about 10 mg of 1,3-dinitrobenzene and stir to dissolve, add several drops of sodium hydroxide TS. A violet red colour is produced.

(2) The light absorption of a solution of 5 mg per ml in water exhibits a maximum at 289 nm, the absorbance is about 0.65, and a minimum at 241 nm.

(3) The infrared absorption spectrum (Appendix IV C) is concordant with the spectrum of Sodium Prasterone Sulfate (Appendix XVI).

(4) Dissolve about 50 mg in 5 ml of water, add 2 ml of 2 mol/L hydrochloric acid, heat in a water bath for 10 minutes, cool, filter, divide the filtrate into two portions: One portion yields the reactions characteristic of sulfates (Appendix III). To the another portion add concentrated

ammonia solution to neutralize, and add acetic acid to acidify, the solution yields the reactions characteristic of sodium salts (Appendix III).

Acidity Dissolve 0.10 g in 10 ml of water, pH 5.0–7.0 (Appendix VI H).

Clarity and colour of solution Dissolve 0.10 g in 10 ml of water by shaking thoroughly, the solution is clear and colourless.

Sulfate Dissolve 0.50 g in 40 ml of acetone-water (1 : 1) in a 50 ml Nessler cylinders, add 2 ml of diluted hydrochloric acid solution, mix well, add 5 ml of 25% barium chloride solution, dilute with water to volume, mix well, heat in a 30°C to 40°C water bath for 10 minutes. Carry out the limit test for sulfate (Appendix VII B). Any opalescence produced is not more pronounced than that of a reference solution using 2.0 ml of potassium sulfate standard solution (0.04%).

Related substances Carry out the method for thin-layer chromatography (Appendix V B), using silica gel G mixed with 0.5% carboxymethylcellulose sodium as the coating substance and a mixture of chloroform-methanol-water (75 : 22 : 3) as the mobile phase. Apply separately to the plate 10 μl of each of solutions in methanol containing (1) 10.0 mg per ml and (2) 0.10 mg per ml of the substance being examined. After developing and removal of the plate, dry in air. Spray with a mixture of sulfuric acid-ethanol (1 : 1) and heat at 80°C for 5 minutes. No more than 1 secondary spot is obtained in the chromatogram with solution (1) and the colour is not more intense than that of the principal spot obtained with solution (2).

Loss on drying when dried in vacuum over phosphorus pentoxide to constant weight at 60°C, loses not more than 9.6% of its weight (Appendix VIII L), using 0.50 g.

Bacterial endotoxin Carry out the test for bacterial endotoxin (Appendix XI E): less than 1.5 EU per mg.

Sterility Complies with the tests for sterility (Appendix XI H) (for directly sterility preparation).

Assay Carry out the method for high performance liquid chromatography (Appendix V D), using a column packed with octadecylsilane bonded silica gel and a mixture of methanol-water-triethylamine (650 : 350 : 4) with a pH value adjusted to 5.3 ± 0.1 by 4 mol/L sulfuric acid solution as the mobile phase. Detection wavelength is 210 nm and the number of theoretical plates of the column is not less than 800, calculated with reference to the peak of sodium prasterone sulfate.

Procedure Dissolve about 50 mg, accurately weighed, in the mobile phase to produce a solution of about 2 mg per ml. Inject 10 μl into the column, record the chromatogram. Repeat the operation, using a quantity of sodium prasterone sulfate CRS instead of the substance being examined. Calculate the content of $\text{C}_{19}\text{H}_{27}\text{NaO}_5\text{S}$ with respect to the peak area obtained in the chromatogram by the external standard method.

Category Androgen.

Storage Preserve in hermetically closed containers, protected from light.

Preparation Sodium Prasterone Sulfate for Injection.

Sodium Prasterone Sulfate for Injection

Sodium Prasterone Sulfate for Injection is a sterile powder or a sterile lyophilized preparation of

Sodium Prasterone Sulfate. It contains not less than 90.0% and not more than 110.0% of the labelled amount of sodium prasterone sulfate ($C_{19}H_{27}NaO_5S$), calculated on the basis of average content weight in containers.

Description White crystals or a crystalline powder (a sterile powder), or a white friable solid or powder (lyophilized preparation).

Identification (1) Complies with the tests (1) and (4) for Identification as described under Sodium Prasterone Sulfate.

(2) The retention time of the principal peak of Sodium Prasterone Sulfate in the substance being examined in the chromatogram obtained in the Assay is identical with that of the principal peak of sodium prasterone sulfate CRS in the chromatogram of the reference solution.

Acidity Dissolve the content of 1 container in 10 ml of water, pH 5.0-7.0 (Appendix VI H).

Clarity and colour of solution Dissolve the contents of 1 container in 10 ml of water, the solution is clear and colourless.

Loss on drying When dried in vacuum over phosphorus pentoxide to constant weight at 60°C, loses not more than 9.3% of its weight (Appendix VIII L).

Related substances Carry out the test for Related substances described under Sodium Prasterone Sulfate, using methanol-water (1 : 1) instead of methanol.

Bacterial endotoxin Carry out the test for bacterial endotoxins (Appendix XI E); less than 1.5 EU per mg of sodium prasterone sulfate.

Sterility Complies with the test for Sterility as described under Sodium Prasterone Sulfate.

Other requirements Comply with the general requirements for injections (Appendix I B).

Assay Weigh accurately a quantity of the well-mixed contents in the test for weight variation of contents, equivalent to about 50 mg of sodium prasterone sulfate, and carry out the Assay as described under Sodium Prasterone Sulfate. Calculate the content of $C_{19}H_{27}NaO_5S$.

Category As described under Sodium Prasterone Sulfate.

Strength 0.1 g

Storage Preserve in tightly closed containers, protected from light.

Sodium Pyrophosphate and Stannous Chloride for Injection

Sodium Pyrophosphate and Stannous Chloride for Injection is a sterile, lyophilized mixture of sodium pyrophosphate ($Na_4P_2O_7 \cdot 10H_2O$) and stannous chloride ($SnCl_2 \cdot 2H_2O$). It contains not less than 80.0% and not more than 115.0% of the labelled amount of sodium pyrophosphate.

Description A white lyophilized powder. Freely soluble in water.

Identification (1) Dissolve the contents of 1 container in 1 ml of water, add 1 drop of magnesium ammonium chloride TS, a white precipitate is produced.

(2) Dissolve the contents of 1 container in 0.5 ml of Sodium

Chloride Injection, apply 1 drop of the solution to a strip of ammonium phosphomolybdate TP, a blue colour is produced.

Clarity and colour of solution Dissolve the contents of 1 container in 10 ml of Sodium Chloride Injection, the solution is clear and colourless.

Stannous chloride Dissolve the contents of 5 containers separately in 8 ml of hydrochloric acid solution (1 mol/L), previously saturated with nitrogen. Carry out the method for potentiometric titration (Appendix VII A) under a current of nitrogen, titrate 2 ml, measured accurately, of the solution with potassium iodate (0.001667 mol/L) VS. Not less than 0.31 ml is consumed for each container. Repeat the test with another 5 containers, if one of them fails to meet the requirement. All the containers in the second test must comply with the requirement.

Acidity The pH value of the solution obtained in the test for Clarity and colour of solution is 5.0-7.0 (Appendix VI H).

Bacterial endotoxin Carry out the test for bacterial endotoxin (Appendix XI E), using suitable amount of sample solution prepared by dissolving the contents in water BET and diluted to 10 times of its volume with water BET; less than 75 EU each container.

Other requirements Comply with the general requirements for injections (Appendix I B).

Assay Dissolve the contents of 3 containers separately in 2 ml of water, accurately measured, combine the solutions and mix well. To 2 ml of the combined solution add 2 ml of 2% hydrochloric acid solution, both accurately measured, mix well and pass hydrogen sulfide into the solution until precipitation is complete. Centrifuge and decant the supernatant liquid, expel the excess hydrogen sulfide with current of air. Transfer 1 ml of the liquid, accurately measured, to a 10 ml volumetric flask, dilute with water to volume and mix well. Measure accurately 1 ml of the solution and transfer it to a 25 ml volumetric flask, add 5 ml of molybdo-ascorbic acid solution (mix 9 ml of dilute sulfuric acid with 3 ml each of 2.5% ammonium molybdate solution and 10% ascorbic acid solution), dilute with water to volume and mix well. Warm for 30 minutes on a water bath at 70°C, measure the absorbance of the solution at 660 nm (Appendix IV A). Dissolve 100 mg of sodium pyrophosphate CRS, accurately weighed, in 10 ml of Sodium Chloride Injection. Transfer 1 ml, accurately measured, add 1 ml of water and proceed as described above, beginning at the words "add 2 ml of 2% hydrochloric solution...". Calculate the content of $Na_4P_2O_7 \cdot 10H_2O$ in each container.

Category Used for the preparation of Technetium [^{99m}Tc] Pyrophosphate Injection.

Strength 10 ml of sodium pyrophosphate and 1.0 mg of stannous chloride ($SnCl_2 \cdot 2H_2O$).

Storage Preserve in tightly closed containers, stored at 2-8°C in a dark place.

Sodium Stibogluconate

[16037-91-5]

Sodium Stibogluconate is a pentavalent antimony compound of indefinite composition. It contains not less than 30.0% and not more than 34.0% of antimony (Sb), calculated on the dried basis.

Description A white to faintly yellow amorphous powder;

odourless. The aqueous solution is dextrorotatory. Freely soluble in hot water; soluble in water; insoluble in ethanol or ether.

Identification (1) Acidify the aqueous solution with dilute hydrochloric acid, add potassium iodide TS, a brown colour is produced which turns to blue on the addition of starch IS. (2) When heated, it chars without melting, emitting an odour of burnt sugar. Continue the heating until charring is complete, the residue yields the reactions characteristic of antimony salts and sodium salts (Appendix III).

Chlorides Dissolve 2.5 g in 100 ml of water. To 5.0 ml of the solution add 0.20 g of tartaric acid, shake to dissolve. Carry out the limit test for chlorides (Appendix VII A). Any opalescence produced is not more pronounced than that of a reference solution using 7.0 ml of sodium chloride standard solution (0.056%).

Sulfates Dissolve 0.20 g of tartaric acid in 20 ml of the remaining solution obtained in the test for chlorides. Carry out the limit test for sulfates (Appendix VII B). Any opalescence produced is not more pronounced than that of a reference solution using 2.0 ml of potassium sulfate standard solution (0.04%).

Loss on drying When dried under vacuum to constant weight at 120°C, loses not more than 15.0% of its weight (Appendix VII L).

Trivalent antimony To 40 ml of the remaining solution obtained in the test for Chlorides add 10 ml of freshly prepared sodium bicarbonate saturated solution and 2 ml of starch IS, mix well, add 0.10 ml of iodine solution (0.05 mol/L), a blue colour is produced and persists for not less than 3 minutes.

Lead Dissolve 1.0 g in 10 ml of water, add 1.0 g of tartaric acid, 10 ml of 10% sodium hydroxide solution, 2 ml of potassium cyanide TS and 5 drops of sodium sulfide TS, mix well and allow to stand for 2 minutes. Any colour produced is not more intense than that of a reference solution using 2.0 ml of lead standard solution (0.002%).

Arsenic To 0.10 g in a Nessler cylinder add 0.3 ml of 0.01% mercuric chloride solution, 9.2 ml of hydrochloric acid and 0.5 ml of stannous chloride solution (dissolve 22.5 g of stannous chloride in 12 ml of hydrochloric acid by warming), mix well, allow to stand for 30 minutes. Any colour produced is not more intense than that of a reference solution (to 0.3 ml of 0.0005% As solution add 0.3 ml of 0.01% mercuric chloride solution, 8.9 ml of hydrochloric acid and 0.5 ml of stannous chloride solution, mix well and allow to stand for 30 minutes) (0.0015%).

Stability of solution Dissolve a quantity equivalent to 2.0 g of antimony in 100 ml of water, the solution is almost colourless. Heat the solution at 115.5°C for 30 minutes in an autoclave, pH 5.0-7.0 (Appendix VI H).

Toxicity Complies with the test for Toxicity of sodium stibogluconate (Appendix VII L).

Assay To about 0.3 g, accurately weighed, in a stoppered conical flask add 100 ml of water, 15 ml of hydrochloric acid and 10 ml of potassium iodide TS, stopper the flask, shake well, allow to stand in the dark for 10 minutes. Titrate with sodium thiosulfate (0.1 mol/L) VS, add starch IS towards the end of the titration, continue the titration until the blue colour disappears. Perform a blank determination and make any necessary correction. Each ml of sodium thiosulfate (0.1 mol/L) VS is equivalent to 6.088 mg of Sb.

Category Antileishmanial.

Storage Preserve in tightly closed containers, protected from light.

Preparation Sodium Stibogluconate Injection

Sodium Stibogluconate Injection

Sodium Stibogluconate Injection is a sterile solution of Sodium Stibogluconate in Water for Injection. Each ml contains not less than 0.095 g and not more than 0.105 g of antimony (Sb).

Description A clear, colourless to faintly yellow liquid.

Identification (1) Complies with test (1) for Identification described under Sodium Stibogluconate.

(2) The residue obtained after evaporation to dryness complies with test (2) for Identification described under Sodium Stibogluconate.

pH value 5.0-6.3 (Appendix VI H).

Trivalent antimony To 3.0 ml add 37 ml of water, then add 10 ml of freshly prepared sodium bicarbonate saturated solution and 2 ml of starch IS, mix well, add 0.10 ml of iodine solution (0.05 mol/L) TS, a blue colour is produced and persists for not less than 3 minutes.

Toxicity Complies with the test for Toxicity of sodium stibogluconate (Appendix VII L).

Other requirements Comply with the general requirements for injections (Appendix I B).

Assay Measure accurately 1 ml, carry out the Assay described under Sodium Stibogluconate. Each ml of sodium thiosulfate (0.1 mol/L) VS is equivalent to 6.088 mg of Sb.

Category As described under Sodium stibogluconate.

Strength 6 ml (contains 0.6 g of pentavalent antimony, equivalent to about 1.9 g of sodium stibogluconate)

Storage Preserve in tightly closed containers, protected from light.

Sodium Thiosulfate

$\text{Na}_2\text{S}_2\text{O}_3 \cdot 5\text{H}_2\text{O}$ 248.19 [10102-17-7]

Sodium Thiosulfate contains not less 99.0% of $\text{Na}_2\text{S}_2\text{O}_3$, calculated on dried basis.

Description Colourless, transparent crystals or crystalline granules; odourless; taste, saline; efflorescents in dry air and hygroscopic in damp air; aqueous solution exhibits weak alkaline reaction.

Very soluble in water; insoluble in ethanol.

Identification (1) Dissolve about 0.1 g in 1 ml of water, a white precipitate is produced on adding hydrochloric acid which turns rapidly to yellow and the pungent odour of sulfur dioxide is perceived.

(2) Dissolve about 0.1 g in 1 ml of water, a transient dark purple colour is produced on addition of ferric chloride TS.

(3) The aqueous solution yields the reactions characteristic of sodium salts (Appendix III).

Loss on drying When dried at 40-50°C and gradually raising the temperature to 105°C until the weight is constant, loses not more than 37.0% and not less than 32.0% of its weight (Appendix VII L).

Calcium Dissolve 0.50 g in 10 ml of water and add ammonium oxalate TS. No turbidity is produced.

Heavy metals Dissolve 1.0 g in 10 ml of water, add slowly 5 ml of dilute hydrochloric acid and evaporate to dryness on a water bath. To the residue add 15 ml of water, boil gently for 10 minutes, filter. Boil the filtrate, add a quantity of bromine TS while hot to make the solution clear. Add a slight excess of bromine TS, boil to expel the excess bromine and allow it to cool. Add 1 drop of phenol-phthalein IS and a quantity of ammonia TS until the solution becomes pink. A. 2 ml of acetic acid. B. (pH 3.5) ... to produce 25 ml. Carry out the limit test for heavy metals (Appendix VIII H, method 1); not more than 0.002%.

Arsenic Dissolve 0.20 g in 5 ml of water, add 3 ml of nitric acid, carefully evaporate to dryness on a water bath. Add several milliliters of water to the residue, stir thoroughly and filter. Wash the residue with water, combine the filtrate and washings and evaporate to dryness. Dissolve the residue in 5 ml of hydrochloric acid and 23 ml of water. Carry out the limit test for arsenic (Appendix VIII J, method 1); not more than 0.001%.

Assay Dissolve about 0.5 g, accurately weighed, in 30 ml of water, add 2 ml of starch IS, titrate with iodine (0.05 mol/L) VS until the blue colour of the solution is persistent. Each ml of iodine (0.05 mol/L) VS is equivalent to 15.81 mg of $\text{Na}_2\text{S}_2\text{O}_3$.

Category Antidote.

Storage Preserve in tightly closed containers.

Preparation Sodium Thiosulfate Injection

Sodium Thiosulfate Injection

Sodium Thiosulfate Injection is a sterile solution of Sodium Thiosulfate in Water for Injection. It contains not less than 95.0% and not more than 105.0% of the labelled amount of sodium thiosulfate ($\text{Na}_2\text{S}_2\text{O}_3 \cdot 5\text{H}_2\text{O}$).

A quantity of stabilizer may be added.

Description A clear, colourless liquid.

Identification Complies with tests for Identification described under Sodium Thiosulfate.

pH value 8.5-10.0 (Appendix VI H).

Pyrogen Complies with the test for pyrogens (Appendix XI D), using 2.0 ml per kg of the rabbit's weight.

Other requirements Complies with the general requirements for injections (Appendix I B).

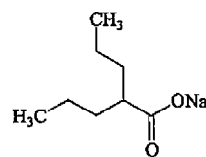
Assay Measure accurately a quantity of the injection equivalent to about 0.5 g of sodium thiosulfate, add 20 ml of water and 2 ml of acetone, allow to stand for 5 minutes. Add 2 ml of dilute acetic acid and 2 ml of starch IS, titrate with iodine (0.05 mol/L) VS until the blue colour of the solution is persistent. Each ml of iodine (0.05 mol/L) VS is equivalent to 24.82 mg of $\text{Na}_2\text{S}_2\text{O}_3 \cdot 5\text{H}_2\text{O}$.

Category As described under Sodium Thiosulfate.

Strength (1) 10 ml : 0.5 g (2) 20 ml : 1 g
(3) 20 ml : 10 g

Storage Preserve in well closed containers.

Sodium Valproate



$\text{C}_8\text{H}_{15}\text{NaO}_2$ 166.2

[1069-66-5]

Sodium Valproate is sodium 2-propylpentanoate. It contains not less than 99.0% of $\text{C}_8\text{H}_{15}\text{NaO}_2$, calculated on the dried basis.

Description A white crystalline powder or granules; taste, slightly astringent; strongly hygroscopic. Very soluble in water, freely soluble in methanol or ethanol, practically insoluble in acetone.

Identification (1) Dissolve 0.1 g in 1 ml of water, add 1 ml of benzene and 1-2 drops of 1% uranyl acetate solution and 1-2 drops of saturated solution of rhodamine B in benzene, a pink colour is produced immediately in benzene layer; examine under ultraviolet light, an orange fluorescence is produced.

(2) Dissolve 1 g in 10 ml of water, acidity with about 4 ml of hydrochloric acid solution (9→50), add 15 ml of ether and mix well. Allow to stand, evaporate the ether layer in an evaporating dish. Refractive index of the residue, 1.423-1.426 (Appendix VI F).

(3) The infrared absorption spectrum (Appendix IV C) is concordant with the reference spectrum of sodium valproate (Appendix XVI).

(4) The aqueous layer described under Identification test (2) yields the reaction characteristic of sodium (Appendix III).

Clarity and colour of solution A solution of 1.0 g in 10 ml of freshly boiled and cooled water is colourless and clear, any opalescence produced is not more pronounced than that of reference suspension I (Appendix IX B).

Alkalinity Dissolve 1.0 g in 20 ml of water, pH 7.5-9.0 (Appendix VI H).

Ethanol-insoluble substance To about 1 g add 10 ml of dehydrated ethanol, it dissolves completely.

Loss on drying When dried to constant weight at 105°C, loses not more than 3.0% of its weight (Appendix VIII L).

Heavy metals Carry out the limit test for heavy metals (Appendix VIII H, method 3), using 1.0 g; not more than 0.002%.

Assay Dissolve about 0.5 g, accurately weighed, in 30 ml of water, add 30 ml of ether. Carry out the method for potentiometric titration using glass-calomel electrode (Appendix VII A), titrate with hydrochloric acid (0.1 mol/L) VS to pH 4.5. Each ml of hydrochloric acid (0.1 mol/L) VS is equivalent to 16.62 mg of $\text{C}_8\text{H}_{15}\text{NaO}_2$.

Category Antiepileptic.

Storage Preserve in tightly closed containers, stored in a dry place.

Preparation Sodium Valproate Tablets

Sodium Valproate Tablets

Sodium Valproate Tablets contain not less than 90.0% and not more than 110.0% of the labelled amount of sodium valproate ($C_8H_{15}NaO_2$).

Description Sugar coated tablets with white or almost white core.

Identification Shake 5 tablets with sugar coating removed in 10 ml of water. Filter, the filtrate complies with tests (1), (2) and (4) for Identification described under Sodium Valproate.

Other requirements Comply with the general requirements for tablets (Appendix I A).

Assay Add about 50 ml of water to 10 tablets (for strength 0.2 g) or 20 tablets (for strength 0.1 g) in a 100 ml volumetric flask, shake thoroughly. Dilute with water to volume and mix well. Filter, measure accurately 25 ml of the successive filtrate. Complete the Assay described under sodium valproate, beginning at the words "add 30 ml of ether...". Each ml of hydrochloric acid (0.1 mol/L) VS is equivalent to 16.62 mg of $C_8H_{15}NaO_2$.

Category As described under Sodium Valproate.

Strength (1) 0.1 g (2) 0.2 g

Storage Preserve in tightly closed containers, stored in a dry place.

Soft Soap

Soft Soap is obtained by the saponification of suitable vegetable oils with potassium hydroxide.

Description A yellowish-white to yellowish-brown or yellowish-green soft lump, transparent or translucent, uniform and unctuous; odour, slight and characteristic. The aqueous solution exhibits an alkaline reaction to phenolphthalein IS. Soluble in water or ethanol.

Ethanol-insoluble substances Dissolve 5.0 g in 100 ml of hot neutral ethanol (previously neutralised to phenolphthalein IS). Filter through a sintered glass crucible previously dried to constant weight at 105°C, wash the residue thoroughly with hot neutral ethanol and dry for 1 hour at 105°C. The amount of residue is not more than 3.0%.

Free potassium hydroxide To the filtrate and the washings obtained in the test for ethanol-insoluble substance add 1-2 drops of phenolphthalein IS and 2.3 ml of sulfuric acid (0.05 mol/L) VS, no red or pink colour is produced.

Carbonates Wash the residue obtained in the test for ethanol-insoluble substances with 50 ml of boiling water. Allow the washings to cool, add 2-3 drops of methyl orange IS and 2.5 ml of sulfuric acid (0.05 mol/L) VS, the colour of the solution is red.

Unsaponified matter To 1.0 g add 20 ml of hot water, it is dissolved completely and the solution is almost clear.

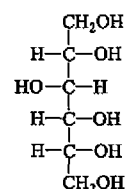
Water Carry out the method for determination of water (Appendix VIII M, method 2). Transfer 250 ml of toluene to bottle A, add 10 g of dried barium chloride. Wrap 1.0 g of the soap with a small piece of cellophane paper and drop it into bottle A. Heat gently until the water is distilled

completely, cool to room temperature and record the volume of distillate as blank. Repeat the operations with 7 g of the soap, accurately weighed, and again record the volume of distillate obtained. The difference between the two readings is the content of water in the substance being examined; not more than 52.0%.

Category Detergent.

Storage Preserve in tightly closed containers.

Sorbitol



$C_6H_{14}O_6$ 182.17

[50-70-4]

Sorbitol is D-glucitol. It contains not less than 98.0% of $C_6H_{14}O_6$, calculated on the dried basis.

Description A white crystalline powder; odourless; taste, sweet; hygroscopic.

Freely soluble in water; slightly soluble in ethanol; insoluble in chloroform or ether.

Specific optical rotation Weigh accurately 5 g to a 50 ml volumetric flask, add 6.4 g of sodium tetraborate and a quantity of water, shake to dissolve and dilute with water to volume. Filter, if necessary. The specific optical rotation of the resulting solution is +4.0° to +7.0° (Appendix VI E).

Identification (1) Dissolve 5 g in 4 ml of water by heating, cool, add 7 ml of methanol, 1 ml of benzaldehyde and 1 ml of hydrochloric acid and mix well. Allow it to stand for 2 hours until crystals are formed. Filter, dissolve the crystals in 20 ml of a boiled 5% solution of sodium bicarbonate, filter while warming. Allow it to cool until crystals are formed. Filter, wash the crystals with 5 ml of a mixture of methanol and water (1 : 1) and dry it over phosphorus pentoxide in vacuum for 24 hours. It melts at 174-179°C (Appendix VI C).

(2) Dissolve about 50 mg in 3 ml of water, add 3 ml of a freshly prepared 10% solution of catechol, mix well, add 6 ml of sulfuric acid and mix well, a pink colour is produced.

(3) The infrared absorption spectrum (Appendix IV C) is concordant with the reference spectrum of sorbitol (Appendix XVI).

Acidity Dissolve 5.0 g in 50 ml of freshly boiled and cooled water, add 3 drops of phenolphthalein IS and 0.30 ml of sodium hydroxide solution (0.02 mol/L) VS, a pink colour is produced.

Clarity and colour of solution A solution of 3.0 g in 20 ml of water is clear and colourless.

Chlorides Carry out the limit test for chlorides (Appendix VII A), using 1.4 g. Any opalescence produced is not more pronounced than that of a reference solution using 7.0 ml of sodium chloride standard solution (0.005%).

Sulfates Carry out the limit test for sulfates (Appendix VII B), using 2.0 g. Any opalescence produced is not more pronounced than that of a reference solution using 2.0 ml of potassium sulfate standard solution (0.01%).

Reducing sugars Dissolve 10.0 g in 35 ml of water in a 400 ml beaker. Add 50 ml of alkaline cupric tartrate TS, cover the beaker with a watch glass, heat the mixture in such a manner that the solution boils in 2-4 minutes. Allow it to continue to boil for a further 2 minutes. Immediately add 100 ml of freshly boiled and cooled water, filter with a tared filter crucible, previously dried to constant weight at 105°C. Wash the precipitate and the beaker with 30 ml of hot water, 10 ml of ethanol and 10 ml of ether successively and dry it to constant weight at 105°C; the weight of the cuprous oxide is not more than 67 mg.

Total sugars Place 2.1 g in a 250 ml flask fitted with a ground-glass joint, add 40 ml of hydrochloric acid solution (9 → 1000), heat under reflux for 4 hours and cool. Transfer the solution to a 400 ml beaker, rinse the flask with 10 ml of water, neutralize with a 24% solution of sodium hydroxide. Complete the test described under the test for Reducing sugars, beginning at the words "Add 50 ml of alkaline cupric tartrate TS": the weight of the cuprous oxide is not more than 50 mg.

Loss on drying When dried over phosphorus pentoxide in vacuum at 60°C to constant weight, loses not more than 1.0% of its weight (Appendix VIII L).

Residue on ignition Not more than 0.1% (Appendix VIII N).

Heavy metals Dissolve 2.0 g in 2 ml of sodium acetate BS (pH 3.5) and a quantity of water to produce 25 ml. Carry out the limit test for heavy metals (Appendix VIII H, method 1); not more than 0.001%.

Arsenic Dissolve 1 g in 10 ml of water, add 5 ml of dilute sulfuric acid and 0.5 ml of potassium bromide-bromine TS, warm on a water bath for 20 minutes, keeping bromine slightly in excess (if necessary, add dropwise potassium bromide-bromine TS), add water to replace the water evaporated and allow to cool. Add 5 ml of hydrochloric acid and a quantity of water to produce 28 ml. Carry out the limit test for arsenic (Appendix VIII J, method 1); not more than 0.0002%.

Assay Dissolve about 0.2 g, accurately weighed, in water in a 250 ml volumetric flask, dilute with water to volume and mix well. Measure accurately 10 ml to an iodine flask, add accurately 50 ml of sodium (potassium) periodate solution [Mix 90 ml of sulfuric acid solution (1 → 20) and 110 ml of sodium (potassium) periodate solution (2.3 → 1000)], heat on a water bath for 15 minutes and cool. Add 10 ml of potassium iodide TS and stopper the flask, allow it to stand for 5 minutes, titrate with sodium thiosulfate (0.05 mol/L) VS, add 1 ml of starch IS towards the end of titration, continue the titration until the blue colour disappears. Perform a blank determination and make any necessary correction. Each ml of sodium thiosulfate (0.05 mol/L) VS is equivalent to 0.9109 mg of $C_6H_{14}O_6$.

Category Diuretics.

Storage Preserve in tightly closed containers, protected from light.

Preparation Sorbitol Injection

Sorbitol Injection

Sorbitol Injection is a sterile solution of sorbitol in Water for Injection. It contains not less than 95.0% and not more than 105.0% of the labelled amount of sorbitol ($C_6H_{14}O_6$).

Description A clear, colourless solution.

Identification (1) Evaporate 20 ml on a water bath to about 10 ml, cool, the solution complies with test (1) for Identification described under Sorbitol.

(2) Dilute 0.2 ml with water to produce 3 ml. It complies with test (2) for Identification described under Sorbitol.

pH value 4.5-6.5 (Appendix VI H).

Pyrogens Complies with the test for pyrogens (Appendix XI D), using 10 ml per kg of the rabbit's weight.

Other requirements Complies with the general requirements for injections (Appendix I B).

Assay Transfer 10 ml, accurately measured, equivalent to about 2.5 g of sorbitol, to a 100 ml volumetric flask, dilute with water to volume and mix well. Transfer 10 ml, accurately measured, to a 250 ml volumetric flask, dilute with water to volume and mix well. Complete the Assay described under Sorbitol, beginning at the words "measure accurately 10 ml to an iodine flask". Each ml of sodium thiosulfate (0.05 mol/L) VS is equivalent to 0.9109 mg of $C_6H_{14}O_6$.

Category As described under Sorbitol.

Strength (1) 100 ml : 25 g (2) 250 ml : 62.5 g

Storage Preserve in well closed containers, protected from light.

Soybean Oil for Injection

Soybean Oil for Injection is the refined fixed oil obtained from the seeds of the soya plant *Glycine soya* Benth.

Description A pale yellow, clear liquid; odourless or almost odourless.

Miscible with ether or chloroform; very slightly soluble in ethanol; practically insoluble in water.

Relative density 0.916-0.922 (Appendix VI A).

Refractive index 1.472-1.476 (Appendix VI F).

Acid value Not more than 0.1 (Appendix VII H).

Saponification value 188-195 (Appendix VII H).

Iodine value 126-140 (Appendix VII H).

Light absorption The light absorption of the substance being examined at 450 nm (Appendix IV A) is not more than 0.045, taking water as the blank.

Peroxide Dissolve 10.0 g in 30 ml of acetic acid-chloroform (60 : 40) in a 250 ml iodine flask with shaking. Add accurately 0.5 ml of saturated potassium iodide solution, stopper the flask, shake thoroughly for 1 minute and add 30 ml of water. Titrate with sodium thiosulfate (0.01 mol/L) VS. Add 0.5 ml of starch TS towards the end point and continue the titration until the blue colour disappears. Perform a blank determination and make any necessary correction. Not more than 3.0 ml of sodium thiosulfate (0.01 mol/L) VS is consumed.

Unsaponifiable matter Place 5.0 g in a 250 ml conical flask, add 50 ml of potassium hydroxide solution in ethanol (dissolve 12 g of potassium hydroxide in 10 ml of water, dilute to 100 ml with ethanol). Reflux the mixture for 1 hour, cool to below 25°C. Transfer the solution to a separator, wash the flask with two portions of water, each of 50 ml, and combine the washings to the separator.

Extract with three portions of ether, each of 100 ml, combine the ether layer to another separator, wash with three portions of water, each of 40 ml, discard the washings. Wash the ether layer with 3% sodium hydroxide solution and water three times respectively, each of 40 ml, then wash with water for several times until no red colour is produced when dropping two drops of phenolphthalein IS, each of 40 ml. Transfer the ether extract to a evaporating dish, previously dried to constant weight, wash the separator with 10 ml of ether, transfer the washing to the evaporating dish, evaporating ether on a 50°C water bath, dissolve the residue with 6 ml of acetone, expel the acetone with current of air. Dry at 105°C until the variation between two continuous weight is less than 1 mg, the content of the unsaponifiable matter is not more than 1.0%.

Dissolve the residue with 20 ml of neutral ethanol, add a few drops of phenolphthalein IS and titrate with ethanolic sodium hydroxide (0.1 mol/L) VS until a pink colour persists 30 seconds, the test is invalid if more than 0.2 ml ethanolic sodium hydroxide (0.1 mol/L) VS is consumed, and the test must be done again.

Note: Ethanolic sodium hydroxide (0.1 mol/L) VS

P-eparation Measure 2 ml of 50% sodium hydroxide solution, add 250 ml of ethanol (allow to stand overnight) the solution is opalescent, and using the supernatant for standardization).

Standardization Dissolve about 0.2 g of benzoic acid, weighed accurately, in 10 ml of ethanol and 2 ml of water, add 2 drops of phenolphthalein IS and titrate with ethanolic sodium hydroxide (0.1 mol/L) VS until a persistent pink colour is produced. Each ml of ethanolic sodium hydroxide (0.1 mol/L) VS is equivalent to 12.21 mg of benzoic acid.

Heavy metals Transfer 5.0 g to a 50 ml porcelain evaporating dish, add 4 ml of sulfuric acid, mix well, heat gently until the sulfuric acid fumes are no longer evolved, add 2 ml of nitric acid and 5 drops of sulfuric acid, heat until nitrous oxide fumes are no longer evolved and ignite at 500-600°C until the incineration is complete. Cool, carry out the limit test for heavy metals (Appendix VIII H, method 2); not more than 0.0002%.

Arsenic Place 5.0 g in a quartz or platinum crucible, add 10 ml of ethanolic magnesium nitrate solution (1→50), ignite it until the incineration is complete. If the incineration is incomplete, moisten the residue with a small quantity of nitric acid, heat to the incineration. Cool, dissolve it in 5 ml of hydrochloric acid by heating on a water bath, add 23 ml of water, carry out the limit test for arsenic (Appendix VIII J, method 1); not more than 0.0004%.

Cottonseed oil Mix 5 ml in a test tube with a mixture of equal volumes of pentanol and 1% solution of sulfur in carbon disulfide. Place the test tube in a saturated sodium chloride water bath, warm the mixture carefully, when no foam is produced (carbon disulfide has been expelled), heat it for 15 minutes, no red colour develops.

Fatty acid composition Carry out the method for gas chromatography (Appendix V E), using a column packed with 12% polyethylene-glycol succinate as the stationary phase, and maintain the column temperature at 175°C, the number of the theoretical plates of the column is not less than 1300, calculated with reference to the peak of linoleate.

Test solution Place 20 mg in a 10 ml test tube with stopper. Add 2 ml of 0.5 mol/L methanolic potassium hydroxide solution, saponify the fatty acid for about 15 minutes in the water bath at 65°C until the oleosome is dissolved. Cool, add 2 ml of 15% methanolic boron trifluoride, esterify the fatty acid for 2 minutes in the water bath at 65°C. Cool, add 2 ml of *n*-hexane, shake well, add 2 ml of saturated sodium

chloride solution. Use the upper layer.

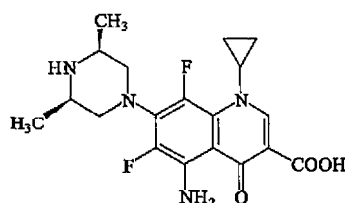
Procedure Inject 1 µl of the upper layer into the column, record the chromatogram. The order of elution is palmitate, stearate, oleate, linoleate and linolenate, and their relative areas, expressed as percentages of the total area of the 5 main peaks, are in the ranges 7.0%-14.0%, 1.0%-6.0%, 18.0%-30.0%, 44.0%-62.0% and 4.0%-11.0%.

Microbial limit test Complies with the requirements for microbial limit test (Appendix XI J).

Category Pharmaceutical aid.

Storage Preserve in well closed containers, protected from light, stored in a cool and dark place.

Sparfloxacin



$C_{19}H_{22}F_2N_4O_3$ 392.41

Sparfloxacin is 5-amino-1-cyclopropyl-7-[(cis-3,5-dimethyl-1-piperazinyl)-6,8-difluoro-1,4-dihydro-4-oxo-3-quinolinecarboxylic acid. It contains not less than 98.5% and not more than 102.0% of $C_{19}H_{22}F_2N_4O_3$, calculated on the dried basis.

Description A yellow crystalline powder; odourless; taste, bitter.

Sparingly soluble in chloroform; slightly soluble in acetonitrile, methanol or ethyl acetate; very slightly soluble in ethanol; practically insoluble in water; soluble in 0.1 mol/L sodium hydroxide solution; sparingly soluble in glacial acetic acid.

Identification (1) The retention time of principal peak of the substance being examined in the chromatogram obtained in the Assay is identical with that of sparfloxacin CRS in the chromatogram.

(2) The infrared absorption spectrum (Appendix IV C) is concordant with the reference spectrum of sparfloxacin (Appendix XVI).

Light absorption The light absorption of a solution of 0.4 mg per ml in 0.1 mol/L sodium hydroxide solution at 440 nm (Appendix IV A) is not greater than 0.15.

Related substances Carry out the method as described under Assay. Dissolve a quantity in methanol to produce solutions containing (1) 0.2 mg per ml and (2) 2 µg per ml, respectively. Inject 20 µl of solution (2) into the column. Adjust the attenuation so that the principal peak height in the chromatogram is 15%-20% of full scale of the chart. Inject separately 20 µl each of solution (1) and (2) into the column, and record the chromatogram for twice the retention time of the principal peak. The sum of the areas of all peaks other than the principal peak is not greater than the area of the principal peak in the chromatogram obtained with solution (2) (1.0%).

Toluene and pyridine Dissolve about 0.5 g, accurately weighed, in 5 ml of 2% sodium hydroxide solution in headspace vial and seal as the test solution. Dilute a quantity

of toluene and pyridine, accurately weighed, with 2% sodium hydroxide solution to produce a mixed solution containing 89 µg of toluene and 20 µg of pyridine per ml. Measure accurately 5 ml to a headspace vial and seal as the reference solution. Carry out the method for residual solvents (Appendix VIII P), using a capillary column packed with polyethylene glycol (PEG-20M) (or stationary phase with similar polarity), maintaining the temperature of the column at 60°C for 5 minutes, then raising the temperature at a rate of 20°C per minute to 150°C and maintaining at 150°C for 6 minutes; maintaining the temperature of the injection port at 200°C and that of the flame-ionisation detector (FID) at 230°C. The static head-space injection conditions may be used as follows: equilibration temperature is 85°C, equilibration time is 30 minutes and injection volume is 1.0 ml. Inject the reference solution into the column and record the chromatogram. The resolution factor between the principal peaks complies with the related requirements. Inject separately the test solution and the reference solution into the column and record the chromatograms. Calculate the content of toluene and pyridine respectively with respect to the peak area obtained in the chromatograms by the external standard method, the contents of toluene and pyridine comply with the relevant requirements.

Chloroform Dissolve about 0.5 g, accurately weighed, in 5 ml of 2% sodium hydroxide solution in headspace vial and seal as the test solution. Dilute a quantity of chloroform, accurately weighed, with 2% sodium hydroxide solution to produce a solution containing 6 µg of chloroform per ml. Measure accurately 5 ml to a headspace vial and seal as the reference solution. Carry out the method for residual solvents (Appendix VIII P), using a capillary column packed with polyethylene glycol (PEG-20M) (or stationary phase with similar polarity), maintaining the temperature of the column at 60°C for 10 minutes, then raising the temperature at a rate of 20°C per minute to 150°C and maintaining at 150°C for 5 minutes; maintaining the temperature of the injection port at 200°C and that of the flame-ionisation detector (FID) at 230°C. The static head-space injection conditions may be used as follows: equilibration temperature is 75°C, equilibration time is 20 minutes and injection volume is 1.0 ml. Inject the reference solution into the column and record the chromatogram. The resolution factor between the peaks complies with the relevant requirements. Inject separately the test solution and the reference solution into the column and record the chromatograms. Calculate the content of chloroform with respect to the peak area obtained in the chromatograms by the external standard method, the content of chloroform complies with the relevant requirement.

Loss on drying When dried to constant weight at 105°C, loses not more than 1.0% of its weight (Appendix VIII L).

Residue on ignition Not more than 0.2% (Appendix VIII N), using 1.0 g in a platinum crucible.

Heavy metals Carry out the limit test for heavy metals (Appendix VIII H, method 2), using the residue obtained in the test for residue on ignition; not more than 0.002%.

Assay Carry out the method for high performance liquid chromatography (Appendix V D), using a column packed with octadecylsilane bonded silica gel and a mixture of phosphate BS (Dissolve 6.8 g of potassium dihydrogen phosphate and 3.0 ml of triethylamine in 1000 ml of water and mix well)-methanol (43 : 57) (adjust pH value to 2.5 with phosphoric acid) as the mobile phase. Detection wavelength is 298 nm and the number of theoretical plates of the column is not less than 2500, calculated with reference to the peak of sparfloxacin.

Procedure Dissolve about 50 mg, accurately weighed,

with a quantity of methanol in a 100 ml volumetric flask and dilute to volume, mix well. Transfer accurately measured 2 ml of the solution into a 25 ml volumetric flask, dilute with mobile phase to volume and mix well. Inject 20 µl into the column. Repeat the operation, using sparfloxacin CRS instead of the substance being examined. Calculate the content of $C_{19}H_{22}F_2N_4O_3$ with respect to the peak area obtained in the chromatogram by the external standard method.

Category Quinolones antibiotic.

Storage Preserve in tightly closed containers, protected from light.

Preparation (1) Sparfloxacin Tablets
(2) Sparfloxacin Capsules

Sparfloxacin Capsules

Sparfloxacin Capsules contain not less than 90.0% and not more than 110.0% of the labelled amount of sparfloxacin ($C_{19}H_{22}F_2N_4O_3$).

Description The contents are yellow granules, powder or crystalline powder.

Identification (1) The retention time of principal peak of the substance being examined in the chromatogram obtained in the Assay is identical with that of sparfloxacin CRS in the chromatogram.

(2) Dissolve a quantity of contents in 0.1% sodium hydroxide solution to produce a solution of 7.5 µg of sparfloxacin per ml, filter. The light absorption of the filtrate exhibits a maximum at 291 nm (Appendix IV A).

Dissolution Carry out the dissolution test (Appendix X C, method 2), using 900 ml of acetic acid-sodium acetate BS (pH 4.5) as the dissolution medium, adjust the rotational speed of the paddle to 50 rpm. Withdraw the solution at exact 45 minutes and filter. Dilute 3 ml of the successive filtrate, accurately measured, with the dissolution medium in a 50 ml of volumetric flask and dilute to volume, mix well. Dissolve sparfloxacin CRS in the dissolution medium to produce a solution of about 6 µg per ml. Measure the absorbances of the resulting solutions at 291 nm (Appendix IV A). Calculate the dissolved amount of $C_{19}H_{22}F_2N_4O_3$ from each capsule. Not less than 80% of the labelled amount is dissolved.

Other requirements Comply with the general requirements for capsules (Appendix I E).

Assay Dissolve a quantity of the mixed contents in the test for weight variation of contents, equivalent to about 50 mg of sparfloxacin, with a quantity of methanol in a 100 ml volumetric flask and dilute to volume, mix well and filter. Transfer accurately measured 2 ml of the successive filtrate into a 25 ml volumetric flask, dilute with mobile phase to volume and mix well. Carry out the method for Assay described under Sparfloxacin.

Category As described under Sparfloxacin.

Strength 0.1 g

Storage Preserve in tightly closed containers, protected from light.

Sparfloxacin Tablets

Sparfloxacin Tablets contain not less than 90.0%

and not more than 110.0% of the labelled amount of sparfloxacin ($C_{19}H_{22}F_2N_4O_3$).

Description Pale yellow or yellow tablets, or film coated tablets with yellow core.

Identification (1) The retention time of principal peak of the substance being examined in the chromatogram obtained in the Assay is identical with that of sparfloxacin CRS in the chromatogram.

(2) Dissolve a quantity of powdered tablets in 0.1% sodium hydroxide solution to produce a solution of 7.5 µg of sparfloxacin per ml, filter. The light absorption of the successive filtrate exhibits a maximum at 291 nm (Appendix IV A).

Dissolution Carry out the dissolution test (Appendix X C, method 1), using 900 ml of acetic acid-sodium acetate BS (pH 4.5) as the dissolution medium, adjust the rotational speed of the basket to 100 rpm. Withdraw the solution at exact 45 minutes and filter. Dilute 3 ml of the successive filtrate, accurately measured, with the dissolution medium in a 50 ml of volumetric flask and dilute to volume, mix well. Dissolve sparfloxacin CRS in the dissolution medium to produce a solution of about 6 µg per ml. Measure the absorbances of the resulting solutions at 291 nm (Appendix IV A). Calculate the dissolved amount of $C_{19}H_{22}F_2N_4O_3$ from each tablet. Not less than 80% of the labelled amount is dissolved.

Other requirements Comply with the general requirements for tablets (Appendix I A).

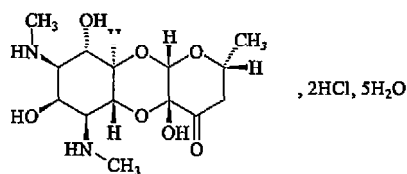
Assay Weigh accurately and powder 20 tablets. Dissolve an accurately weighed quantity of powdered tablets equivalent to about 50 mg of sparfloxacin, with a quantity of methanol in a 100 ml volumetric flask and dilute to volume, mix well and filter. Transfer accurately measured 2 ml of the successive filtrate into a 25 ml volumetric flask, dilute with mobile phase to volume and mix well. Carry out the method for Assay described under Sparfloxacin.

Category As described under Sparfloxacin.

Strength 0.1 g

Storage Preserve in tightly closed containers, protected from light.

Spectinomycin Hydrochloride



$C_{14}H_{24}N_2O_7 \cdot 2HCl \cdot 5H_2O$ 495.35 [22189-32-8]

Spectinomycin Hydrochloride is [2R-(2α, 4aβ, 5aβ, 6β, 7β, 8β, 9α, 9αa, 10aβ)]-decahydro-4a,7,9-trihydroxy-2-methyl-6,8-bis(methylamino)-4H-pyrano[2,3-b][1,4] benzodioxin-4-one di-hydrochloride pentahydrate. It has a potency of not less than 779 Spectinomycin Units per mg, calculated on the anhydrous basis.

Description A white or almost white crystalline powder. Freely soluble in water; practically insoluble in ethanol, chloroform or ether.

Specific optical rotation +15° to +21°, in a solution of 100 mg per ml in water (Appendix VI E).

Identification (1) The infrared absorption spectrum (Appendix IV C) is concordant with the spectrum of spectinomycin (Appendix XVI).

(2) The aqueous solution yields the reactions characteristic of chlorides (Appendix III).

Crystallinity Complies with the test for Crystallinity (Appendix IX D).

Acidity An aqueous solution of 10 mg per ml, pH 3.8-5.6 (Appendix VI H).

Clarity and colour of solution Dissolve 0.75 g each of 5 portions in 5 ml water respectively, the solutions are clear and colourless; any opalescence produced is not more pronounced than that of reference suspension 1 (Appendix IX B); any colour produced is not more intense than that of reference solution Y₆ (Appendix IX A, method 1).

Related substances Carry out the method for thin layer chromatography (Appendix V B), using silica gel G as the coating substance and a mixture of n-propanol-water-glacial acetic acid-pyridine (50 : 40 : 5 : 5) as the mobile phase. Develop the plate with mobile phase over 12 cm previously. Apply separately to the plate 10 µl each of two solutions in water containing (1) 20 mg per ml and (2) 0.2 mg per ml of the substance being examined. After developing and removal of the plate, allow it to dry in air and spray with 0.5% potassium permanganate solution. Any secondary spot in the chromatogram obtained with solution (1) is not more intense than the principal spot obtained with solution (2).

Water 16.0%-20.0% (Appendix VIII M, method 1).

Residue on ignition Not more than 1.0% (Appendix VIII N).

Consistence A suspension of 2 g per 3.2 ml in Phenylmethanol Injection passes readily through a No. 7 hypodermic needle without blockage.

Bacterial endotoxin Carry out the test for bacterial endotoxin (Appendix XI E); less than 0.09 EU per 1000 Spectinomycin Units.

Sterility Dissolve a quantity in 500 ml of 0.9% sterile Sodium Chloride Solution, the solution complies with the test for sterility (Appendix XI H, membrane filtration method).

Assay Carry out the Microbiological Assay of Antibiotics (Appendix XI A), using a solution of about 1000 Units per ml in sterile phosphate BS (pH 7.0). 1000 Spectinomycin Units is equivalent to 1 mg of $C_{14}H_{24}N_2O_7$.

Category Aminoglycoside antibiotics.

Storage Preserve in tightly closed containers, stored in a dry place.

Preparation Spectinomycin Hydrochloride for Injection

Spectinomycin Hydrochloride for Injection

Spectinomycin Hydrochloride for Injection is a sterile powder of spectinomycin hydrochloride. It has a potency of not less than 779 Spectinomycin Units per mg, calculated on the anhydrous basis; It contains not less than 90.0% and not more than

110.0% of the labelled amount of spectinomycin ($C_{14}H_{24}N_2O_7$).

Description A white or almost white crystalline powder.

Identification Complies with the tests for Identification described under Spectinomycin Hydrochloride.

Suspending and consistence Add 3.2 ml of Phenylmethanol Injection to one container, shake thoroughly to obtain a suspension, allow it to stand for 2 minutes; neither sediment is produced nor the suspension is separated distinctly into layers. The suspension passes readily through a No. 7 hypodermic needle without blockage.

Clarity and colour of solution To each of 5 containers add water to produce solutions of 0.12 g per ml according to the labelled amount respectively, the solutions are clear and colourless; any opalescence produced is not more pronounced than that of reference suspension 1 (Appendix IX B); any colour produced is not more intense than that of reference solution Y₆ (Appendix IX A, method 1).

Acidity, Related substances, Water, Bacterial endotoxin, and Sterility Comply with the corresponding requirements described under Spectinomycin Hydrochloride.

Other requirements Comply with the general requirements for injections (Appendix I B).

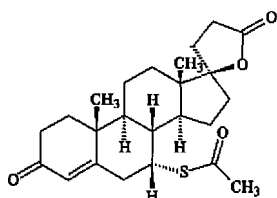
Assay Carry out the Assay described under Spectinomycin Hydrochloride, using an accurately weighed quantity of the mixed contents obtained in the test for weight variation of contents.

Category As described under Spectinomycin Hydrochloride.

Strength Calculated as $C_{14}H_{24}N_2O_7$
2 g (2000000 Units)

Storage Preserve in tightly closed containers, stored in a dry place.

Spironolactone



$C_{24}H_{32}O_4S$ 416.57

[52-01-7]

Spironolactone is 17β-hydroxy-7α-acetylsulfanyl-3-oxo-17α-pregn-4-ene-21-carboxylic acid acetate. It contains not less than 97.0% and not more than 103.0% of $C_{24}H_{32}O_4S$, calculated on the dried basis.

Description A white or almost white crystalline powder, with a faint odour of thiols.

Very soluble in chloroform; freely soluble in benzene or ethyl acetate; soluble in ethanol; insoluble in water.

Melting range 203-209°C, with decomposition (Appendix VI C).

Specific optical rotation -33° to -37° , in a solution of 10 mg per ml in chloroform (Appendix VI E), calculated on the dried basis.

Identification (1) To 10 mg add 2 ml of sulfuric acid and

mix well; the solution is orange yellow in colour, with a strong yellowish-green fluorescence, changes to scarlet on gentle warming, and hydrogen sulfide is evolved which blackens moist lead acetate test paper. Pour the solution into 10 ml of water, a yellowish-green emulsion is formed.

(2) The infrared absorption spectrum (Appendix IV C) is concordant with the reference spectrum of spironolactone (Appendix XVI).

Crystal fineness Place the crystals on a slide, add 1 drop of water and cover it with a cover glass. Examine under a microscope equipped with eyepiece micrometer, shift the slide to a position where the crystals in the visual field are found to be evenly distributed, count the number of crystals above and below 10 μm in size, not less than 90% of the crystals below 10 μm in size.

Mercapto compounds Dissolve 2.0 g in 30 ml of water and filter. To 15 ml of the filtrate add starch IS and titrate with iodine (0.005 mol/L) VS. Perform a blank determination and make any necessary correction. The volume of iodine (0.005 mol/L) VS consumed is not more than 0.10 ml.

Related substances Carry out the method for thin layer chromatography (Appendix V B), using silica gel G as the coating substance and butyl acetate as the mobile phase. Apply separately to the plate 5 μl each of two solutions of the substance being examined in chloroform containing (1) 20 mg per ml and (2) 0.20 mg per ml. After developing and removal of the plate, dry in air and repeat the process once more, spray with a 10% solution of sulfuric acid in methanol and dry at 105°C for 10 minutes. Any spot other than the principal spot in the chromatogram obtained with solution (1) is not more intense than the principal spot obtained with solution (2).

Loss on drying When dried to constant weight at 105°C, loses not more than 0.5% of its weight (Appendix VIII L).

Assay Dissolve an accurately weighed quantity in dehydrated ethanol to produce a solution of about 10 μg per ml, measure the absorbance at 238 nm (Appendix IV A). Calculate the content of $C_{24}H_{32}O_4S$, taking 471 as the value of A (1%, 1 cm).

Category Diuretic.

Storage Preserve in tightly closed containers.

Preparation (1) Spironolactone Capsules
(2) Spironolactone Tablets

Spironolactone Capsules

Spironolactone Capsules contain not less than 93.0% and not more than 107.0% of the labelled amount of spironolactone ($C_{24}H_{32}O_4S$).

Identification Shake a quantity of the contents equivalent to about 0.1 g of spironolactone with 5 ml of chloroform, filter, evaporate the filtrate to dryness on a water bath. The residue complies with tests for Identification described under Spironolactone.

Related substances Shake a quantity of the contents equivalent to about 0.2 g of spironolactone with 10 ml of chloroform, filter, use the filtrate as test solution. Measure accurately 1 ml to a 100 ml volumetric flask, dilute with chloroform to volume and mix well, use the resulting solution as reference solution. Carry out the test for Related substances described under Spironolactone. It complies with the requirement.

Dissolution Carry out the dissolution test (Appendix X C, method 2), using 1000 ml of 0.1 mol/L hydrochloric acid solution containing 0.1% of sodium lauryl sulfate as the dissolution medium, adjust the rotational speed of the paddle to 100 rpm, withdraw 10 ml of the solution at exact 60 minutes and filter. Transfer 5 ml of the successive filtrate, accurately measured, to a 10 ml volumetric flask, dilute to volume with the dissolution medium and mix well. Measure the absorbance of the resulting solution at 242 nm (Appendix IV A); dissolve about 20 mg of spironolactone CRS, accurately weighed, in 2 ml of ethanol in a 200 ml volumetric flask, dilute to volume with the dissolution medium, mix well, transfer 5 ml of the solution, accurately measured, to a 50 ml volumetric flask, dilute to volume with the dissolution medium and mix well. Measure the absorbance in the same manner. Calculate the dissolution of $C_{24}H_{32}O_4S$ from each capsule. Not less than 80% of the labelled amount is dissolved.

Other requirements Comply with the general requirements for capsules (Appendix I E).

Assay Shake an accurately weighed quantity of the mixed contents obtained in the test for Weight variation of contents equivalent to about 10 mg of spironolactone in a 100 ml volumetric flask with a quantity of dehydrated ethanol, dilute to volume with the same solvent, mix well and filter. Measure accurately 5 ml of the successive filtrate to a 50 ml volumetric flask, dilute with dehydrated ethanol to volume and mix well. Measure the absorbance of the resulting solution at 238 nm (Appendix IV A), calculate the content of $C_{24}H_{32}O_4S$, taking 471 as the value of A (1%, 1 cm).

Category As described under Spironolactone.

Strength 20 mg

Storage Preserve in tightly closed containers and stored in dry place.

Spironolactone Tablets

Spironolactone Tablets contain not less than 95.0% and not more than 105.0% of the labelled amount of spironolactone ($C_{24}H_{32}O_4S$).

Description White tablets.

Identification Extract a quantity of finely powdered tablets equivalent to 0.1 g of spironolactone with 5 ml of chloroform and filter. Evaporate the filtrate to dryness on a water bath and dry the residue at 105°C. It complies with the tests for Identification described under Spironolactone.

Related substances Extract a quantity of finely powdered tablets equivalent to 0.20 g of spironolactone, accurately weighed, with 10 ml of chloroform, filter (solution 1). Measure accurately 1 ml of this solution into a 100 ml volumetric flask and dilute with chloroform to volume (solution 2). Carry out the test for related substance described under Spironolactone, the same result is obtained.

Dissolution Carry out the dissolution test (Appendix X C, method 2), using 1000 ml of 0.1 mol/L hydrochloric acid solution containing 0.1% of sodium lauryl sulfate as the dissolution medium, adjust the rotational speed of the paddle to 75 rpm, withdraw 10 ml of the solution at exact 60 minutes and filter. Transfer 5 ml of the successive filtrate, accurately measured, to a 10 ml volumetric flask, dilute to volume with the dissolution medium and mix well. Measure the absorbance of the resulting solution at 242 nm (Appendix IV A); dissolve about 20 mg of spironolactone

CRS, accurately weighed, in 2 ml of ethanol in a 200 ml volumetric flask, dilute to volume with the dissolution medium, mix well, transfer 5 ml of the solution, accurately measured, to a 50 ml volumetric flask, dilute to volume with the dissolution medium and mix well. Measure the absorbance in the same manner. Calculate the dissolution of $C_{24}H_{32}O_4S$ from each tablet. Not less than 80% of the labelled amount is dissolved.

Other requirements Comply with the general requirements for tablets (Appendix I A).

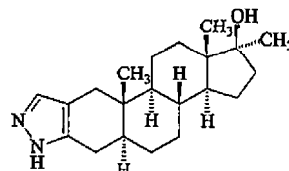
Assay Weigh accurately and powder 10 tablets. Weigh accurately a quantity of the powder, equivalent to 10 mg of spironolactone, into a 100 ml volumetric flask, add dehydrated ethanol to volume and shake thoroughly. Filter, transfer 5 ml of the successive filtrate, accurately measured, to a 50 ml volumetric flask, add dehydrated ethanol to volume and mix well. Measure the absorbance of the resulting solution at 238 nm (Appendix IV A). Calculate the content of $C_{24}H_{32}O_4S$, taking 471 as the value of A (1%, 1 cm).

Category As described under Spironolactone.

Strength 20 mg

Storage Preserve in tightly closed containers, stored in a dry place.

Stanozolol



$C_{21}H_{32}N_2O$ 328.48

[10418-08-3]

Stanozolol is 17-methyl-2'-H-5 α -androst-2-en-3,20-dione pyrazol-17 β -ol. It contains not less than 96.0% of $C_{21}H_{32}N_2O$, calculated on the dried substance.

Description A white crystalline powder; odourless. Sparingly soluble in ethanol or chloroform; slightly soluble in ethyl acetate or acetone; very slightly soluble in benzene; practically insoluble in methanol or water.

Specific optical rotation +34° to +40°, in a solution of 20 mg per ml in dehydrated ethanol (Appendix VI E).

Identification (1) To about 2 mg add 3 ml of *p*-dimethylaminobenzaldehyde TS, a yellow colour is produced, and a yellowish-green fluorescence is exhibited under the ultraviolet light (365 nm).

(2) The light absorption of a solution of 0.04 mg per ml in dehydrated ethanol exhibits a maximum at 224 nm (Appendix IV A).

(3) The infrared absorption spectrum (Appendix IV C) is concordant with the reference spectrum of stanozolol (Appendix XVI).

Related substances Carry out the method for thin-layer chromatography (Appendix V D), using silica gel G as the coating substance and a mixture of chloroform-methanol (9 : 1) as the mobile phase. Apply separately to the plate 10 μ l of solution in a mixture of chloroform-methanol (19 : 1) (1) containing 15 mg of the substance being examined per ml and 7.5 μ l of solution (2) containing 0.6 mg per ml. After developing and removal the plate, dry in air, spray

with a 20 % of sulfuric acid solution and heat for 15 minutes at 100°C. Any spot other than the principal spot obtained in the chromatogram with solution (1) is not more intense than the principal spot with solution (2) (3.0%).

Loss on drying When dried to constant weight at 105°C, loses not more than 3.0 % of its weight (Appendix VIII L).

Residue on ignition Not more than 0.1 % (Appendix VIII N).

Assay Dissolve about 0.5 g, accurately weighed, in 25 ml of glacial acetic acid by heating, allow to cool, add a drop of crystal violet TS, and titrate with perchloric acid (0.1 mol/L) VS to a green endpoint. Perform a blank determination and make any necessary correction. Each ml of perchloric acid (0.1 mol/L) VS is equivalent to 32.85 mg of $C_{21}H_{32}N_2O$.

Category Anabolic steroid.

Storage Preserve in tightly closed container, protected from light.

Preparation Stanozolol Tablets

Stanozolol Tablets

Stanozolol Tablets contain not less than 90% and not more than 110% of the labelled amount of stanozolol ($C_{21}H_{32}N_2O$).

Description White tablets.

Identification Boil a quantity of powdered tablets, equivalent to about 2 mg of stanozolol, with 5 ml of ethanol, filter, and evaporate on a water bath to dryness. Add 3 ml of *p*-dimethylaminobenzaldehyde TS to the residue; a yellow colour develops, which exhibits a green fluorescence under ultraviolet light (365 nm).

Content uniformity Comply with the requirements (Appendix X E) with a limit of $\pm 20\%$. Disintegrate a tablet in a 25 ml volumetric flask with 0.5 ml of water by shaking. Add about 20 ml of ethanol, heat on a water bath with occasional swirling for 10 to 15 minutes, then cool, dilute with ethanol to volume and mix well. Filter, taking precautions to minimize evaporation, and proceed as directed in the Assay, beginning at the words "Transfer 5 ml of the filtrate".

Dissolution Carry out the dissolution test (Appendix X C, method 3), using 250 ml of hydrochloric acid (9→1000) as the dissolution medium, adjust the rotational speed of the paddle to 50 rpm, withdraw the solution at exact 45 minutes and filter, use the successive filtrate as the test solution. Dissolve 20 mg stanozolol CRS, accurately measured in a 50 ml volumetric flask, add 15 ml ethanol, warm the solution in water bath, cool, add 5.0 ml 1.0 mol/L hydrochloric acid solution, and add water to volume, mix well. Transfer 2 ml of the solution, accurately measured, into a 100 ml volumetric flask, add hydrochloric acid (9→1000) to volume and mix well as reference solution freshly prepared. Measure the absorbances of the resulting solutions at 230 nm. Calculate the dissolution of $C_{21}H_{32}N_2O$ from each tablets. Not less than 75% of the labelled amount is dissolved.

Other requirements Comply with the general requirements for tablets (Appendix I A).

Assay Weigh accurately and powder 20 tablets. To an accurately weighed quantity of the powder equivalent to about 8 mg of stanozolol in a 100 ml volumetric flask add 70 ml of

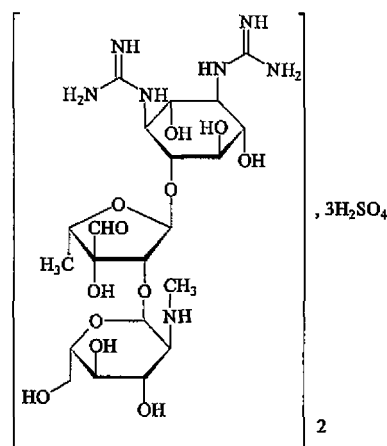
ethanol and heat in a hot water bath with constant shaking for 30 minutes. Cool, dilute with ethanol to volume, mix well. Filter, transfer 5 ml of the filtrate to a 10 ml volumetric flask, dilute to volume with ethanolic solution of hydrochloric acid (1.6→100) and mix well to prepare the acidic test solution. Transfer another 5.0 ml of the filtrate to another 10 ml volumetric flask, dilute to volume with ethanol to prepare the blank solution, measure the absorbance at 235 nm (Appendix IV A). Repeat the operation, using stanozolol CRS instead of the substance being examined. Calculate the content of $C_{21}H_{32}N_2O$.

Category As described under Stanozolol.

Strength 2 mg

Storage Preserve in tightly closed containers, protected from light.

Streptomycin Sulfate



$(C_{21}H_{39}N_7O_{12})_2 \cdot 3H_2SO_4$ 1457.40 [3810-74-0]

Streptomycin Sulfate is *O*-2-deoxy-2-(methyl-amino)- α -L-glucopyranosyl-(1→2)-*O*-5-deoxy-3-*C*-formyl- α -L-lyxofuranosyl-(1→4)-*N*¹,*N*³-bis (aminoimino-methyl)-D-streptamine sulfate(2 : 3)(salt). It has a potency of not less than 720 Streptomycin Units per mg, calculated on the dried basis.

Description A white, or almost white powder; odourless or almost odourless; taste, slightly bitter; hygroscopic. Freely soluble in water; insoluble in ethanol or chloroform.

Identification (1) Dissolve 0.5 mg in 4 ml of water, add 2.5 ml of sodium hydroxide TS and 1 ml of a 0.1% solution of 8-hydroxyquinoline in ethanol, cool to about 15°C and add 3 drops of sodium hypobromite TS; an orange-red colour is produced.

(2) Dissolve 20 mg in 5 ml of water, add 0.3 ml of sodium hydroxide TS, heat on a water bath for 5 minutes and add 0.5 ml of ferric ammonium sulfate solution prepared by dissolving 0.1 g of ferric ammonium sulfate in 5 ml of 0.5 mol/L sulfuric acid solution, a purplish red colour is produced.

(3) The infrared absorption spectrum (Appendix IV C) is concordant with the spectrum of streptomycin sulfate (Appendix XVI).

(4) The aqueous solution yields the reactions characteristic of sulfates (Appendix III).

Acidity Dissolve a quantity in water to produce a solution of

200000 Units per ml, pH 4.5-7.0 (Appendix VI H).

Clarity and colour of solution Dissolve each 1.5 g of 5 portions in 5 ml of water the solutions are clear and colourless; any opalescence produced is not more pronounced than that of reference suspension 2 (Appendix IX B); any colour produced is not more intense than that of reference solution 5 (Appendix IX A, method 1).

Sulfates Dissolve about 0.25 g, accurately weighed, in 100 ml of water and adjust the solution to pH 11 using ammonia TS. Add 10 ml of barium chloride (0.1 mol/L) VS and 5 drops of phthalein purple IS. Titrate with disodium edetate (0.1 mol/L) VS, make sure to keep the pH value 11 during the titration, add 50 ml of ethanol when the colour of the solution begins to change, and continue the titration until the bluish-purple colour disappears. Perform a blank determination and make any necessary correction. Each ml of barium chloride (0.1 mol/L) VS is equivalent to 9.606 mg of sulfate (SO_4). The content of SO_4 is 18.0%-21.5%, calculated on the dried basis.

Streptomycin B Carry out the method for thin-layer chromatography (Appendix V B), using silica gel G as the a mixture of coating substance and toluene-acetate-methanol (50 : 25 : 25) as the mobile phase. Weigh accurately about 0.25 g to a circumfluence flask, dissolve in a 5 ml freshly prepared solution of sulfuric acid-methanol (3 : 97) then heat and circumfluence for 1 hour. Cool, flush the condenser with methanol and amalgamate the wash solution and dilute the solution to 10 mg per ml by methanol as the test solution. Weigh accurately about 36 mg of mannose CRS to a circumfluence flask, use the same method to produce a solution containing 72 μg per ml as the reference solution. Apply separately to the plate 10 μl . After developing and removal of the plate, allow to dry in air. Spray with a developer freshly prepared (a mixture solution of equivalent volume of 0.2% 1,3-hydronaphthoquinone ethanol solution and 20% sulfuric acid, heat it at 110°C for several minutes. Any spot obtained with test solution is not more intense than the principal spot obtained with reference solution (3.0%).

Loss on drying When dried over phosphorus pentoxide in vacuum at 60°C for 4 hours, loses not more than 6.0% of its weight (Appendix VIII L).

Undue toxicity Complies with the test for undue toxicity (Appendix XI C), using a solution of 2600 Units per ml in Sodium Chloride Injection, injected intravenously and observed for 24 hours.

Bacterial endotoxin Carry out the test for bacterial endotoxin (Appendix XI E); less than 0.25 EU per 1000 Streptomycin Units.

Sterility Carry out the test for sterility (Appendix XI H, membrane filtration method), each portion add not less than 500 ml of 0.9% sterile sodium chloride solution. Concomitantly transfer 0.25-0.5 ml of a solution of 20000 Units per ml to each of six tubes containing 10 ml of a 0.5% glucose broth; incubate three tubes at 30-35°C and the remainder at 20-25°C. All the results comply with the requirement.

Assay Dissolve a quantity, accurately weighed, in sterile water to prepare a solution of 1000 Units per ml and carry out the Microbiological Assay of Antibiotics (Appendix XI A). 1000 Streptomycin Units are equivalent to 1 mg of $\text{C}_{21}\text{H}_{39}\text{N}_7\text{O}_{12}$.

Category Aminoglycoside antibiotic.

Storage Preserve in hermetically sealed containers, stored in a dry place.

Preparation Streptomycin Sulfate for Injection

Streptomycin Sulfate for Injection

Streptomycin Sulfate for Injection is a sterile powder of Streptomycin Sulfate. It has a potency of not less than 720 Streptomycin Units per mg, calculated on the dried basis. It contains not less than 93.0% and not more than 107.0% of the labelled potency of streptomycin ($\text{C}_{21}\text{H}_{39}\text{N}_7\text{O}_{12}$), calculated on the basis of the average weight of contents.

Description A white, or almost white powder.

Identification Complies with the tests for Identification described under Streptomycin Sulfate.

Clarity and colour of solution Add water to each of 5 containers to produce solutions of 200000 Units per ml, the solutions are clear and colourless; any opalescence produced is not more pronounced than that of reference suspension 2 (Appendix IX B); any colour produced is not more intense than that of reference solution 7 (Appendix IX A, method 1).

Loss on drying When dried in vacuum over phosphorus pentoxide at 60°C for 4 hours, loses not more than 7.0% of its weight (Appendix VIII L).

Acidity, Streptomycin B, Undue toxicity, Bacterial endotoxin and Sterility Complies with the corresponding requirements described under Streptomycin Sulfate.

Other requirements Complies with the general requirements for injections (Appendix I B).

Assay Carry out the Assay described under Streptomycin Sulfate, using an accurately weighed quantity of the mixed contents obtained from the test for weight variation of contents.

Category As described under Streptomycin Sulfate.

Strength (1) 0.75 g (750000 Units)
(2) 1 g (1000000 Units)
(3) 2 g (2000000 Units)
(4) 5 g (5000000 Units)

Storage Preserve in tightly closed containers, stored in a dry place.

Strophanthin K

Strophanthin K is a mixture of different kinds of Glycosides made from the dried ripe seed of *Strophanthus kombe* Oliv. (Fam. Apocynaceae). The potency of each mg is equivalent to 0.4-0.5 mg of Strophanthin G standard (calculated on the anhydrous basis).

Description A white or slightly yellow powder; deteriorates on exposure to light.

Soluble in water or 90% ethanol; very slightly soluble in chloroform; practically insoluble in ether or benzene.

Identification (1) Dissolve in a mixture of sulfuric acid and water (4 : 1); a green colour is produced (distinction from strophanthin G).

(2) Dissolve about 50 mg in 5 ml of water, add 2 ml of

tannic acid TS; a deposit is formed.

Loss on drying When dried in vacuum over phosphorous pentoxide to constant weight, loses not more than 3.0% of its weight (Appendix VIII L).

Residue on ignition Not more than 1.0% (Appendix VIII N).

Assay *Standard solution* Weigh rapidly and accurately a quantity of strophanthin G standard, calculated on anhydrous basis of the labelled potency. To every 1 mg add 4 ml of water.

Before use, dilute the standard solution, accurately measured, with sodium chloride injection so that the mean lethal dose of the diluted solution will be 25-34 ml per kg of pigeon's body weight (usually 1→40-60).

Test solution To a quantity of substance being examined, accurately weighed, add a quantity of water to produce a solution of 0.5 mg per ml. Before use, dilute the test solution as described under standard solution.

Procedure Carry out the biological assay of digitalis (Appendix XIII K), it complies with the requirement for potency.

Category Cardiotonic glycoside.

Storage Preserve in tightly closed containers, protected from light.

Preparation Strophanthin K Injection

Strophanthin K Injection

Strophanthin K Injection is a sterile solution of strophanthin K in Water for Injection. It has a potency of not less than 83% and not more than 120% of the labelled potency.

Description A clear, colourless or slightly yellow liquid; deteriorates on exposure to light.

Identification Evaporate the injection to dryness, the residue complies with the tests for Identification described under Strophanthin K.

Other requirements Complies with the general requirements for injections (Appendix I B).

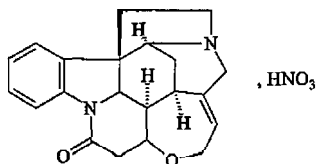
Assay Accurately measure a quantity of the injection, carry out the Assay described under Strophanthin K.

Category As described under Strophanthin K.

Strength (1) 1 ml : 0.25 mg (2) 2 ml : 0.5 mg

Storage Preserve in well closed containers, protected from light.

Strychnine Nitrate



$C_{21}H_{22}N_2O_2 \cdot HNO_3$ 397.44

[66-32-0]

Strychnine Nitrate is strychnidin-10-one mononitrate, contains not less than 99.0% of $C_{21}H_{22}N_2O_2 \cdot HNO_3$.

Description Colourless needle or a white crystalline powder; odourless; taste, very bitter. Freely soluble in boiling water; sparingly soluble in water; slightly soluble in ethanol or chloroform; insoluble in ether.

Identification (1) Dissolve about 0.5 mg in 1 drop of sulfuric acid in an evaporating dish, add 1 grain of potassium dichromate crystals, a violet colour is produced around. (2) The aqueous solution yields the reactions characteristic of nitrates (Appendix III).

Acidity Dissolve 0.5 g in 25 ml of water, add 1 drop of methyl red IS and 0.5 ml of sodium hydroxide (0.02 mol/L) VS, a yellow colour is produced.

Bucine To about 0.1 g add 1 ml of a mixture of nitric acid and water (1 : 1), no red or pale reddish brown colour is produced, except a yellow colour.

Residue on ignition Not more than 0.1 % (Appendix VIII N).

Assay Shake thoroughly and dissolve about 0.3 g, accurately weighed, in 20 ml of glacial acetic acid. Carry out the method for potentiometric titration, titrate with perchloric acid (0.1 mol/L) VS. Perform a blank determination and make any necessary correction. Each ml of perchloric acid (0.1 mol/L) VS is equivalent to 397.44 mg of $C_{21}H_{22}N_2O_2 \cdot HNO_3$.

Category Central stimulant.

Storage Preserve in tightly closed container, protected from light.

Preparation Strychnine Nitrate Injection

Strychnine Nitrate Injection

Strychnine Nitrate Injection is a sterile solution of Strychnine Nitrate in Water for Injection. It contains not less than 90.0% and not more than 110.0% of the labelled amount of strychnine nitrate ($C_{21}H_{22}N_2O_2 \cdot HNO_3$).

Description A clear, colourless liquid.

Identification (1) Evaporate a few drops to dryness in an evaporating dish, add 1 drop of sulfuric acid, and 1 grain of potassium dichromate crystals, a violet colour is produced around.

(2) To 1 drop add 1 drop of diphenylamine TS in a porcelain dish, a blue colour is produced.

pH value 3.0-4.5 (Appendix VI H).

Other requirements Complies with the general requirements for injections (Appendix I B).

Assay Measure accurately a quantity and add water to produce a solution of about 16 µg per ml, measure the absorbance at 254 nm (Appendix IV A). Calculate the content of $C_{21}H_{22}N_2O_2 \cdot HNO_3$, taking 316 as the value of A (1%, 1 cm).

Category As described under Strychnine nitrate.

Strength (1) 1 ml : 1 mg (2) 1 ml : 2 mg

Storage Preserve in tightly closed containers, protected from light.

Sublimed Sulfur

S 32.06

[7704-34-9]

Sublimed Sulfur contains not less than 98.0% of S.

Description A yellow crystalline powder; odour, slight. Practically insoluble in water or ethanol.

Identification (1) Burn with a blue flame and a characteristic odour of sulfur dioxide.

(2) Melt at about 115°C to a yellow liquid; turns to a deep colour and thick liquid at about 160°C.

Acidity Shake 1.0 g with 25 ml of freshly boiled and cooled water, add a few drops of phenolphthalein IS and 0.10 ml of sodium hydroxide (0.1 mol/L) VS, a pink colour is produced.

Particle Size Sift 10.0 g through a No. 8 sieve, any masses may be pressed gently to powder if necessary, then sift. Not less than 85.0% of the powder passes through the sieve.

Residue on ignition Not more than 0.2% (Appendix VIII N).

Arsenic Immerse 0.50 g in 15 ml of ammonia TS for 3 hours and filter. Evaporate 5 ml of the filtrate on a water bath to dryness, add 1 ml of nitric acid and evaporate to dryness again. Add 5 ml of hydrochloric acid and 23 ml of water, carry out the limit test for arsenic (Appendix VII J, method 1); complies with the requirement (0.0012%).

Assay Weigh accurately about 35 mg, previously dried over phosphorous pentoxide for 4 hours, carry out the method for oxygen flask combustion (Appendix VII C), using 5 ml of hydrogen peroxide TS and 10 ml of water as the absorbing liquid. When the combustion is complete, cool the combustion flask in ice bath with frequent shaking for 20 minutes. When the fumes produced is completely absorbed, boil the solution for 2 minutes, cool to room temperature, add 2 drops of phenolphthalein IS and titrate with sodium hydroxide (0.1 mol/L) VS. Perform a blank determination and make any necessary correction. Each ml of sodium hydroxide (0.1 mol/L) VS is equivalent to 1.603 mg of S.

Category Insecticide.

Storage Preserve in tightly closed containers.

Preparation Sulfur Ointment

Sulfur Ointment

Sulfur Ointment contains not less than 9.0% and not more than 11.0% of sulfur (S).

Description Yellow ointment; odour, characteristic of sulfur.

Other requirements Complies with the general requirements for ointment (Appendix I F).

Assay Heat about 0.5 g, accurately weighed, with 40 ml of 5% sodium sulfite solution under reflux for about 1.5 hours until the sulfur is completely dissolved. Cool and allow the ointment base to solidify, filter. Wash the residue with 30 ml of hot water, cool, filter, and repeat the washing operation for several times. Combine the filtrate and washings, add 10 ml of formaldehyde TS and 6 ml of acetic acid, dilute to 150 ml with water, add starch IS and titrate with iodine (0.05 mol/L) VS. Each ml of iodine (0.05

mol/L) VS is equivalent to 3.206 mg of S.

Category Insecticide.

Storage Preserve in well closed containers, stored at a temperature below 30°C.

Sucralfate

C₁₂H₂₂Al₁₆O₈S₈

[54182-58-0]

Sucralfate is sucrose octakis (hydrogen sulfate) aluminium complex. It contains not less than 18.0% and not more than 22.0% of Al and not less than 8.5% and not more than 12.5% of S, calculated on the dried basis.

Description A white or almost white powder; odourless; almost tasteless; hygroscopic.

Practically insoluble in water, ethanol or chloroform, freely soluble in dilute hydrochloric acid or dilute sulfuric acid; sparingly soluble in dilute nitric acid.

Identification (1) Dissolve about 0.1 g in 1 ml of dilute hydrochloric acid by boiling, cool, neutralize with sodium hydroxide TS and add slowly to warm alkaline cupric tartrate TS, a red cuprous oxide precipitate is produced.

(2) Dissolve 0.1 g in 1 ml of dilute hydrochloric acid, add barium chloride TS and filter if a precipitate is produced. Boil the filtrate, a lot of white precipitate is produced.

(3) Dissolve 0.1 g in 1 ml of dilute hydrochloric acid, make alkaline with ammonia hydroxide TS, boil and filter. Dissolve the precipitate in hydrochloric acid, the solution yields the reactions characteristic of aluminium salts (Appendix III).

Neutralizing capacity To about 0.5 g, accurately weighed, in a 250 ml conical flask add accurately 100 ml of hydrochloric acid (0.1 mol/L) VS, stopper, shake frequently for 1 hour at 37°C, cool to room temperature, filter and discard the initial filtrate. To 50 ml, accurately measured, of the successive filtrate add a few drops of bromophenol blue IS. Titrate with sodium hydroxide (0.1 mol/L) VS. Each g consumes not less than 130 ml of hydrochloric acid (0.1 mol/L) VS, calculated on the dried basis.

Acidity Heat 0.20 g with 20 ml of water on a boiling water bath for 2-3 minutes, cool to room temperature, pH 3.5-5.5 (Appendix VI H).

Clarity of solution A solution of 1.0 g in 10 ml of dilute hydrochloric acid is clear. Any opalescence produced is not more pronounced than that of reference suspension 3 (Appendix IX B).

α-Methylpyridine Pulverize a quantity of the substance being examined, heat 2.0 g in a 10 ml test tube with stopper with 5.0 ml of water on a water bath at 80-90°C for 30 minutes, shake frequently, cool; transfer it to a centrifugal tube and centrifuge, use the supernate as the test solution; Dissolve a quantity of α-methylpyridine CRS in water to produce a solution of 20 µg per ml as the reference solution. Carry out the method for gas chromatography (Appendix V E), using a column packed with ethylvinylbenzene cross-linked with divinylbenzene porous polymer beads (diameter 0.25-0.18 mm); maintain the column temperature at 200-225°C. Inject separately 2 µl of each of the test solution and the reference solution into the column. The response of the peak height of α-methylpyridine in the chromatogram obtained with the test solution is not greater than that of the

reference solution (0.005%).

Loss on drying When dried at 105°C for 3 hours, loses not more than 14.0% of its weight (Appendix VIII L).

Heavy metals Dissolve 1.0 g in 20 ml of hydrochloric acid solution (9→100), by stirring, make alkaline with ammonia hydroxide TS, add 20 ml of ammonia TS in excess and allow to stand for a few minutes, a precipitate is produced. Filter, wash the precipitate with a quantity of water, combine the filtrate and washings, dilute with water to 25 ml, Carry out the limit test for heavy metals (Appendix VIII H, method 3); not more than 0.001%.

Arsenic To 1.0 g add 10 ml of dilute sulfuric acid and 5 ml of bromine TS, boil and allow it to cool. Add a few drops of acidic stannous chloride TS until the colour disappears, then add 3 ml of hydrochloric acid and dilute with water to 28 ml. Carry out the limit test for arsenic (Appendix VIII J, method 1); not more than 0.0002%.

Assay Aluminium Dissolve about 1.0 g, accurately weighed, in 10 ml of dilute hydrochloric acid in a 200 ml volumetric flask, dilute with water to volume, mix well. Neutralize 20 ml, accurately measured, with ammonia TS until the precipitate is just produced, add dropwise dilute hydrochloric acid until the precipitate is just dissolved. Add 20 ml of acetic acid-ammonium acetate BS (pH 6.0) and then 25 ml, accurately measured, of disodium edetate (0.05 mol/L) VS. Boil for 3-5 minutes, cool to room temperature and add 1 ml of xylene orange IS. Titrate with Zinc (0.05 mol/L) VS until the colour changes from yellow to red. Perform a blank determination and make any necessary correction. Each ml of Zinc (0.05 mol/L) VS is equivalent to 1.349 mg of Al.

Sulfur Boil gently about 1.0 g, accurately weighed, in a beaker with 10 ml of nitric acid solution (1→2) and 10 ml of water for 10 minutes, cool, make alkaline with ammonia TS and add 5 ml of ammonia TS in excess, boil for 1 minute, and allow to cool. Transfer it to a 100 ml volumetric flask, dilute with water to volume, mix well. Filter with dry filter paper, discard the initial filtrate and measure accurately 10 ml of successive filtrate, acidify with hydrochloric acid (1 mol/L) VS and add 3 drops of hydrochloric acid (1 mol/L) VS in excess. Add 10 ml, accurately measured, of barium chloride-magnesium chloride solution (dissolve 6 g barium chloride and 5 g magnesium chloride in water and dilute with water to 500 ml), mix well. Allow it to stand for a few minutes, add 15 ml of ammonia-ammonia chloride BS (pH 10.0), 5 ml of triethanolamine solution (1→2) and a small amount of eriochrome black T indicator mixture, titrate with disodium edetate (0.05 mol/L) VS. Perform a blank determination and make any necessary correction. Each ml of disodium edetate (0.05 mol/L) VS is equivalent to 1.603 mg of S.

Category Antacid.

Storage Preserve in tightly closed containers, stored in a dry place.

Preparation (1) Sucralfate Capsules
(2) Sucralfate Dispersible Tablets
(3) Sucralfate Oral Suspension
(4) Sucralfate Tablets

Sucralfate Capsules

Sucralfate Capsules contain not less than 15.0% and not more than 21.0% of the labelled amount of sucralfate, calculated with respect to Al.

Identification Weigh a quantity of the contents equivalent to about 0.5 g of sucralfate, comply with the tests for Identification described under Sucralfate.

Neutralizing capacity Mix the contents obtained from the test for weight variation of contents, an accurately weighed quantity equivalent to about 0.5 g of sucralfate, comply with the test for Neutralizing capacity described under Sucralfate. Each g of sucralfate consumes not less than 120 ml of hydrochloric acid (0.1 mol/L) VS.

Other requirements Comply with the general requirements for capsules (Appendix I E); in the disintegration test, no particle of the contents remaining on the gauze within 15 minutes.

Assay Mix the contents obtained from the test for weight variation of contents, weigh accurately a quantity equivalent to about 1 g of sucralfate, carry out the Assay of Aluminium described under Sucralfate. Each ml of zinc (0.05 mol/L) VS is equivalent to 1.349 mg of Al.

Category As described under Sucralfate.

Strength 0.25 g

Storage Preserve in tightly closed containers.

Sucralfate Dispersible Tablets

Sucralfate Dispersible Tablets contain not less than 15.0% and not more than 21.0% of the labelled amount of sucralfate, calculated with reference to Aluminum (Al).

Description White tablets.

Identification To a quantity of the powdered tablets equivalent to about 0.5 g of sucralfate, add 10 ml each of water and dilute hydrochloric acid, shake to dissolve sucralfate and filter. Retain the filtrate for the following identification tests.

(1) Neutralize 4 ml of the filtrate with sodium hydroxide TS and pour the solution into warm alkaline cupric tartrate TS slowly, a red precipitate of cuprous oxide is produced immediately.

(2) To 4 ml of the filtrate add barium chloride TS, if a precipitate is produced, filter and boil the filtrate, a large amount of white precipitate is produced.

(3) To 4 ml of the filtrate add ammonia TS to make the solution alkaline, boil and filter, dissolve the precipitate in dilute hydrochloric acid. The solution yields the reactions characteristic of aluminium salts (Appendix III).

Neutralizing Capacity Weigh accurately a quantity of the powdered tablets obtained in assay, equivalent to about 0.5 g of sucralfate, into a 250 ml conical flask with stopper, add 100 ml of hydrochloric acid (0.1 mol/L) VS, accurately measured, stopper tightly. Allow to stand at 37°C for 1 hour with frequent shaking, cool and filter. To 50 ml of the successive filtrate, accurately measured, add several drops of bromophenol blue IS, titrate with sodium hydroxide (0.1 mol/L) VS. Each g of sucralfate consumes not less than 120 ml of sodium hydroxide (0.1 mol/L) VS.

Other requirements Comply with the general requirements for tablets (Appendix I A), except for dissolution test.

Assay Weigh accurately and powder 20 tablets. Weigh accurately a quantity of the powdered tablets equivalent to about 1 g of sucralfate into a 200 ml volumetric flask, add 10 ml of dilute hydrochloric acid, shake to dissolve sucralfate, dilute to volume with water and mix well.

Filter, neutralize with ammonia TS 20 ml of the successive filtrate, accurately measured, until a precipitate is just produced, then add dropwise dilute hydrochloric acid until the precipitate is just dissolved. Add 20 ml of acetic acid-ammonium acetate BS (pH 6.0) and 25 ml of disodium edeate (0.05 mol/L) VS, accurately measured, boil for 3-5 minutes and cool. Add 1 ml of xylenol orange IS, titrate with zinc (0.05 mol/L) VS until the colour turns from yellow to red. Perform a blank determination and make any necessary correction. Each ml of disodium edeate (0.05 mol/L) VS is equivalent to 1.349 mg of Al.

Category Antacid.

Strength 0.25 g

Storage Preserve in tightly closed containers, stored in a dry place.

Sucralfate Oral Suspension

Sucralfate Oral Suspension contains not less than 16.0% and not more than 24.0% of the labelled amount of sucralfate, calculated with reference to Aluminum (Al).

Description A white or almost white creamy suspension.

Identification Weigh a quantity equivalent to about 0.5 g of sucralfate into a beaker, add 100 ml of water and stir thoroughly, allow to stand. Shake the precipitate with 10 ml of dilute hydrochloric acid and filter. Retain the filtrate for the following identification tests.

(1) To a quantity of the filtrate equivalent to about 0.1 g of sucralfate, add 1 ml of dilute hydrochloric acid, boil and cool. Neutralize with sodium hydroxide TS, pour the solution into warm alkaline cupric tartrate TS slowly and heat on a water bath, a red precipitate of cuprous oxide is produced immediately.

(2) To a quantity of the filtrate equivalent to about 0.1 g of sucralfate, add barium chloride TS, if a precipitate is produced, filter and boil the filtrate, a large amount of white precipitate is produced.

(3) To a quantity of the filtrate equivalent to about 0.1 g of sucralfate, add ammonia TS to make the solution alkaline, boil and filter, dissolve the precipitate in dilute hydrochloric acid. The solution yields the reactions characteristic of aluminium salts (Appendix III).

Relative density 1.030-1.090 (for strength 10%); 1.120-1.200 (for strength 20%) (Appendix VI A).

Neutralizing Capacity Weigh accurately a quantity equivalent to about 0.5 g of sucralfate into a 250 ml conical flask with stopper, add 100 ml of hydrochloric acid (0.1 mol/L) VS, accurately measured, stopper, tightly. Allow to stand at 37°C for 1 hour with frequent shaking, cool and filter. To 50 ml of the successive filtrate, accurately measured, add several drops of bromophenol blue IS, titrate with sodium hydroxide (0.1 mol/L) VS. Each g of sucralfate consumes not less than 120 ml of hydrochloric acid (0.1 mol/L) VS, calculated on basis of relative density.

pH value 4.5-6.5 (Appendix VI H)

Particle size After shaking thoroughly, mix several drops with a quantity of water. Examine under a microscope in 3 fields of view, using 300-400 X magnification. Not less than 85% of the particles have a dimension of not more than 10 µm.

Other requirements Complies with the general requirements for oral suspension (Appendix I O).

Assay Weigh accurately a quantity equivalent to about 1.0 g of sucralfate into a 200 ml volumetric flask, add 10 ml of dilute hydrochloric acid, shake to dissolve sucralfate, dilute to volume with water and mix well. Measure accurately 20 ml of the solution and neutralize with ammonia TS until a precipitate is just produced, then add dropwise dilute hydrochloric acid until the precipitate is just dissolved. Add 20 ml of acetic acid-ammonium acetate BS (pH 6.0) and 25 ml of disodium edeate (0.05 mol/L) VS, accurately measured, boil for 3-5 minutes and cool. Add 1 ml of xylenol orange IS, titrate with zinc (0.05 mol/L) VS until the colour turns from yellow to red. Perform a blank determination and make any necessary correction. Calculate the content on the basis of relative density. Each ml of disodium edeate (0.05 mol/L) VS is equivalent to 1.349 mg of Al.

Category Antacid.

Strength (1) 10 ml : 1 g (2) 200 ml : 20 g
(3) 200 ml : 40 g (4) 120 ml : 24 g

Storage Preserve in tightly closed containers, stored in a cool and dry place and protected from light.

Sucralfate Tablets

Sucralfate Tablets contain not less than 15.0% and not more than 21.0% of the labelled amount of sucralfate, calculated on Al.

Description White tablets.

Identification To a quantity of the powdered tablets equivalent to about 0.5 g of sucralfate add 10 ml of water and 10 ml of dilute hydrochloric acid, shake to dissolve sucralfate and filter, the filtrate complies with the tests for Identification described under Sucralfate.

Neutralizing capacity Weigh accurately a quantity of the powder obtained from Assay equivalent to about 0.5 g of sucralfate, comply with the test for Neutralizing capacity described under Sucralfate. Each g of sucralfate consumes not less than 120 ml of hydrochloric acid (0.1 mol/L) VS.

Other requirements Comply with the general requirements for tablets (Appendix I A).

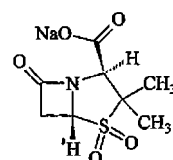
Assay Weigh accurately and powder 20 tablets. Weigh accurately a quantity equivalent to about 1 g of sucralfate, carry out the Assay described under Sucralfate. Each ml of zinc (0.05 mol/L) VS is equivalent to 1.349 mg of Al.

Category As described under Sucralfate.

Strength (1) 0.25 g (2) 1.0 g

Storage Preserve in tightly closed containers.

Sulbactam Sodium



$C_8H_{10}NNaO_5S$ 255.23

[69388-84-7]

Sulbactam sodium is sodium (2S, 5R)-3,3-

dimethyl-7-oxo-4-thia-1-azabicyclo [3.2.0] heptane-2-carboxylate-4,4-dioxide. It contains not less than 88.6% of sulbactam ($C_8H_{11}NO_5S$), calculated on the anhydrous basis.

Description A white or almost white powder or crystalline powder; odour, faint; taste, slightly bitter. Freely soluble in water; slightly soluble in methanol, practically insoluble in ethanol, acetone and ethyl acetate.

Specific optical rotation $+223^\circ$ to $+237^\circ$, in a solution of 10 mg per ml in water (Appendix VI E).

Identification (1) The retention time of principal peak of sulbactam of the substance being examined in the chromatogram obtained in the Assay is identical with that of the principal peak of the sulbactam CRS in the chromatogram of the reference solution.

(2) The infrared absorption spectrum (Appendix IV C) is concordant with the reference spectrum of sulbactam (Appendix XVI).

(3) Yields the flame reaction of sodium salts (Appendix III).

Crystallinity Complies with the test for Crystallinity (Appendix IX D).

Clarity and colour of solution To 5 portions each of 0.3 g add 5 ml of water respectively, the solutions are clear and colourless; any opalescence produced is not more pronounced than that of reference suspension 1 (Appendix IX B); any colour produced is not more intense than that of reference solution Y_3 or YG_3 (Appendix IX A, method 1).

Acidity To a quantity add water to produce a solution of 50 mg per ml, pH 4.5-6.5 (Appendix VI H).

Related substances Carry out the method as described under Assay. Inject $10\ \mu\text{l}$ of the reference solution into the column. Adjust the attenuation so that the principal peak height in the chromatogram is 20%-25% of full scale of the chart. Dissolve a quantity of the substance being examined, accurately weighed, in mobile phase to produce a solution of 5 mg per ml as test solution. Transfer 1 ml of test solution, measured accurately in a 100 ml volumetric flask, dilute with mobile phase to volume as reference solution. Inject accurately $10\ \mu\text{l}$ of test solution and reference solution respectively into column and record the chromatogram for three times the retention time of the principal peak. In the chromatogram obtained with the test solution, secondary area of sulbactam penicillamine (response factor is 0.3) is not greater than that of the principal peak in the chromatogram obtained with the reference solution (1.0%). (Disregard any peak with an area less than 0.05 times that of the principal peak in the chromatogram obtained with reference solution.)

Water Not more than 1.0% (Appendix VIII M, method 1).

Heavy metals Not more than 0.002% (Appendix VIII H, method 1).

Bacterial endotoxin Carry out the test for bacterial endotoxin (Appendix XI E); less than 0.10 EU per mg.

Sterility Complies with the test for sterility (Appendix XI H, membrane filtration method), dissolve a quantity in appropriate solvent, transfer the solution to at least 500 ml of 0.9% sterile sodium chloride solution.

Assay Carry out the method for high performance liquid chromatography (Appendix V D), using a column packed with octadecylsilane bonded silica gel and a mixture of 0.005

mol/L tetrabutylammonium hydroxide solution (dilute 6.6 ml of 40% tetrabutylammonium hydroxide solution with water to 1800 ml. Adjust pH value to 5.0 ± 0.1 with 1 mol/L phosphoric acid solution, dilute with water to 2000 ml and mix well) and acetonitrile (75 : 25) as the mobile phase. The flow rate is 1.0 ml per minute and detection wavelength is 230 nm. Inject $10\ \mu\text{l}$ of system suitability solution (Dissolve about 40 mg in a 100 ml volumetric flask, add 2 ml of water and 0.5 ml of 1 mol/L sodium hydroxide and allow to stand for 30 minutes to produce sulbactam penicillamine. Add 0.5 ml of 1 mol/L hydrochloric acid solution and dilute to volume with mobile phase and mix well. Transfer 5 ml of the solution into a 50 ml volumetric flask. Add 20 mg of sulbactam CRS and dissolve in mobile phase, then dilute to volume and mix well) to column and record the chromatogram. The elute order is sulbactam penicillamine and sulbactam. The number of the theoretical plates of sulbactam is not less than 3500 and the tailing factor is not more than 1.5. The resolution factor between peaks of sulbactam and sulbactam penicillamine is not less than 6.0.

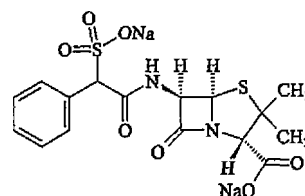
Procedure Dissolve a quantity of the substance being examined, accurately weighed, in mobile phase to produce a solution of 1 mg per ml. Inject $10\ \mu\text{l}$ into the column and record the chromatogram. Repeat the operation, using sulbactam CRS instead of the substance being examined, calculate the content of $C_8H_{11}NO_5S$ with respect to the peak area obtained in the chromatogram by the external standard method.

Category β -Lactamase inhibitor.

Storage Preserve in hermetically sealed containers, stored in a cool and dry place.

Preparation (1) Ampicillin Sodium and Sulbactam Sodium for Injection
(2) Cefoperazone Sodium and Sulbactam Sodium for Injection

Sulbenicillin Sodium



$C_{16}H_{16}N_2Na_2O_7S_2$ 458.42

Sulbenicillin Sodium is (2S, 5R, 6R)-3,3-dimethyl-6-(2-phenyl-2-sulfoacetyl-amido)-7-oxo-4-thia-1-azabicyclo[3.2.0]heptane-2-carboxylic acid, disodium salt. It has a potency of not less than 900 Sulbenicillin Units per mg, calculated on the anhydrous basis.

Description A white or pale-yellow powder; odourless; taste, slightly saline; hygroscopic.

Very soluble in water; freely soluble in methanol; sparingly soluble in ethanol; very slightly soluble in dehydrated ethanol; insoluble in acetone, chloroform or benzene.

Specific optical rotation $+167^\circ$ to $+182^\circ$, in a solution of 50 mg per ml in water (Appendix VI E).

Identification (1) Dissolve about 20 mg in 15 ml of water, add 2 ml of hydroxylamine hydrochloride TS and 2 ml of

sodium hydroxide TS, allow to stand for 5 minutes, add 3 ml of hydrochloric acid solution (9→100) and 1 ml of ferric chloride TS, a red-brown colour is produced on shaking.

(2) The infrared absorption spectrum is concordant with the reference spectrum of sulbenicillin sodium RS (Appendix IV C).

(3) Yield the flame reaction of sodium salts (Appendix III).

Acidity Dissolve a quantity in water to produce a solution of 20 mg per ml, pH 4.5-7.0 (Appendix VI H).

Clarity and colour of solution To each of 5 portions add water to produce a solution of 0.12 g per ml, the solution is clear and colourless. Any opalescence produced is not more pronounced than that of reference suspension 1 (Appendix IX B); any colour produced is not more intense than that of reference solution Y₄ (Appendix IX A, method 1).

W 6.0% (pp VIII M, 1 A).

Bacterial endotoxin Carry out the test for bacterial endotoxin (Appendix XI E); not more than 0.05 EU per 1000 Units of Sulbenicillin Sodium.

Assay Dissolve an accurately weighed quantity in sterile water to produce a solution of about 1000 Units per ml and carry out the Microbiological Assay of Antibiotics (Appendix XI A). 1000 Sulbenicillin Units are equivalent to 1 mg of C₁₆H₁₈N₂O₇S₂.

Category β-lactam antibiotics, penicillins.

Storage Preserve in tightly closed containers, stored in a cool, dark and dry place.

Preparation Sulbenicillin Sodium for Injection

Sulbenicillin Sodium for Injection

Sulbenicillin Sodium for Injection is a sterile lyophilized powder of Sulbenicillin Sodium. It has a potency of not less than 900 Sulbenicillin Units per mg, calculated on the anhydrous basis. It contains not less than 93.0% and not more than 107.0% of the labelled amount of sulbenicillin (C₁₆H₁₈N₂O₇S₂), calculated on the basis of the average weight of content.

Description A white to pale-yellow lyophilized powder.

Identification Complies with the tests for Identification described under Sulbenicillin Sodium.

Clarity and Colour of Solution To each of 5 portions add water to produce a solution of 0.1 g per ml, the solution is clear and colourless; any opalescence produced is not more pronounced than that of reference suspension 1 (Appendix IX B); any colour produced is not more intense than that of reference solution Y₄ (Appendix IX A, method 1).

Water Not more than 6.0% (Appendix VIII M, method 1 A).

Sterility Complies with the test for sterility (Appendix XI H, membrane filtration method). Dissolve a quantity in appropriate solvent, transfer the solution to at least 500 ml of 0.9% sterile sodium chloride solution.

Acidity and Bacterial endotoxin Complies with the corresponding tests described under Sulbenicillin Sodium.

Other requirements Complies with the general requirements for injections (Appendix I B).

Assay Carry out the Assay described under Sulbenicillin

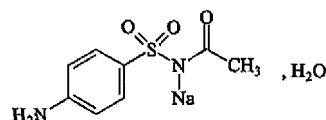
Sodium, using an accurately weighed quantity of mixed contents obtained from the test for weight variation of contents.

Category As described under Sulbenicillin Sodium.

Strength Calculated as C₁₆H₁₈N₂O₇S₂
(1) 1 g (1000000 Units)
(2) 2 g (2000000 Units)
(3) 4 g (4000000 Units)

Storage Preserve in tightly closed containers, protected from light, stored in a cool, dark and dry place.

Sulfacetamide Sodium



C₈H₉N₂NaO₃S • H₂O 254.24 [6209-17-2]

Sulfacetamide Sodium is *N*-sulfanilyl-acetamide monosodium salt monohydrate. It contains not less than 99.0% of C₈H₉N₂NaO₃S, calculated on the dried basis.

Description A white crystalline powder; odourless; taste, slightly bitter.

Freely soluble in water; sparingly soluble in ethanol.

Identification (1) Dissolve 1 g in 10 ml of water, add 2 ml of acetic acid; a precipitate is produced. Filter, wash the precipitate with a quantity of water, dry at 105°C. It melts at a temperature of 180-184°C (Appendix VI C).

(2) Dissolve 0.1 g in 3 ml of water, add 5 drops of copper sulfate TS; a bluish green precipitate is produced.

(3) The infrared absorption spectrum (Appendix IV C) is concordant with the reference spectrum of sulfacetamide sodium (Appendix XVI).

(4) The filtrate obtained in identification test (1) yields the reactions characteristic of sodium salts (Appendix III).

Alkalinity Dissolve 0.50 g in 10 ml of water, pH 8.0-9.5 (Appendix VI H).

Clarity and colour of solution A solution of 2.0 g in 10 ml of water is clear and colourless. Any colour produced is not more intense than that of 5 ml of reference solution Y₃ diluted with water to 10 ml (Appendix IX A, method 1).

Related substances Carry out the method for thin-layer chromatography (Appendix V B), using silica gel G as the coating substance and a mixture of *n*-butanol-dehydrated ethanol-water-concentrated ammonia solution (10 : 5 : 5 : 2) as the mobile phase. Apply separately to the plate 5 μl of each of three solutions in water containing (1) 100 mg of the substance being examined per ml, (2) 0.50 mg of sulfanilamide CRS per ml, (3) 0.25 mg of sulfanilamide CRS per ml. After developing and removal of the plate, dry in air and spray with ethanolic dimethylamino-benzaldehyde TS and examine immediately. Not more than one secondary spot, in the chromatogram obtained with solution (1) is more intense than the spot in the chromatogram obtained with solution (3) and none of such spot may be more intense than the spot obtained with solution (2).

Loss on drying When dried to constant weight at 150°C, loses 6.0%-8.0% of its weight (Appendix VIII L).

Heavy metals Carry out the limit test for heavy metals

(Appendix VIII H, method 3) using 1.0 g; not more than 0.001%.

Assay Weigh accurately about 0.45 g, carry out the method for dead-stop titration (Appendix VII A), titrate with sodium nitrite (0.1 mol/L) VS. Each ml of sodium nitrite (0.1 mol/L) VS is equivalent to 23.62 mg of $C_8H_9N_2NaO_3S$.

Category Sulfonamide.

Storage Preserve in tightly closed containers.

Preparation Sulfacetamide Sodium Eye Drops

Sulfacetamide Sodium Eye Drops

Sulfacetamide Sodium Eye Drops contain not less than 90.0% and not more than 110.0% of the labelled amount of sulfacetamide Sodium ($C_8H_9N_2NaO_3S \cdot H_2O$).

Description A clear, colourless to pale yellow liquid.

Identification Add cupric sulfate TS dropwise to about 2 ml of the eye drops, a bluish green precipitate is formed, remaining unchanged on standing.

pH value 8.0-9.8 (Appendix VI C).

Colour Not more intensely coloured than reference solution Y_6 or OY_6 (Appendix IX A, method 1).

Sulfanilamide Carry out the method for thin-layer chromatography (Appendix V B), using silica gel G as coating substance and the organic layer of a mixture of butanol-concentrated ammonia solution-water (4 : 1 : 3) as the mobile phase. Apply separately to the plate 2 μ l each of two solutions in water containing (1) 6.0 mg of sulfacetamide sodium per ml and (2) 0.25 mg of sulfanilamide CRS per ml. After developing and removal of the plate, allow the solvent to evaporate in air and dry at 105°C for 10 minutes. Cool, spray with ethanolic dimethylamino-benzaldehyde TS and examine immediately. Any spot in the chromatogram obtained with solution (1) at the position corresponding to that of sulfanilamide is not more intense than the principal spot obtained with solution (2) (4.2%).

Other requirements Comply with the general requirements for eye preparations (Appendix I G).

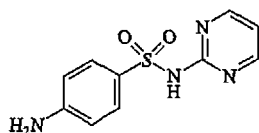
Assay Carry out the assay described under Sulfacetamide Sodium, using a quantity equivalent to 0.6 g of sulfacetamide sodium. Each ml of sodium nitrite (0.1 mol/L) VS is equivalent to 25.42 mg of $C_8H_9N_2NaO_3S \cdot H_2O$.

Category As described under Sulfacetamide Sodium.

Strength 15%

Storage Preserve in tightly closed containers, protected from light and stored in a cool place.

Sulfadiazine



$C_{10}H_{10}N_4O_2S$ 250.28

[68-35-9]

Sulfadiazine is 4-amino-*N*-2-pyrimidinyl benzene-sulfonamide. It contains not less than 99.0% of $C_{10}H_{10}N_4O_2S$.

Description White or almost white crystals or a powder; odourless; tasteless; darkens gradually on exposure to light.

Slightly soluble in ethanol or acetone; practically insoluble in water; freely soluble in sodium hydroxide TS or ammonia TS; soluble in dilute hydrochloric acid.

Identification (1) Dissolve about 0.1 g in 3 ml each of water and 0.4% sodium hydroxide solution with shaking and filter. To a portion of the filtrate, add 1 drop of copper sulfate TS, a yellowish-green precipitate is produced, changing to purple on standing.

(2) The infrared absorption spectrum (Appendix IV C) is concordant with the reference spectrum of sulfadiazine (Appendix XVI).

(3) Yields the reactions characteristic of primary aromatic amines (Appendix III).

Acidity Heat 2.0 g with 100 ml of water on a water bath for 10 minutes, cool immediately and filter. To 25 ml of the filtrate, add 2 drops of phenolphthalein TS and 0.20 ml of sodium hydroxide (0.1 mol/L) VS; a pink colour is produced.

Clarity and colour of alkaline solution A solution of 2.0 g in 10 ml of sodium hydroxide TS and 15 ml of water is clear and colourless. Any colour produced is not more intense than that of reference solution Y_3 (Appendix IX A, method 1).

Chlorides Carry out the limit test for chlorides (Appendix VII A), using 25 ml of the remaining filtrate obtained in the test for Acidity. Any opalescence produced is not more pronounced than that of a reference using 5.0 ml of sodium chloride standard solution (0.01%).

Residue on ignition Not more than 0.1% (Appendix VIII N).

Heavy metals Carry out the limit test for heavy metals (Appendix VIII H, method 3), using 1.0 g; not more than 0.001%.

Assay Weigh accurately about 0.5 g, carry out the method for dead-stop titration (Appendix VII A), titrate with sodium nitrite (0.1 mol/L) VS. Each ml of sodium nitrite (0.1 mol/L) VS is equivalent to 25.03 mg of $C_{10}H_{10}N_4O_2S$.

Category Sulfonamide.

Storage Preserve in tightly closed containers, protected from light.

Preparation (1) Sulfadiazine Eye Ointment
(2) Sulfadiazine Ointment
(3) Sulfadiazine Suspension
(4) Sulfadiazine Tablets
(5) Compound Sulfadiazine Tablets

Sulfadiazine Eye Ointment

Sulfadiazine Eye Ointment contains not less than 90.0% and not more than 110.0% of the labelled amount of sulfadiazine ($C_{10}H_{10}N_4O_2S$).

Description A pale yellow to yellow ointment.

Identification To about 0.5 g add 20 ml of water and 1 ml of sodium hydroxide TS, heat with stirring to dissolve sulfadiazine. Allow it to cool. Acidify slightly the water layer with acetic acid. Filter. Wash the residue with a little

of water, dry it at 105°C for 1 hour. Complies with the tests (1) and (3) for Identification described under sulfadiazine.

Other requirements Complies with the general requirements for eye preparations (Appendix I G).

Assay Weigh accurately a quantity of the substance being examined equivalent to about 0.5 g of sulfadiazine, add 10 ml of hydrochloric acid and 40 ml of hot water, heat in a water bath for 15 minutes with constant stirring. Allow it to cool and the ointment base to congeal, separate the solution. To the ointment base add 3 ml of hydrochloric acid and 25 ml of water, heat in the water bath for 10 minutes with constant stirring, allow it to cool and separate the solution again, mix the two solutions well. Carry out the method for dead-stop titration (Appendix VII A), titrate with sodium nitrite (0.1 mol/L) VS. Each ml of sodium nitrite (0.1 mol/L) VS is equivalent to 25.03 mg of $C_{10}H_{10}N_4O_2S$.

Category As described under Sulfadiazine.

Strength 5%

Storage Preserve in well closed containers, stored in a cool and dark place.

Sulfadiazine Ointment

Sulfadiazine Ointment contains not less than 90.0% and not more than 110.0% of the labelled amount of Sulfadiazine ($C_{10}H_{10}N_4O_2S$).

Description A pale yellow to yellow ointment.

Identification To a quantity of ointment equivalent to 0.1 g of sulfadiazine add 3 ml each of water and 0.4% sodium hydroxide solution, heat with stirring. Allow it to cool, filter. To the filtrate add 0.5 ml of copper sulfate TS, a blue-green precipitate is produced, changing to purple on standing.

Other requirements Comply with the general requirements for ointment (Appendix I F).

Assay Weigh accurately a quantity of the substance being examined equivalent to about 0.5 g of sulfadiazine, add 10 ml of hydrochloric acid and 40 ml of hot water, heat in a water bath for 15 minutes with constant stirring. Allow it to cool and the ointment base to congeal, separate the solution. To the ointment base add 3 ml of hydrochloric acid and 25 ml of water, heat in the water bath for 10 minutes with constant stirring, allow it to cool and separate the solution again, mix the two solutions well. Carry out the method for dead-stop titration (Appendix VII A), titrate with sodium nitrite (0.1 mol/L) VS. Each ml of sodium nitrite (0.1 mol/L) VS is equivalent to 25.03 mg of $C_{10}H_{10}N_4O_2S$.

Category As described under Sulfadiazine.

Strength (1) 10 g : 0.5 g (2) 10 g : 1 g

Storage Preserve in well closed containers, stored in a cool and dark place.

Sulfadiazine Suspension

Sulfadiazine Suspension contains not less than 95.0% and not more than 105.0% of the labelled amount of sulfadiazine ($C_{10}H_{10}N_4O_2S$).

Description A suspension of fine particles in water, allow to stand, the particles precipitate and a white suspension appears after shaking.

Identification Shake well and dilute about 10 ml with 100 ml of hot water, decant the supernatant liquid, filter. Wash the residue with a little of hot water and dry it at 105°C. The residue complies with the test (1) and (3) for Identification and described under Sulfadiazine.

Other requirements Complies with the general requirements for oral suspension (Appendix I O).

Assay Place 5 ml, thoroughly shaken and accurately measured, in a beaker, wash away all suspension from the pipette with 35 ml of water, combine the washings in the beaker. Add 10 ml of hydrochloric acid and 5 ml of water, stir to dissolve Sulfadiazine. Carry out the method for dead-stop titration (Appendix VII A), titrate with sodium nitrite (0.1 mol/L) VS. Each ml of sodium nitrite (0.1 mol/L) VS is equivalent to 25.03 mg of $C_{10}H_{10}N_4O_2S$.

Category As described under Sulfadiazine.

Strength 10% (g/ml)

Storage Preserve in well closed containers, stored in a cool place and protected from light.

Sulfadiazine Tablets

Sulfadiazine Tablets contain not less than 95.0% and not more than 105.0% of the labelled amount of sulfadiazine ($C_{10}H_{10}N_4O_2S$).

Description White to pale yellow tablets; darkens gradually on exposure to light.

Identification Triturate a quantity of the powdered tablets equivalent to about 0.5 g of sulfadiazine with 10 ml of ammonia TS, add 10 ml of water and filter. Heat the filtrate on a water bath until most of ammonia is expelled. Cool and acidify with acetic acid; a precipitate is produced, filter, wash the precipitate with water and dry at 105°C, and complies with tests (1) and (3) for Identification described under Sulfadiazine.

Dissolution Carry out the dissolution test (Appendix X C, method 2), using 1000 ml of hydrochloric acid solution (9→1000) as the dissolution medium, adjust the rotational speed of the paddle to 100 rpm. Withdraw 5 ml of the solution at 60 minutes and filter. Transfer 1 ml of the successive filtrate, accurately measured, to a 50 ml volumetric flask. Dilute with sodium hydroxide (0.01 mol/L) VS to volume and mix well. Measure the absorbance at 254 nm (Appendix IV A) and calculate the dissolution of $C_{10}H_{10}N_4O_2S$ from each tablet, taking 866 as the value of A (1%, 1 cm), not less than 70% of the labelled amount is dissolved.

Other requirements Comply with the general requirements for tablets (Appendix I A).

Assay Weigh accurately and powder 10 tablets. Weigh accurately a quantity of the powdered tablets equivalent to about 0.5 g of sulfadiazine, carry out the method for dead-stop titration (Appendix VII A), titrate with sodium nitrite (0.1 mol/L) VS. Each ml of sodium nitrite (0.1 mol/L) VS is equivalent to 25.03 mg of $C_{10}H_{10}N_4O_2S$.

Category As described under Sulfadiazine.

Strength 0.5 g

Storage Preserve in tightly closed containers, protected from light.

reference solution into the column, adjust the attenuation so that the principal peak height in the chromatogram is about 10%-25% full scale of the chart. Inject 20 μ l each of the test solution and the reference solution into column separately, record the chromatograms for 8 times the retention time of the principal peak. The area of each secondary peak and the sum of secondary peaks are not more than 2 and 2.5 times of the area of the principal peak in the chromatogram obtained with the reference solution respectively.

Chloride Carry out the limit test for chloride (Appendix VIII A), using 0.20 g. Any opalescence produced is not more pronounced than that of a reference solution using 6.0 ml of sodium chloride standard solution (0.03%).

6-Aminohexanoic acid Transfer 0.50 g in a test tube with stopper, add 10 ml of water, stopper tightly, shake for 30 minutes, filter, and take the successive filtrate as test solution. Prepare a reference solution of 100 μ g 6-Aminohexanoic Acid CRS per ml in water. Carry out the method for thin-layer chromatography (Appendix V B), using silica gel G as the coating substance and a mixture of ethanol-concentrated ammonia solution-water (68 : 2 : 30) as the mobile phase. Apply to the plate 10 μ l each of above two solutions separately, after developing and removal of the plate, dry it in air, spray with 0.2% ninhydrin in butanol solution [butanol-2 mol/L acetic acid solution (95 : 5)], heat at 105°C for about 15 minutes. The colour of the spot in the chromatogram obtained with the test solution corresponding to that of the reference substance, if appear, is not more intense than that of the principal spot obtained with the reference solution (0.2%).

Loss on drying When dried to constant weight at 105°C, loses not more than 0.5% of its weight (Appendix VIII L).

Cadmium and lead Transfer 1.0 g in a 25 ml volumetric flask, add 8% nitric acid solution and dilute with the same solution to volume, mix well as test solution. Transfer another 1.0 g in a 25 ml volumetric flask, add 1.0 ml of cadmium solution (5.0 μ g cadmium per ml) and 1.0 ml of lead solution (10.0 μ g lead per ml), dilute with 8% nitric acid solution to volume, mix well as reference solution. Carry out the method for atomic absorption spectrophotometry (Appendix IV D, method 2). Measure the absorbance of the test solution (b) and that of the reference solution (a) at 228.8 nm and 217.0 nm separately, b is less than (a-b) (0.0005% for cadmium; 0.001% for lead).

Arsenic To 1.0 g add 23 ml of water and 5 ml of hydrochloric acid. Carry out the limit test for arsenic (Appendix VIII J): not more than 0.0002%.

Assay Dissolve 0.4 g, weigh accurately, in 50 ml of water by slightly warming, add 10 ml of ammonia-ammonium chloride BS pH 10.0 and a quantity of eriochrome black T indicator mixture, titrate with disodium edetate (0.05 mol/L) VS until the colour changes from mauve to pure blue. Perform a blank determination and make any necessary correction. Each ml of disodium edetate (0.05 mol/L) VS is equivalent to 20.49 mg of $C_{16}H_{28}N_2O_6Zn$.

Category Protective to stomach mucous membrane.

Storage Preserve in tightly closed containers.

Preparation Zinc Acexamate Capsules

Zinc Acexamate Capsules

Zinc Acexamate Capsules contain not less than 98.0% and not more than 102.0% of the labelled

amount of zinc acexamate ($C_{16}H_{28}N_2O_6Zn$).

Description Capsules containing white or almost white granules and powder.

Identification To a quantity of the contents of the capsules, equivalent to about 0.5 g of zinc acexamate, add 50 ml of water, warmly heat, shake to dissolve zinc acexamate, filter. The filtrate complies with the tests (1) and (3) for Identification described under Zinc Acexamate.

Dissolution Carry out the dissolution test (Appendix X C, method 1), using 900 ml of water as the dissolution medium and adjust the rotational speed of the basket to 100 rpm. Withdraw the solution after exactly 30 minutes and filter. Transfer accurately 3 ml (for 0.15 g) or 1.5 ml (for 0.3 g) of the successive filtrate to a 50 ml volumetric flask, add 10.0 ml of borate-potassium chloride BS (pH 9.0) and 1.0 ml of freshly prepared zincon solution (to 0.13 g of zincon, add 2 ml of sodium hydroxide TS, dilute to 100 ml with water), dilute with water to volume, mix well, allow to stand for 30 minutes, measure the absorbance at 620 nm (Appendix IV A). Measure accurately 3 ml of zinc standard solution [measure accurately 3 ml of zinc (0.05 mol/L) VS, dilute with water to 500 ml (20 μ g Zn per ml)] to a 50 ml volumetric flask. Proceed the measurement described above, beginning at the words "add 10.0 ml of borate-potassium chloride BS (pH 9.0)...". Calculate the dissolution of $C_{16}H_{28}N_2O_6Zn$ from each capsule, multiply the result by 6.267. Not less than 80% of the labelled amount is dissolved.

Other requirements Comply with the general requirements for Capsules (Appendix I E).

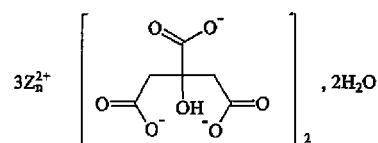
Assay Dissolve a quantity of the mixed contents obtained from the test for weight variation of contents, equivalent to about 0.45 g of zinc acexamate, in 35 ml of water, add 10 ml of ammonia-ammonium chloride BS (pH 10.0) and a quantity of eriochrome black T indicator mixture, titrate with disodium edetate (0.05 mol/L) VS until the colour changes from mauve to pure blue. Perform a blank determination and make any necessary correction. Each ml of disodium edetate (0.05 mol/L) VS is equivalent to 20.49 mg of $C_{16}H_{28}N_2O_6Zn$.

Category As described under Zinc Acexamate.

Strength (1) 0.15 g (2) 0.3 g

Storage Preserve in tightly closed containers, stored in a dry place.

Zinc Citrate



$(C_6H_5O_7)_2Zn_3 \cdot 2H_2O$ 610.35

[546-46-3]

Zinc Citrate contains not less than 98.5% of $(C_6H_5O_7)_2Zn_3 \cdot 2H_2O$, calculated on the dried basis.

Description White granular crystals or a crystalline powder; odourless; tasteless; efflorescent.

Slightly soluble in water; soluble in hydrochloric acid

Identification Yields the reactions characteristic of zinc salts and citrates (Appendix III).

Acidity To about 0.10 g add 10 ml of water, stir for 5 minutes and filter, add 1 drop of methyl orange IS to the filtrate, no orange red colour is produced.

Alkalinity To about 1.0 g add 10 ml of hot water, stir for 5 minutes, allow to cool and filter, add 2 drops of phenolphthalein IS to the filtrate, no pink colour is produced.

Loss on drying When dried for 6 hours at 180°C, loses not more than 6.5% of its weight (Appendix VII L).

Iron Dissolve 0.20 g in 4 ml of dilute hydrochloric acid solution and a quantity of water by shaking. Carry out the limit test for iron (Appendix VIII G), any colour produced is not more intense than that of a reference solution, prepared in the same manner, using 1.0 ml of iron standard solution (0.005%).

Lead Mix 0.50 g with 3 ml of nitric acid and 1 ml of 30% hydrogen peroxide solution in a beaker. Boil for 2 minutes at electric heater, cool and add sufficient water to produce 10 ml as test solution. The light absorption of the test solution at 217.0 nm Appendix IV D is not more than that of a reference solution prepared in the same manner, using 0.5 ml, measured accurately, of lead standard solution (0.001%).

Arsenic Dissolve 1.0 g in 5 ml of hydrochloric acid and 21 ml of water with shaking. Carry out the limit test for arsenic (Appendix VIII J, method 1); not more than 0.0002%.

Assay Dissolve about 0.2 g, accurately weighed, in 20 ml of water and 10 ml of ammonia-ammonium chloride BS (pH 10.0), add a small amount of eriochrome black T indicator. Titrate with disodium edetate (0.05 mol/L) VS until the colour changes from purple to pure blue. Each ml of disodium edetate (0.05 mol/L) VS is equivalent to 9.572 mg of $(C_6H_5O_7)_2Zn_3 \cdot 2H_2O$.

Category Zinc replenisher.

Storage Preserve in tightly closed containers.

Preparation Zinc Citrate Tablets

Zinc Citrate Tablets

Zinc Citrate Tablets contain not less than 95.0% and not more than 105.0% of the labelled amount of zinc citrate $(C_6H_5O_7)_2Zn_3 \cdot 2H_2O$.

Description White tablets.

Identification Yields the reactions characteristic of zinc salts and citrates (Appendix III).

Dissolution Carry out the dissolution test (Appendix X C, method 1), using 1000 ml of an aqueous solution containing 24 ml of dilute hydrochloric acid as the dissolution medium, adjust the rotational speed of the basket at 100 rpm. Withdraw a quantity of the solution after exactly 30 minutes and filter. Dilute 3 ml of the successive filtrate, accurately measured, with the dissolution medium to 25 ml as the test solution. Dissolve a quantity of zinc citrate CRS in the dissolution medium to produce 3 solutions of about 2 µg, 4 µg and 6 µg per ml, respectively, as the reference solutions. Measure the absorbances of the resulting solutions at 213.9 nm (Appendix IV D, method 1), calculate the dissolution of $(C_6H_5O_7)_2Zn_3 \cdot 2H_2O$ from each tablet. Not less than 80% of the labelled amount is dissolved.

Other requirements Comply with the general requirements

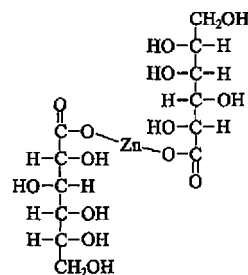
Assay Weigh accurately and powder 10 tablets. To an accurately weighed quantity of the powdered tablets, equivalent to about 0.4 g of zinc citrate in a 100 ml volumetric flask, add 2 ml of dilute hydrochloric acid, shake, dilute to volume with water, mix well and filter. Measure accurately 50 ml of the successive filtrate, add a drop of 0.025% methyl red solution in ethanol, add dropwise ammonia TS until the colour changes to slightly yellow, add ammonia-ammonium chloride BS (pH 10.0) and a small amount of eriochrome black T indicator. Titrate with disodium edetate (0.05 mol/L) VS until the colour changes from purple to pure blue. Each ml of disodium edetate (0.05 mol/L) VS is equivalent to 10.17 mg of $(C_6H_5O_7)_2Zn_3 \cdot 2H_2O$.

Category As described under Zinc Citrate.

Strength 12.5 mg (calculated as Zn)

Storage Preserve in tightly closed containers.

Zinc Gluconate



$C_{12}H_{22}O_{14}Zn$ 455.68

Zinc Gluconate contains not less than 97.0% and not more than 102.0% of $C_{12}H_{22}O_{14}Zn$, calculated on the dried basis.

Description A white crystalline or granular powder; odourless; taste, slightly acerbity.

Very soluble in boiling water, soluble in water, insoluble in dehydrated ethanol, chloroform or ether.

Identification (1) Dissolve about 0.5 g in 5 ml of water in a tube by warming, add 0.7 ml of glacial acetic acid and 1 ml of freshly distilled phenylhydrazine, heat in a water bath for 30 minutes and cool. Scratch the inner surface of the test tube with a glass rod, yellow crystals are produced gradually. Filter, recrystallize using 10 ml of hot water with a small quantity of active carbon, filter again, dry the precipitate at 105°C for 1 hour, the melting range is 195 to 200°C (Appendix VI C).

(2) Dissolve about 0.1 g in 50 ml of water, add 1 drop of ferric chloride TS, a deep yellow colour is produced.

(3) The aqueous solution yields the reactions characteristic of zinc salts (Appendix III).

Acidity or alkalinity Dissolve 0.5 g in 50 ml of water, pH is 5.5 to 7.5 (Appendix VI H).

Chloride Carry out the limit test for chlorides (Appendix VIII A) using 0.1 g. Any opalescence produced is not more pronounced than that of a reference solution using 5.0 ml of sodium chloride standard solution (0.05%).

Sulfate Carry out the limit test for sulfates (Appendix VIII B), using 1 g. Any opalescence produced is not more pronounced than that of a reference solution using 5.0 ml of potassium sulfate standard solution (0.05%).

hydrochloric acid and about 0.5 g of high pure zinc granules, boil for 1 minute, allow to stand for 2 minutes, add 0.25 ml of freshly prepared phenylhydrazine hydrochloride solution (1→100), heat to boiling, cool immediately, add 6 ml of hydrochloric acid and 0.25 ml of freshly prepared potassium ferricyanide solution (5→100). Any colour produced is not more intense than that of a reference solution using 4 ml of sodium oxalate solution (1→10000) (0.06%).

Reducing substances Dissolve 1 g in 10 ml of water in a conical flask with stopper, add 25 ml of alkaline cupric citrate TS, boil gently for 5 minutes exactly, cool rapidly to room temperature. Add 25 ml of 0.6 mol/L acetic acid solution, 10 ml of iodine (0.1 mol/L) VS and 10 ml 3 mol/L hydrochloric acid and titrate with sodium thiosulfate (0.1 mol/L) VS, add 3 ml of starch IS towards the end of the titration, continue the titration until blue colour disappears. Perform a blank determination and make any necessary correction. Each ml of sodium thiosulfate (0.1 mol/L) VS is equivalent to 2.7 mg of reducing substances. The limit it contains is not more than 1.0%.

Loss on drying When dried in vacuum over phosphorous pentoxide to constant weight at 80°C, loses not more than 11.6% of its weight (Appendix VIII L).

Cadmium Transfer about 1 g, accurately weighed, to a 50 ml of Kjeldahl flask, add 6 ml of each of nitric acid and hydrogen peroxide, place a small funnel on top of the kjeldahl flask inclined at an angle of 45°. Heat slowly until the solution becomes to clear, cool, transfer completely to a 25 ml volumetric flask and dilute with water to volume, mix well, as solution (B). Measure accurately 1 ml of cadmium nitrate solution (Dissolve 1 g of cadmium, accurately weighed, in 20 ml of nitric acid in a 1000 ml volumetric flask, dilute with water to volume, mix well. Transfer 1 ml of the solution to a 100 ml volumetric flask, dilute with 1% (g/ml) nitric acid solution to volume, mix well. Each ml is equivalent to 10 µg of cadmium), perform the same procedure as solution B, the resulting solution is as solution A. Measure the absorbance of the solution A and solution B at 228.8 nm respectively (Appendix IV D), calculate the content of cadmium; not more than 0.0005%.

Lead Dissolve 1 g in 5 ml of water, add 10 ml of potassium cyanide TS, mix well, allow to stand until the solution becomes clear, add 5 drops of sodium sulfide TS and allow to stand for 2 minutes. Any colour produced is not more intense than that of a reference solution using 1 ml of lead standard solution (0.001%).

Arsenic Dissolve 1 g in 23 ml of water, add 5 ml of hydrochloric acid, carry out the limit test for arsenic (Appendix VIII J): not more than 0.0003%.

Assay Dissolve 0.7 g, accurately weighed, in 100 ml of water by warming, add 5 ml of ammonia-ammonium chloride BS (pH 10.0) and several drops of eriochrome black T IS. Titrate with disodium edetate (0.05 mol/L) VS until the purple solution becomes pure blue. Each ml of disodium edetate (0.05 mol/L) VS is equivalent to 22.78 mg of $C_{12}H_{22}O_{14}Zn$.

Category Zinc replenisher.

Storage Preserve in tightly closed containers, protected from light.

Preparation Zinc Gluconate Tablets

Zinc Gluconate Tablets

and not more than 107.0% of the labelled amount of zinc gluconate ($C_{12}H_{22}O_{14}Zn$).

Description White tablets.

Identification Dissolve a quantity of the powdered tablets equivalent to about 1 g of zinc gluconate in 20 ml of water by warming, cool, filter. The filtrate complies with the test for Identification described under Zinc Gluconate.

Dissolution Carry out the dissolution test (Appendix X C, method 1), using 1000 ml of water as the dissolution medium, adjust the rotation speed of the paddle to 100 rpm ± 5 rpm. Withdraw a quantity of the solution after exactly 30 minutes and filter, using the successive filtrate as a test solution. Dissolve about 50 mg of zinc gluconate CRS, accurately weighed, in water and dilute to 1000 ml with water as a reference solution. Measure accurately 2 ml (for 174 mg tablets), or 5 ml (for 70 mg tablets), or 10 ml (for 35 mg per tablets) of the test solution and 5 ml of the reference solution into separate 50 ml volumetric flasks, add to each volumetric flask 10 ml of borate-potassium chloride BS (pH 9.0) and 3 ml accurately measured of freshly prepared zinc solution (dissolve 0.13 g of zinc reagent in 2 ml of 1 mol/L sodium hydroxide, add water to 1000 ml), mix well, dilute to volume with water, mix well. Measure the absorbance of the resulting solutions at 213.9 nm (Appendix IV D, method 1), calculate the dissolution of $C_{12}H_{22}O_{14}Zn$ from each tablet. Not less than 75% of the labelled amount is dissolved.

Other requirements Comply with the general requirements for Tablets (Appendix I A).

Assay Weigh accurately and powder 20 tablets, weigh accurately a quantity of the powdered tablets equivalent to about 0.7 g of zinc gluconate, carry out the Assay described under Zinc Gluconate. Each ml of disodium edetate (0.05 mol/L) VS is equivalent to 22.78 mg of $C_{12}H_{22}O_{14}Zn$.

Category As described under Zinc Gluconate.

Strength (1) 35 mg (2) 70 mg (3) 174 mg

Storage Preserve in tightly closed containers, protected from light.

Zinc Oxide

ZnO 81.38 [1314-13-2]

Zinc Oxide contains not less than 99.0% of ZnO, calculated with reference to the substance freshly ignited to constant weight.

Description A white to faintly yellowish-white fine powder, odourless; gradually absorbs carbon dioxide from the air. Insoluble in water or ethanol; soluble in dilute acids or sodium hydroxide solution.

Identification (1) Become yellow when strongly heated. The yellow colour disappears on cooling. (2) Its solution in dilute hydrochloric acid yields the reactions characteristic of zinc salts (Appendix III).

Alkalinity Shake 1.0 g in 10 ml of boiling water for 5 minutes, cool, filter and add 2 drops of phenolphthalein IS to the filtrate. If the filtrate is pink, the colour is discharged on adding 0.10 ml of hydrochloric acid (0.1 mol/L) VS.

Carbonate and acid-insoluble substances Mix 2.0 g with 10 ml of water, add 30 ml of dilute sulfuric acid and heat on a water bath. No effervescence occurs and the resulting

Loss on ignition Ignite about 1.0 g, accurately weighed, at 800°C to constant weight, loses not more than 1.0% of its weight.

Iron Dissolve 0.40 g in 8 ml of dilute hydrochloric acid, 15 ml of water and 2 drops of nitric acid by boiling for 5 minutes, allow to cool, add water to 50 ml, mix well. To 25 ml of the solution add 10 ml of water, carry out the limit test for iron (Appendix VIII G). Any colour produced is not more intense than that of a reference solution using 1.0 ml of standard iron solution (0.005%).

Lead Stir well 2.0 g with 20 ml of water, add 5 ml of glacial acetic acid and heat on a water bath. Allow to cool and filter. Add 5 drops of potassium chromate IS to the filtrate, no opalescence is produced.

Arsenic Dissolve 1.0 g in 5 ml of hydrochloric acid and 23 ml of water. The solution complies with the limit test for arsenic (Appendix VIII J, method 1) (0.0002%).

Assay Dissolve about 0.1 g, accurately weighed, in 2 ml of dilute hydrochloric acid. Add 25 ml of water and 1 drop of 0.025% methyl red ethanolic solution. Add ammonia TS dropwise until the colour of the solution becomes slightly yellow. Add 25 ml of water, 10 ml of ammonia-ammonium chloride BS (pH 10.0) and a small quantity of eriochrome black T indicator, titrate with disodium edetate (0.05 mol/L) VS until the colour changes from violet to pure blue. Each ml of disodium edetate (0.05 mol/L) VS is equivalent to 4.069 mg of ZnO.

Category Astringent.

Storage Preserve in tightly closed containers.

Preparation Zinc Oxide Ointment

Zinc Oxide Ointment

Zinc Oxide Ointment contains not less than 14.0% and not more than 16.0% of zinc oxide (ZnO).

Description Pale yellow ointment.

Identification Heat and stir 1 g with 10 ml of dilute hydrochloric acid to dissolve zinc oxide. Allow to cool and filter. The filtrate yields the reactions characteristic of zinc salt (Appendix III).

Other requirements Complies with the general requirements for ointments (Appendix I F).

Assay Weigh accurately about 0.5 g, add 10 ml of chloroform, warm slightly and allow vaseline to melt. Add 10 ml of sulfuric acid (0.5 mol/L) VS, stir until zinc oxide is dissolved. Carry out the Assay described under Zinc Oxide, beginning at the words "add 1 drop of 0.025% methyl red ethanolic solution...". Each ml of disodium edetate (0.05 mol/L) VS is equivalent to 4.069 mg of ZnO.

Category As described under Zinc Oxide.

Strength (1) 20 g : 3 g (2) 500 g : 75 g

Storage Preserve in tightly closed containers.

Zinc Sulfate

$\text{ZnSO}_4 \cdot 7\text{H}_2\text{O}$ 287.56

[7446-20-0]

Zinc Sulfate contains not less than 99.0% and not

Description Colourless, transparent prisms, fine needles or a granular crystalline powder; odourless; taste, astringent, efflorescent.

Very soluble in water; freely soluble in glycerine; insoluble in ethanol.

Identification The aqueous solution yields the reactions characteristic of zinc salts and sulfates (Appendix III).

Acidity Dissolve 0.5 g in 10 ml of water, add 1 drop of methyl orange IS; no orange-red colour is produced.

Clarity of solution A solution of 2.5 g in 10 ml of water is clear.

Alkali and alkaline earth metals Dissolve 2.0 g in 150 ml of water in a 200 ml volumetric flask, precipitate zinc completely by means of ammonium sulfide TS and dilute with water to volume, mix and filter. To 100 ml of filtrate add 0.5 ml of sulfuric acid, evaporate to dryness in a tared dish and ignite to constant weight; the residue is not more than 5 mg (0.5%).

Lead Dissolve 0.50 g in 5 ml of water, add 10 ml of potassium cyanide TS, mix well and allow the mixture to stand. Add 5 drops of sodium sulfide TS, allow to stand for further 2 minutes. The colour produced is not more intense than that of reference solution prepared in a similar manner using 0.50 ml of standard lead solution (0.001%).

Aluminum, iron, copper and other heavy metals Dissolve 1.0 g in 10 ml of water, add 10 ml of concentrated ammonia solution, allow to stand for 30 minutes; the solution is clear and colourless; add a quantity of sodium sulfide TS, only a white precipitate is formed.

Assay Dissolve about 0.3 g, accurately weighed, in 30 ml of water, add 10 ml of ammonia-ammonium chloride BS (pH 10.0) and a small quantity of eriochrome black T IS. Titrate with disodium edetate (0.05 mol/L) VS until the violet red colour changes to pure blue. Each ml of disodium edetate (0.05 mol/L) VS is equivalent to 14.38 mg of $\text{ZnSO}_4 \cdot 7\text{H}_2\text{O}$.

Category Zinc replenisher and astringent.

Storage Preserve in tightly closed containers.

Preparations (1) Zinc Sulfate Granules
(2) Zinc Sulfate Oral Solution
(3) Zinc Sulfate Tablets

Zinc Sulfate Granules

Zinc Sulfate Granules contain not less than 90.0% and not more than 110.0% of labelled amount of zinc sulfate ($\text{ZnSO}_4 \cdot 7\text{H}_2\text{O}$).

Description White, almost white to slightly yellow granules.

Identification The aqueous solution yields the reactions characteristic of zinc salts and sulfates (Appendix III).

Other requirements Comply with the general requirements for Granules (Appendix I N).

Assay Weigh accurately and powder 25 (for 5 g strength) or 70 (for 2 g strength) containers. Dissolve a quantity equivalent to 0.2 g of zinc sulfate, accurately weighed, in 50 ml of water by shaking, add 10 ml of ammonia-ammonium chloride BS (pH 10.0), 1 g of ammonium fluoride and a few drops of eriochrome black T IS. Titrate with disodium edetate (0.05 mol/L) VS until the violet red colour changes to pure blue or dark green. Each ml of

mg of $\text{ZnSO}_4 \cdot 7\text{H}_2\text{O}$.

Category As described under Zinc Sulfate.

Strength (1) 2 g : 8 mg (2) 5 g : 20 mg

Storage Preserve in tightly closed containers, protected from light.

Zinc Sulfate Oral Solution

Zinc Sulfate Oral Solution contains not less than 0.18% and not more than 0.22% of zinc sulfate ($\text{ZnSO}_4 \cdot 7\text{H}_2\text{O}$).

Description A pale yellow to pale yellowish-green liquid; taste, sweetish, slightly astringent.

Identification Yields the reactions characteristic of zinc salts and sulfates (Appendix III).

Other requirements Complies with the general requirements for Oral Solutions (Appendix I O).

Assay To 100 ml measured accurately, equivalent to about 0.2 g of zinc sulfate, add 10 ml of ammonia-ammonium chloride BS (pH 10.0), 1 g of ammonium fluoride and a few drops of eriochrome black T IS. Titrate with disodium edetate (0.05 mol/L) VS until the colour changes from dark purplish-red to dark green. The end point is reached when the dark green colour persists for 1 minute. Each ml of disodium edetate (0.05 mol/L) VS is equivalent to 14.38 mg $\text{ZnSO}_4 \cdot 7\text{H}_2\text{O}$.

Category As described under Zinc Sulfate.

Strength 100 ml : 0.2 g (calculated as $\text{ZnSO}_4 \cdot 7\text{H}_2\text{O}$)

Storage Preserve in tightly closed containers.

Zinc Sulfate Tablets

Zinc Sulfate Tablets contain not less than 90.0% and not more than 110.0% of the labelled amount of zinc sulfate ($\text{ZnSO}_4 \cdot 7\text{H}_2\text{O}$).

Description Sugar coated tablets, with white core.

Identification Remove the sugar coating of the tablets. dissolve a quantity of the powdered tablets, equivalent to about 100 mg of zinc sulfate with 10 ml of water and filter. The filtrate yields the reactions characteristic of zinc salts and sulfates (Appendix III).

Other requirements Comply with the general requirements for tablets (Appendix I A).

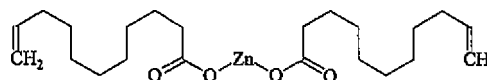
Assay Weigh and powder 20 tablets with sugar coat removed. Weigh accurately a quantity of powdered tablets equivalent to about 0.2 g of Zinc Sulfate, carry out the Assay as described under Zinc Sulfate.

Category As described under Zinc Sulfate.

Strength (1) 25 mg (2) 50 mg

Storage Preserved in tightly closed containers.

Zinc Undecylenate



$\text{C}_{22}\text{H}_{38}\text{O}_4\text{Zn}$ 431.92

[557-08-4]

Zinc Undecylenate is 10-undecenoic acid, zinc (2^+) salt. It contains not less than 98.0% and not more than 102.0% of $\text{C}_{22}\text{H}_{38}\text{O}_4\text{Zn}$.

Description A white, amorphous powder. Practically insoluble in water or ethanol.

Melting range 116-121°C (Appendix VI C).

Identification (1) To about 3 g add 20 ml of water and 25 ml of dilute sulfuric acid, extract with two portions, each of 25 ml, of ether, combine the ethereal extracts, evaporate ether on a water bath. The residue complies with the tests (1) for Identification described under Undecenoic Acid.

(2) Dissolve about 0.1 g in 10 ml of water and 1 ml of concentrated ammonia TS, add a few drops of sodium sulfide TS; a white precipitate is produced.

(3) The infrared absorption spectrum (Appendix IV C) is concordant with the reference spectrum of Zinc Undecylenate (Appendix XVI).

Loss on drying When dried to constant weight at 105°C, loses not more than 1.0% of its weight (Appendix VIII L).

Alkali and alkaline earth metals Boil 1.5 g with 50 ml of water and 10 ml of hydrochloric acid and filter while hot with a moistened filter paper. Wash the residue with hot water until the washing is no longer acidic, combine the washings and the filtrate in a 200 ml volumetric flask and add ammonia TS until the solution is just alkaline. Add ammonium sulfide TS until the zinc is completely precipitated, add water to volume, mix well and filter. To 100 ml of the filtrate add 0.5 ml of sulfuric acid, evaporate to dryness and ignite to constant weight, the residue is not more than 7.5 mg.

Assay To about 0.5 g, accurately weighed, add 10 ml of 1 mol/L hydrochloric acid solution and 10 ml of water, boil for 10 minutes, filter while hot. Wash the residue with hot water, combine the washings and the filtrate, cool, add 1 drop of ethanolic methyl red solution (0.025%) and a quantity of ammonia TS until the solution is pale yellow; add water to produce about 35 ml, add 10 ml of ammonia-ammonium chloride BS (pH 10.0) and a small quantity of eriochrome black T indicator mixture, titrate with disodium edetate (0.05 mol/L) VS until the purple colour changes to pure blue. Each ml of disodium edetate (0.05 mol/L) VS is equivalent to 21.60 mg of $\text{C}_{22}\text{H}_{38}\text{O}_4\text{Zn}$.

Category Antifungal disinfectant.

Storage Preserve in tightly closed containers.

Preparation Compound Zinc Undecylenate Ointment

Compound Zinc Undecylenate Ointment

Compound Zinc Undecylenate Ointment contains not less than 18.5% and not more than 21.5% of zinc undecylenate ($\text{C}_{22}\text{H}_{38}\text{O}_4\text{Zn}$).

Undecylenic Acid	50 g
Base	a sufficient quantity
<hr/>	
Total	1000 g

Description A white to pale yellow ointment.

Identification (1) Heat about 5 g in 25 ml of ethanol with shaking, cool and filter. To the filtrate add a few drops of potassium permanganate TS, the colour of potassium permanganate is discharged on shaking.

(2) To the residue obtained in test (1) add 10 ml of chloroform, warm gently to dissolve, cool. Add 20 ml of dilute sulfuric acid, shake and allow to stand, the acid layer yields the reactions characteristic of zinc (Appendix III).

Other requirements Complies with the general requirements

for ointments (Appendix I F).

Assay To about 2.5 g, accurately weighed, in a conical flask add 10 ml of 1 mol/L hydrochloric acid solution and 20 ml of water, heat in a water bath for about 15 minutes, with frequent shaking until the oil layer is clear. Add 20 ml of hot water, stir, allow to stand and cool. Complies with the Assay described under Zinc Undecylenate, beginning at the words "Add 1 drop of ethanolic methyl red solution (0.025%)...". Each ml of disodium edetate (0.05 mol/L) VS is equivalent to 21.60 mg of $C_{22}H_{38}O_4Zn$.

Category As described under Zinc Undecylenate.

Storage Preserve in tightly closed containers.

MONOGRAPHS

PART II

Acetic Acid

Acetic Acid contains not less than 36% and not more than 37% (g/g) of $C_2H_4O_2$.

Description A colourless clear liquid; odour, strong and characteristic; taste, extremely sour.

Relative density 1.04-1.05, at 25°C (Appendix VI A).

Identification When neutralized with sodium hydroxide TS, yields the reactions characteristic of acetates (Appendix III).

Chloride Dilute 1.0 ml with water to 10 ml. Carry out the limit test for chlorides (Appendix VIII A), using 2.0 ml. Any opalescence produced is not more pronounced than that of a reference using 7.0 ml of sodium chloride standard solution (0.035%).

Sulfate Carry out the limit test for sulfates (Appendix VIII B), using 2.0 ml of the diluted solution obtained in the test for Chloride. Any opalescence produced is not more pronounced than that of a reference using 3.0 ml of potassium sulfate standard solution (0.15%).

Formic acid and readily oxidizable substances Add 2.5 ml of potassium dichromate (0.01667 mol/L) solution and 6 ml of sulfuric acid to 5.0 ml of the substance being examined, allow to stand for 1 minute. Add 20 ml of water, cool to 15°C, add 1 ml of potassium iodide TS. A yellow or brown colour is produced.

Non-volatile matter Place 20 ml in an evaporating dish, previously dried to constant weight at 105°C, evaporate on a water bath to dryness and dry at 105°C to constant weight. The residue is not more than 1 mg.

Foreign odour Neutralize 5 ml with sodium hydroxide TS and boil. No other odour is produced except a faint odour of acetic acid.

Heavy metals Add 8 ml of hydrochloric acid solution (9→1000) to the residue obtained in the test for Non-volatile matter, warm to effect dissolution, dilute with water to 100 ml, mix well. To 10 ml of the solution add 2 ml of acetate BS (pH 3.5) and sufficient water to produce 25 ml. Carry out the limit test for heavy metals (Appendix VIII H, method 1); not more than 0.001%.

Assay Weigh accurately about 4 ml in a tared conical flask, dilute with 40 ml of freshly boiled and cooled water, add 3 drops of phenolphthalein IS and titrate with sodium hydroxide (1 mol/L) VS. Each ml of sodium hydroxide (1 mol/L) VS is equivalent to 60.05 mg of $C_2H_4O_2$.

Category Pharmaceutical aid, antiseptic.

Storage Preserve in tightly closed glass bottles.

Agar

Agar is a dehydrated mucilaginous substance extracted from *Gelidium amansii* Lamx or other related red algae.

Description Slender strips, almost white or pale yellow; translucent, surface crumpled and slightly lustrous. Light, flexible and difficult to break; brittle and easy to break when dry; odourless; taste, slight. Agar powder is scaly, colourless or pale yellow; irregular polygonal mucilaginous

odourless; taste, slight.

Soluble in boiling water; insoluble in cold water but swelled into gelatinous mass. Its aqueous solution is neutral.

Identification (1) Boil with constant stirring to dissolve about 1 g in 65 ml of water, replenish evaporated water with hot water. It coagulates into translucent elastic gelations; substance when cooled to 32-39°C and remelts when heated to 85°C.

(2) When immersed in 0.02 mol/L iodine solution for a few minutes, it is dyed brownish black. The fragments gradually become purple after macerating in water.

(3) Dissolve about 0.1 g in 20 ml of water by heating. To 4 ml of the solution add 0.5 ml of hydrochloric acid and heat on a water bath for 30 minutes. Add 3 ml of sodium hydroxide TS and 6 ml of alkaline cupric tartrate TS, heat in water bath. A red colour precipitate is produced.

Starch Dissolve 0.10 g in 100 ml of water by boiling. Allow to cool. Add 2 drops of iodine TS, no blue colour is produced.

Loss on drying When dried at 105°C for 5 hours, loses not more than 22.0% of its weight (Appendix VIII L). Strip agar must be reduced to small fragments before drying.

Ash Ignite slowly about 1 g, accurately weighed, in a crucible, previously ignited to constant weight, until the substance being examined is completely carbonized, raise the temperature gradually to 600-700°C, incinerate completely to constant weight. The residual ash is not more than 5.0% of its weight.

Water-insoluble substances Dissolve 1.5 g in 200 ml of water in a beaker by boiling, filter while hot through a No. 3 sintered glass crucible, previously dried to constant weight at 105°C. Wash the beaker with hot water for several times, filter the washings. Dry the residue to constant weight at 105°C. The residue does not exceed 15 mg (1.0%).

Water absorbability Place 5.0 g in a 100 ml measuring cylinder and add water to volume, mix well. Allow to stand at 25°C for 24 hours, filter through a layer of moistened glass wool into another measuring cylinder. Total volume of the filtrate does not exceed 75 ml.

Category Pharmaceutical aid, excipient.

Storage Preserve in tightly closed containers, stored in a dry place.

Anhydrous Sodium Sulfite

Na_2SO_3 126.04

Anhydrous Sodium Sulfite contains not less than 95.0 % of Na_2SO_3 .

Description White crystals or a powder; odourless. Freely soluble in water; very slightly soluble in ethanol; practically insoluble in ether.

Identification (1) The aqueous solution (1→10) is alkaline and yields the reaction characteristic of sulfite (Appendix III).

(2) Yields the reaction characteristic of sodium salts (Appendix III).

Clarity and colour of solution A solution of 1.0 g in 20 ml of water is clear and colourless.

Thiosulfate Dissolve 1.0 g in 15 ml of water, add 5 ml of dilute hydrochloric acid, shake, and allow to stand for 5

Iron To 1.0 g add 2 ml of hydrochloric acid, evaporate to dryness on a water bath. Dissolve the residue in a quantity of water, and carry out the limit test for iron (Appendix VIII G). Any colour produced is not more intense than that of a reference solution using 2.0 ml of iron standard solution (0.002 %).

Heavy metals Carry out the limit test for heavy metals (Appendix VIII H, method 1), using 1.0 g; not more than 0.002 %.

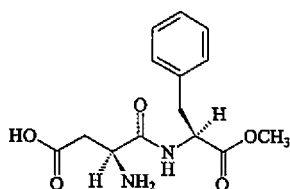
Arsenic Dissolve 0.5 g in 10 ml of water, add 1 ml of sulfuric acid, evaporate on a sand bath until white fumes are evolved. Cool, add 21 ml of water and 5 ml of hydrochloric acid. Carry out the limit test for arsenic (Appendix VIII J, method 2); not more than 0.0004 %.

Assay To about 0.2 g, accurately weighed, add 50 ml of iodine (0.05 mol/L) VS, accurately measured, stopper and shake until dissolved. Allow to stand in dark for 5 minutes. Titrate with sodium thiosulfate (0.1 mol/L) VS, add 1 ml of starch IS towards the end of the titration and continue the titration until the blue colour disappears. Perform a blank determination and make any necessary correction. Each ml of iodine (0.05 mol/L) VS is equivalent to 6.302 mg of Na_2SO_3 .

Category Pharmaceutical aid.

Storage Preserve in tightly closed containers.

Aspartame



$\text{C}_{14}\text{H}_{18}\text{N}_2\text{O}_5$ 294.31

[22839-47-0]

Aspartame is 3-amino-*N*-(α -carboxyphenethyl) succinamic acid *N*-methyl ester. It contains not less than 98.0% and not more than 102.0% of $\text{C}_{14}\text{H}_{18}\text{N}_2\text{O}_5$, calculated on the dried basis.

Description A white crystalline powder; taste, sweet.

Specific optical rotation $+14.5^\circ$ to $+16.5^\circ$, in a solution of 40 mg per ml in 70% formic acid solution (Appendix VI E). Perform the determination immediately.

Identification The infrared absorption spectrum (Appendix IV C) is concordant with the reference spectrum of aspartame (Appendix XVI).

Acidity Dissolve 1.0 g in 125 ml of water, pH 4.0-6.0 (Appendix VI H).

Clarity of solution The transmittance of a solution of 1% in 2 mol/L hydrochloric acid solution at 430 nm (Appendix IV A) is not less than 95.0%.

Loss on drying When dried at 105°C for 4 hours, loses not more than 4.5% of its weight (Appendix VIII L).

Residue on ignition Not more than 0.2% (Appendix VIII N), using 1.0 g.

Heavy metals Carry out the limit test for heavy metals (Appendix VIII H, method 2), using the residue obtained in

Arsenic Mix 0.67 g with 1.0 g of calcium hydroxide, triturate with 2 ml of water, and dry at 40°C . Ignite gently to carbonize and then ignite at $500-600^\circ\text{C}$ until the incineration is complete. Cool, add 8 ml of hydrochloric acid and 23 ml of water. Carry out the limit test for arsenic (Appendix VIII J, method 1); not more than 0.0003%.

Related substance Carry out the method for high performance liquid chromatography (Appendix V D), using a column packed with octadecylsilane bonded silica gel and a mixture of citrate BS (dissolve 9.6 g citric acid in about 800 ml of water, adjust to pH 4.7 with 1 mol/L sodium hydroxide and dilute with water to 1000 ml.)-methanol (67 : 33) as the mobile phase. Detection wavelength is 254 nm, the number of the theoretical plates of the column is not less than 2000 calculated with reference to the peak of aspartame.

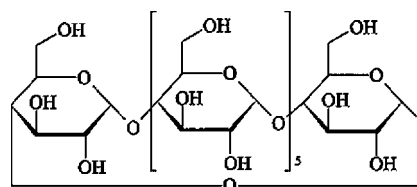
Procedure Dissolve a quantity of the substance being examined, accurately weighed, in mobile phase to produce a solution of 6 mg per ml (solution (1)) and 0.12 mg per ml (solution (2)). Inject $10\ \mu\text{l}$ of solution (2) into the column, adjust the sensitivity of the system so that the height of the principal peak obtained in the chromatogram is 20% of the full scale of the recorder. Inject $10\ \mu\text{l}$ each of solution (1) and (2) into the column, and record the chromatogram for twice the retention time of the principal peak. The sum of impurity peak areas of solution (1) is not greater than the principal peak area of solution (2).

Assay Dissolve about 0.3 g, accurately weighed, in 3 ml of methanol and 50 ml of glacial acetic acid, add 2 drops of crystal violet IS. Titrate immediately with perchloric acid (0.1 mol/L) VS until the solution becomes blue. Perform a blank determination and make any necessary correction. Each ml of perchloric acid (0.1 mol/L) VS is equivalent to 29.43 mg of $\text{C}_{14}\text{H}_{18}\text{N}_2\text{O}_5$.

Category Pharmaceutical aid.

Storage Preserve in tightly closed containers, stored in a dry place.

Betacyclodextrin



$(\text{C}_6\text{H}_{10}\text{O}_5)_7$ 1134.99

[7585-39-9]

Betacyclodextrin is a cyclic oligosaccharide compound composed of seven α -1,4 linked D-glucopyranosyl units and is obtained from the action of cyclodextrin glucosyltransferase on starch. It contains not less than 96.0% and not more than 102.0% of $(\text{C}_6\text{H}_{10}\text{O}_5)_7$, calculated on the dried basis.

Description White crystals or a crystalline powder; odourless; taste, slightly sweet. Sparingly soluble in water; practically insoluble in methanol, ethanol, acetone or ether.

Specific optical rotation $+159^\circ$ to 164° , in a solution of 10 mg per ml in water (Appendix VI E).

TS by warming in a water bath, and cool to room temperature. A yellowish-brown precipitate is produced.

(2) The retention time of the principal peak of the substance being examined in the chromatogram obtained in the Assay is identical with that of the reference standard.

Acidity or alkalinity Dissolve 0.2 g in 20 ml of water, add 0.2 ml of a saturated solution of potassium chloride, pH 5.0-8.0 (Appendix VI H).

Clarity and colour of solution Dissolve 0.50 g in 50 ml of water, the solution is clear and colourless; any opalescence produced is not more pronounced than that of reference suspension 2 (Appendix IX B).

Chloride Carry out the limit test for chloride (Appendix VIII A), using 0.39 g. Any opalescence produced is not more pronounced than that of a reference solution using 7.0 ml of sodium chloride standard solution (0.018%).

Reducing sugars Dissolve about 1.0 g, accurately weighed, in 25 ml of water, add 40 ml of alkaline cupric tartrate TS. Boil gently for 3 minutes and allow to stand overnight at room temperature. Filter with a G₄ sintered glass filter, wash the precipitate with warm water until the washings are neutral. Discard the filtrates and washings. Dissolve the precipitate in 20 ml of hot ferric sulfate TS and filter. Wash the filter with 100 ml of water. Combine the filtrates and washings, and heat to 60°C. Titrate the hot solution immediately with potassium permanganate (0.02 mol/L) VS. The potassium permanganate (0.02 mol/L) VS consumed is not more than 3.2 ml (0.2%) for each g of substance taken, calculated on the dried basis.

Loss on drying When dried to constant weight at 105 °C, loses not more than 14.0% of its weight (Appendix VIII L).

Residue on ignition Not more than 0.1% (Appendix VIII N), using 1.0 g.

Heavy metals Carry out the limit test for heavy metals (Appendix VIII H, method 2), using the residue obtained in the test for Residue on ignition; not more than 0.001%.

Assay Carry out the method for high performance liquid chromatography (Appendix V D), using a column packed with octadecylsilane bonded silica gel, a mixture of water-methanol (85 : 15) as the mobile phase and a differential refractometer as detector. The number of the theoretical plates of the column is not less than 1500, calculated with reference to the peak of Betacyclodextrin.

Procedure Shake about 50 mg, accurately weighed, with a quantity of water in a 10 ml volumetric flask, dilute with water to volume and mix well. Inject 10 µl of the resulting solution into the column. Repeat the operation, using Betacyclodextrin CRS in stead of the substance being examined, calculate the content of (C₆H₁₀O₅)₇ with respect to the peak area obtained in the chromatogram by the external standard method.

Category Pharmaceutical aid, Excipient.

Storage Preserve in tightly closed containers, store in a dry place.

Black Ferric Oxide

Fe₃O₄ 231.53

Black Ferric Oxide contains not less than 96.0% of Fe₃O₄, calculated on the dried basis.

Insoluble in water; freely soluble in boiling hydrochloric acid.

Identification Boil about 0.1 g with 5 ml of dilute hydrochloric acid, allow to cool, the solution yields the reactions characteristic of ferric salts (Appendix III).

Water soluble substances Dissolve 2.0 g in 100 ml of water, heat under reflux on a water bath for 2 hours and filter. Wash the residue with a quantity of water, evaporate the combined filtrate and washings to dryness in an evaporating dish previously dried to constant weight at 105°C, dry the residue to constant weight at 105°C; not more than 10 mg (0.5%).

Acid insoluble substances Dissolve 2.0 g in 25 ml of hydrochloric acid by heating in a water bath, add 100 ml of water, filter through a sintered glass crucible (No. 4) previously dried to constant weight at 105°C, wash the residue with hydrochloric acid solution (1→100) until the washings become colourless, then wash the residue with water until the washings give no reaction of chlorides, dry the residue to constant weight at 105°C; not more than 20 mg (1.0%).

Loss on drying When dried to constant weight at 105°C, loses not more than 1.0% of its weight (Appendix VIII L).

Barium To 0.2 g add 5 ml of hydrochloric acid, heat to dissolve. Add 1 drop of hydrogen peroxide TS and 20 ml of 10% sodium hydroxide solution, filter, wash the residue with 10 ml of water. Combine the filtrate and washings, add 10 ml of sulfuric acid solution (2→10), no opalescence is produced.

Lead To 0.5 g add 10 ml of hydrochloric acid, heat to dissolve. Add 3 ml of nitric acid, boil for 1 minute, allow to cool. Extract with ether for 4 times (30 ml, 20 ml, 20 ml and 20 ml), discard the ether layer. Heat the acid solution to expel the remaining ether, add ammonia TS to make the solution alkaline, add 1 ml of potassium cyanide TS and sufficient water to produce 50 ml. Add a few drops of sodium sulfide TS and mix well. Any colour produced is not more intense than that of a reference solution prepared in the same manner using 1.5 ml of lead standard solution (0.003%).

Arsenic To 0.2 g add 7 ml of hydrochloric acid, heat to dissolve. Add 21 ml of water and acid stannous chloride TS dropwise until the yellow colour disappears. Carry out the limit test for arsenic (Appendix VIII J, method 1); not more than 0.001%.

Assay Dissolve about 0.15 g, accurately weighed, in a conical flask with stopper in 30 ml of hydrochloric acid solution (1→2), heat to dissolve. Continue to heat until the solution begins to boil. Add freshly prepared stannous chloride TS dropwise until the solution is just colourless. Then add 1 drop of freshly prepared stannous chloride TS in excess and 200 ml of water, allow to cool, add 4 ml of mercuric Chloride TS, mix well, then add 3 ml of sulfuric acid and 3 ml of phosphoric acid. Add 6 drops of 0.2% diphenylamine sulfonic acid sodium IS, titrate with potassium dichromate (0.01667 mol/L) VS until a purple blue colour persists for 30 seconds. Each ml of potassium dichromate (0.01667 mol/L) VS is equivalent to 7.72 mg of Fe₃O₄.

Category Pharmaceutical aid, colouring agent.

Storage Preserve in tightly closed containers.

Brown Ferric Oxide

proportion of red ferric oxide, black ferric oxide and yellow ferric oxide. It contains not less than 98.0% of Fe_2O_3 , calculated on dried basis.

Description A red-brown powder; odourless; tasteless.

Insoluble in water; freely soluble in boiling hydrochloric acid.

Identification Boil about 0.1 g with 5 ml of dilute hydrochloric acid, allow to cool, the solution yields the reactions characteristic of ferric salts (Appendix III).

Water soluble substances To 2.0 g add 100 ml of water, heat under reflux on a water bath for 2 hours and filter. Wash the residue with a quantity of water, evaporate the combined filtrate and washings to dryness in an evaporating dish previously dried to constant weight at 105°C, dry the residue to constant weight at 105°C; not more than 10 mg (0.5%).

Acid insoluble substances Dissolve 2.0 g in 25 ml of hydrochloric acid by heating in a water bath, add 100 ml of water, filter through a sintered glass crucible (No. 4) previously dried to constant weight at 105°C, wash the residue with hydrochloric acid solution (1→100) until the washings become colourless, then wash the residue with water until the washings give no reaction of chlorides, dry the residue to constant weight at 105°C; not more than 20 mg (1.0%).

Loss on drying When dried to constant weight at 105°C, loses not more than 1.0% of its weight (Appendix VII L).

Barium To 0.2 g add 5 ml of hydrochloric acid, heat to dissolve. Add 1 drop of hydrogen peroxide TS and 20 ml of 10% sodium hydroxide solution, filter, wash the residue with 10 ml of water. Combine the filtrate and washings, add 10 ml of sulfuric acid solution (2→10), no opalescence is produced.

Lead To 0.5 g add 10 ml of hydrochloric acid, heat to dissolve. Add 3 ml of nitric acid, boil for 1 minute, allow to cool. Extract with anhydrous ether for 4 times (30 ml, 20 ml, 20 ml and 20 ml), discard the ether layer. Heat the acid solution to expel the remaining ether, add ammonia TS to make the solution alkaline, add 1 ml of potassium cyanide TS and sufficient water to produce 50 ml. Add a few drops of sodium sulfide TS and mix well. Any colour produced is not more intense than that of a reference solution prepared in the same manner using 1.5 ml of lead standard solution (0.003%).

Arsenic To 0.2 g add 7 ml of hydrochloric acid, heat to dissolve. Add 21 ml of water, and add acid stannous chloride TS dropwise until the yellow colour disappears. Carry out the limit test for arsenic (Appendix VII J, method 1); not more than 0.001%.

Assay Add to about 0.15 g, accurately weighed, in a conical flask with stopper 2.5 ml of hydrochloric acid, heat to dissolve on a water bath. Add 1 ml of hydrogen peroxide TS, heat to boil for a few minutes, add 25 ml of water, allow to cool. Add 1.5 g of potassium iodide and 2.5 ml of hydrochloric acid, stopper and shake thoroughly, allow to stand in a dark place for 15 minutes. Titrate with sodium thiosulfate (0.1 mol/L) VS, add 2.5 ml of starch TS towards the end of titration, continue the titration until the blue colour disappears. Each ml of sodium thiosulfate (0.1 mol/L) VS is equivalent to 7.985 mg of Fe_2O_3 .

Category Pharmaceutical aid, colouring agent.

Storage Preserve in tightly closed containers.

Calcium Sulfate

$\text{CaSO}_4 \cdot 2\text{H}_2\text{O}$ 172.17

[10101-41-4]

Calcium Sulfate contains not less than 99.0% of CaSO_4 , Calculated on the ignited basis.

Description White powder, odourless; tasteless. Slightly soluble in water; insoluble in ethanol; soluble in dilute hydrochloric acid.

Identification The dilute hydrochloric acid solution yields the reactions characteristic of calcium salts and sulfates (Appendix III).

Chloride To 0.50 g add 5 ml of nitric acid (1→2) add 40 ml of water, shake to dissolve, carry out the limit test for chlorides (Appendix VIII A). Any in the same manner opalescence produced is not more intense than that of a reference solution prepared using 9.0 ml of sodium chloride standard solution (0.018%).

Carbonate Mix 1 g with 5 ml of water, add dropwise dilute hydrochloric acid; no effervescence is produced.

Loss on ignited When ignited to constant weight, loses not less than 18.0% and not more than 23.0% of its weight, using 1.0 g.

Iron To 0.20 g add 50 mg of ammonium persulfate and 10 ml of dilute hydrochloric acid, shake to dissolve, dilute with water to 50 ml, add 5 ml of Ammonium Thiocyanate TS, mix well. Carry out the limit test for iron (Appendix VIII G). Any colour produced is not more intense than that of the reference solution treated in similar manner using 3.0 ml of iron standard solution (0.015%).

Heavy metals To 1.0 g add 5 ml of dilute hydrochloric acid and 15 ml of water, heat to dissolve. Allow to cool, add 1 drop of phenolphthalein IS, then add dropwise concentrated ammonia solution until the solution becomes light red. Add 2 ml of acetate BS (pH 3.5), filter, dilute the filtrate with water to 25 ml and add 0.5 g of vitamin C. Carry out the limit test for heavy metals (Appendix VIII H, method 1); not more than 0.0015%.

Assay Dissolve 0.2 g, accurately weighed in 10 ml of dilute hydrochloric acid and 100 ml of water on shaking. Add accurately 20 ml of disodium edetate (0.05 mol/L) VS under stirring, mix well, then 15 ml of sodium hydroxide solution (1→5) and 0.2-0.3 g of murexide indicator mixture (triturate 0.1 g murexide, with sodium chloride to 20 g). Titrate with disodium edetate (0.05 mol/L) VS until the colour turns from pink to violet. Each ml of disodium edetate (0.05 mol/L) VS is equivalent to 6.807 mg of CaSO_4 .

Category Pharmaceutical aid.

Storage Preserve in tightly closed containers, protected from light.

Carbomer

Carbomer is a high molecular weight polymer of acrylic acid cross-linked with allylsucrose or allyl ethers of pentaerythritol. It contains not less than 56.0% and not more than 68.0% of carboxylic acid

Description A white, fluffy powder; odour, slight and characteristic; hygroscopic.

Identification Disperse 0.1 g in 20 ml of water and add 0.4 ml of 10% sodium hydroxide solution; a gel is produced.

Acidity Swell 0.10 g in 10 ml of water till uniformly dispersed, pH 2.5-3.5 (Appendix VI H).

Benzene Dissolve a quantity of benzene, accurately weighed, in *p*-xylene to produce a solution of 10 µg per ml as the reference solution. Place about 1 g of carbomer, accurately weighed, in a test tube with stopper, add 10.0 ml of *p*-xylene, and shake to disperse carbomer. Add 10.0 ml of 0.1 mol/L sodium hydroxide solution, stopper, shake for 1 hour and use the supernatant liquid as the test solution. Carry out the method for gas chromatography (Appendix V E), using a glass column 3 m long packed with 201 pink support (60 to 80 mesh) coated with 10% of a mixture of equal parts of dinonyl phthalate and bentone as the stationary phase, and maintain the column temperature at 100°C. Inject separately 1 µl of the test solution and of the reference solution into the column, calculate the content of benzene, not more than 0.01%.

Loss on drying When dried in vacuum at 80°C for 1 hour, loses not more than 2.0% of its weight (Appendix VIII L).

Residue on ignition Not more than 2.0% (Appendix VIII N), using 1.0 g.

Heavy metals Carry out the limit test for heavy metals (Appendix VIII H, method 2), using the residue obtained in the test for Residue on ignition; not more than 0.002%.

Viscosity Disperse uniformly 0.5 g in 98 ml of water, mix well after fully swelled, adjust pH to 7.3-7.8 (tested by precision pH test paper) with 15% sodium hydroxide solution, add water to 100 ml, and mix well with taking care to avoid the formation of air bubbles. The kinematic viscosity at 25°C is 15-30 Pa · s (Appendix VI G, method 2).

Assay Disperse uniformly 0.4 g, accurately weighed, in 400 ml of water, stir to dissolve carbomer. Carry out the method for potentiometric titration (Appendix VII A). Titrate with sodium hydroxide (0.25 mol/L) VS (towards the end of the titration, stir the mixture for at least 2 minutes after each addition). Each ml of sodium hydroxide (0.25 mol/L) VS is equivalent to 11.25 mg of carboxylic acid (—COOH) groups.

Category Pharmaceutical aid.

Storage Preserve in tightly closed containers.

Carboxymethylstarch Sodium

Carboxymethylstarch Sodium is the sodium salt of starch carboxymethyl ether prepared of starch reacted with chloroacetic acid under alkaline condition. It contains not less than 2.0% and not more than 4.0% of sodium (Na), calculated on the dried basis.

Description A white or almost white powder; odourless; hygroscopic in air. Disperses in water to viscous colloidal solution; insoluble in ethanol or ether.

Identification (1) Shake well about 0.1 g with 5 ml of water, add 1 drop of iodine TS, a blue colour is produced

(Appendix III).

Acidity or alkalinity Shake 1.0 g with 100 ml with water, pH 5.5-7.5 (Appendix VI H).

Total chlorine content Shake well about 0.5 g, accurately weighed, with 150 ml of water in a 250 ml conical flask, add 1 ml of potassium chromate IS and titrate with silver nitrate (0.1 mol/L) VS. Each ml of silver nitrate (0.1 mol/L) VS is equivalent to 3.545 mg of Cl. The total chlorine content is not more than 3.5%, calculated on the dried basis.

Loss on drying When dried at 130°C for 90 minutes, loses not more than 10.0% of its weight (Appendix VIII L).

Iron Ignite gently of 0.5 g in crucible to carbonize, cool, moisten the residue with 0.5 ml of sulfuric acid and heat at low temperature to expel the vapour of sulfuric acid, then raise the temperature to 550-600°C until free from carbon. Allow it to cool, warm in a water bath at 60°C for 10 minutes on adding 4 ml of dilute hydrochloric acid with stirring. Allow the solution to cool, filter if necessary and transfer it into a 50 ml Nessler cylinder. Carry out the limit test for iron (Appendix VII G), using the resulting solution. The colour produced is not more intense than that of a standard using 2.0 ml of iron standard solution (0.004%).

Heavy metals Carry out the test for heavy metals (Appendix VIII H, method 2), using 1.0 g; not more than 0.002%.

Assay To 0.45 g obtained in Loss on drying, accurately weighed, add 50 ml of glacial acetic acid in a 250 ml stoppered conical flask, shake well, Heat it on a water bath for 2 hours, shake well in an interval of 30 minutes until disperses completely. Cool, transfer the solution to a 100 ml beaker. Wash the flask with glacial acetic acid for 3 times, each of 5 ml, and combine the washings with the solution. Titrate potentiometrically (Appendix VII A) with perchloric acid (0.1 mol/L) VS. Each ml of perchloric acid (0.1 mol/L) VS is equivalent to 2.299 mg of Na.

Category Pharmaceutical aid.

Storage Preserve in tightly closed containers, stored in a dry place.

Cellacefate

Cellacefate is a condensation compound of partially acetylated cellulose acetate and phthalic anhydride. It contains not less than 30.0% and not more than 40.0% of phthalyl ($C_8H_5O_3$) and not less than 17.0% and not more than 26.0% of acetyl (C_2H_3O), calculated on the anhydrous basis after deducting the amount of free acid.

Description A white or grey white amorphous fibriform of fine strip or powder; tast, slightly characteristic of acetic acid.

Soluble in dioxane, acetone, or aqueous solution over pH 6; insoluble in water or ethanol.

Identification (1) To 10 mg add 1 ml of ethanol and 5 drops of sulfuric acid, a characteristic odour of ethyl acetate is perceptible by heating.

(2) Mix 0.1 g and 20 mg of resorcinol in a test tube, melt by heating for several minutes on a gentle flame, allow to cool, pour the solution into 20 ml of 10% sodium hydroxide solution, a green fluorescence is produced it disappears by

Water Dissolve about 0.5 g, accurately weighed, in 20 ml of a mixture of dehydrated methanol-chloroform (1 : 1). Carry out the determination for Water (Appendix VIII M, method 1 A); not more than 5.0%.

Free acid Transfer 1.5 g to a 250 ml conical flask, accurately weighed, add 50 ml of a mixture of neutral methanol (neutral to phenolphthalein IS)-water (1 : 2), shake for 15 minutes, wash the conical flask with 10 ml of neutral methanol in divided portions, filter. To the filtrate add phenolphthalein IS, titrate with sodium hydroxide (0.1 mol/L) VS. Each ml of sodium hydroxide (0.1 mol/L) VS is equivalent to 8.306 mg of $C_8H_6O_4$. The free acid is not more than 6.0%, calculated as anhydrous benzene dicarboxylic acid.

Residue on ignition Not more than 0.2% (Appendix VIII N).

Heavy metals Carry out the limit test for heavy metals (Appendix VIII H, method 2), using 1.0 g: not more than 0.002%.

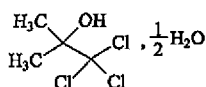
Assay Phthalyl Dissolve about 1 g, accurately weighed, in 50 ml of a mixture of acetone-ethanol-water (2 : 2 : 1) with shaking, add phenolphthalein IS, titrate with sodium hydroxide (0.1 mol/L) VS. Perform a blank determination and make any necessary correction. Each ml of sodium hydroxide (0.1 mol/L) VS is equivalent to 14.91 mg of $C_8H_5O_3$, calculate the content by subtracting the amount of free acid multiplying by 1.795.

Acetyl Dissolve about 0.5 g, accurately weighed, in 50 ml of a mixture of ethanol-acetone (1 : 1) with shaking, add 50 ml of water and accurately 25 ml of sodium hydroxide (1 mol/L) VS, mix well, allow to stand over night. Add phenolphthalein IS, titrate with hydrochloric acid (1 mol/L) VS. Perform a blank determination and make any necessary correction. Each ml of sodium hydroxide (1 mol/L) VS is equivalent to 43.0 mg of C_2H_3O . Calculate the content by subtracting the amount of phthalyl multiplying by 0.5772 and the amount of free acid multiplying by 0.5182.

Category Pharmaceutical aid.

Storage Preserve in tightly closed containers, protected from light.

Chlorobutanol



$C_4H_7Cl_3O \cdot \frac{1}{2}H_2O$ 186.47 [6001-64-5]

Chlorobutanol is 1,1,1-trichloro-2-methyl-2-propanol hemihydrate. It contains not less than 98.5% of $C_4H_7Cl_3O \cdot \frac{1}{2}H_2O$.

Description White crystals; odour, camphoraceous; readily volatile.

Freely soluble in ethanol, chloroform, ether or volatile oil; slightly soluble in water.

Melting point Not lower than 77°C (Appendix VI C), determined without drying.

Identification (1) Dissolve about 25 mg in 5 ml of water,

iodine TS; a yellow precipitate with the odour of iodoform develops.

(2) Dissolve 0.1 g in 5 ml of sodium hydroxide TS, mix well, heat on adding 3-4 drops of aniline, the odour of phenylisocyanide is produced (poisonous!).

Chloride Dissolve 0.10 g in 25 ml of dilute ethanol, add 1.0 ml of nitric acid and a quantity of dilute ethanol to 50 ml, add 1.0 ml of silver nitrate TS, mix well, and allow to stand for 5 minutes in the dark. Any opalescence produced is not more pronounced than that of a reference using 5.0 ml of sodium chloride standard solution (0.05%).

Residue on ignition Not more than 0.1% (Appendix VIII N).

Assay Dissolve about 0.1 g, accurately weighed, in 5 ml of ethanol, add 5 ml of 20% sodium hydroxide solution and heat under reflux for 15 minutes. Cool to room temperature, add 20 ml of water and 5 ml of nitric acid, then add accurately 30 ml of silver nitrate (0.1 mol/L) VS and 5 ml of dibutyl phthalate, shake vigorously. Add 2 ml of ammonium ferric sulfate IS, titrate with ammonium thiocyanate (0.1 mol/L) VS. Perform a blank determination and make any necessary correction. Each ml of silver nitrate (0.1 mol/L) VS is equivalent to 6.216 mg of $C_4H_7Cl_3O \cdot \frac{1}{2}H_2O$.

Category Pharmaceutical aid, antiseptics.

Storage Preserve in tightly closed containers.

Chloroform

$CHCl_3$ 119.38 [67-66-3]

Chloroform is trichloromethane. It may contain 0.5%-1.5% (ml/ml) of dehydrated ethanol as stabilizer.

Description A colourless volatile liquid; odour, characteristic; taste, slight sweet with burning sensation; deteriorates on exposure to light.

Freely miscible with ethanol, ether, fatty oils, volatile oils or common organic solvents; slightly soluble in water.

Relative density 1.474-1.479, at 25°C (Appendix VI A, hydrostatic method).

Boiling range 60-62°C (Appendix VI B); the liquid distilled below 60°C is not more than 5% (ml/ml).

Identification Heat a quantity with 2 drops of aniline and 1 ml of sodium hydroxide TS, a characteristic odour of phenylisocyanide is produced (poisonous!).

Acidity and carbonyl chloride Add 4 drops of phenolphthalein IS to 20 ml of water, add dropwise with shaking sodium hydroxide (0.01 mol/L) VS until the solution becomes pink. Divide the solution into two equal parts and pour them separately into two 50 ml Nessler cylinders (A and B). To cylinder A add accurately 20 ml of the substance being examined, shake well. Add dropwise with shaking sodium hydroxide (0.01 mol/L) VS until the pink colour of the aqueous layer matches that of the liquid in cylinder B, and persists for 15 minutes; not more than 0.20 ml of sodium hydroxide (0.01 mol/L) VS is consumed.

Chloride Shake 10 ml with 25 ml of freshly boiled and cooled water for 3 minutes and allow to separate. To 10 ml of the aqueous layer add 3 drops of silver nitrate TS. No

Free chlorine To 10 ml of the aqueous layer obtained in the test for chloride add a few drops each of potassium iodide TS and starch IS. No blue colour is produced.

Aldehyde and ketone Shake 3 ml with 10 ml of ammonia-free distilled water for 5 minutes and allow to separate. To 5 ml of the aqueous layer in a 50 ml Nessler cylinder with stopper add 40 ml of ammonia-free distilled water and 5 ml of alkaline mercuric potassium iodide TS, shake well. No turbidity or precipitate is produced within 1 minute.

Readily carbonizable substances To 40 ml in a Nessler cylinder with stopper, washed with 95% sulfuric acid, add 10 ml of 95% sulfuric acid, stopper the cylinder and shake for 5 minutes, allow to separate. The chloroform layer is colourless. Any colour produced in the acid layer is not more intense than that of a reference solution (mix 0.3 ml of standard cobaltous chloride CS, 1.0 ml of standard potassium dichromate CS with 8.7 ml of water. To 2 ml of the resulting solution add water to produce 10 ml).

Decomposition product containing chlorine To 4 ml of the acid layer obtained above add carefully 10 ml of water, mix well. The solution is clear, only a very faint odour of ethanol, ether or ester is perceived on heating. Dilute with 10 ml of water, the solution remains clear. Add 3 drops of silver nitrate TS, no opalescence is produced within 1 minute.

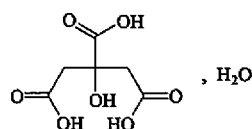
Non-volatile matter Evaporate slowly 25 ml in an evaporating dish previously dried to constant weight at 105°C on a water bath to dryness and dry to constant weight at 105°C. The residue is not more than 1 mg.

Foreign odour Evaporate 20 ml on a water bath of 50°C to almost dryness. No foreign odour is perceived.

Category Pharmaceutical aid, Solvent, antiseptic agent.

Storage Preserve in tightly closed containers, protected from light and stored below 30°C.

Citric Acid



$C_6H_8O_7 \cdot H_2O$ 210.14

[5949-29-1]

Citric Acid is 2-hydroxy-1, 2, 3-propanetricarboxylic acid, monohydrate. It contains not less than 99.5% of $C_6H_8O_7$, calculated on the anhydrous basis.

Description Colourless, translucent crystals, white granules or a crystalline powder, odourless; taste, strongly sour; slightly efflorescent in dry air. The aqueous solution exhibits an acidic reaction.

Very soluble in water, freely soluble in ethanol, sparingly soluble in ether.

Identification (1) Decompose gradually on igniting, but no caramel odour is perceptible (distinction from tartaric acid).

(2) The infrared absorption spectrum (Appendix IV C) is concordant with the reference spectrum of citric acid (Appendix XVI).

(3) Yields the reactions characteristic of citrates (Appendix III).

Sulfate Carry out the limit test for sulfates (Appendix VII

pronounced than that of a reference using 3.0 ml of potassium sulfate standard solution (0.03%).

Oxalate Dissolve 1.0 g in 10 ml of water, neutralize the solution with ammonia TS, add 2 ml of calcium chloride TS, allow to stand for 30 minutes at room temperature. No opalescence is produced.

Readily carbonizable substances Transfer 1.0 g to a Nessler cylinder, add 10 ml of 95% sulfuric acid, heat for 1 hour at $90^\circ\text{C} \pm 1^\circ\text{C}$, allow to cool immediately. Any colour produced is not more intense than that of a reference (a mixture of 0.9 ml of standard cobaltous chloride CS, 8.9 ml of standard potassium dichromate CS and 0.2 ml of standard copper sulfate CS).

Water 7.5%-9.0% (Appendix VIII M, method 1 A).

Residue on ignition Not more than 0.1% (Appendix VIII N).

Calcium Dissolve 1.0 g in 10 ml of water, neutralize with ammonia TS, add a few drops of ammonium oxalate TS. No opalescence is produced.

Iron Carry out the limit test for iron (Appendix VIII G), using 1.0 g, extract with *n*-butanol. Any colour produced is not more intense than that of a reference solution using 1.0 ml of iron standard solution (0.001%).

Heavy metals Dissolve 4.0 g in 10 ml of water, add 1 drop of phenolphthalein IS and a few drops of ammonia TS until a pink colour is produced. Add 2 ml of acetate BS (pH 3.5) and sufficient water to produce 25 ml. Carry out the limit test for heavy metals (Appendix VIII H, method 1); not more than 0.0005%.

Arsenic Dissolve 2.0 g in 23 ml of water, add 5 ml of hydrochloric acid. Carry out the limit test for arsenic (Appendix VIII J, method 1); not more than 0.0001%.

Assay Dissolve about 1.5 g, accurately weighted, in 40 ml of freshly boiled and cooled water. Add 3 drops of phenolphthalein IS, titrate with sodium hydroxide (1 mol/L) VS. Each ml of sodium hydroxide (1 mol/L) VS is equivalent to 64.04 mg of $C_6H_8O_7$.

Category Pharmaceutical aid, flavouring agent.

Storage Preserve in tightly closed containers.

Dextrin

Description A white or almost white amorphous powder; odourless; taste, slightly sweet.

Freely soluble in boiling water; insoluble in ethanol or ether.

Identification To 1 ml of an aqueous solution (1→10) add 1 drop of iodine TS, a purplish-red colour is produced.

Acidity Dissolve 5.0 g in 50 ml of water by heating, cool, add 2 drops of phenolphthalein IS and 2.0 ml of sodium hydroxide (0.1 mol/L) VS, a pink colour is produced.

Reducing sugar Shake 2.0 g with 100 ml of water for 5 minutes, allow to stand, filter. To 50 ml of filtrate add 50 ml of alkaline cupric tartrate TS and boil for 3 minutes. Filter with a sintered glass crucible previously dried to constant weight at 105°C. Wash the residue successively with water, ethanol and ether, then dry at 105°C for 2 hours. The residual cuprous oxide is not more than 0.20 g.

Loss on drying When dried to constant weight at 105°C, loses not more than 10.0% of its weight (Appendix VIII L).

Iron Ignite and incinerate 2.0 g. Add 1 ml of hydrochloric acid and 3 drops of nitric acid to the residue and evaporate on a water bath to almost dryness, cool. Dissolve the residue in 1 ml of hydrochloric acid, transfer the solution with water to a 50 ml volumetric flask and dilute to volume, mix well. Measure accurately 10 ml and carry out the limit test for iron (Appendix VII G). Any colour produced is not more intense than that of a reference using 2.0 ml of iron standard solution (0.005%).

Microbial limit Comply with the test for microbial limit (Appendix XI J), except that number of bacterial is not more than 1000 and that of fungi is not more than 100 per g, *Escherichia coli* is not detected.

Category Pharmaceutical aid.

Storage Preserve in tightly closed containers, stored in a dry place.

Dilute Hydrochloric Acid

Dilute Hydrochloric Acid contains 9.5%-10.5% of HCl.

Description A clear, colourless liquid; strongly acidic.

Identification Yields the reactions characteristic of chlorides (Appendix III).

Free chlorine or bromine To 20 ml add 0.2 ml of zinc starch iodide IS, no blue colour is perceived within 10 minutes.

Sulfate Dilute 3 ml with 5 ml of water, add 5 drops of 25% barium chloride solution, no opalescence or precipitate is produced within 1 hour.

Sulfite Dilute 15 ml with 40 ml of freshly boiled and cooled water, add to the solution 50 ml of freshly boiled and cooled water, 1.0 g of potassium iodide, 0.15 ml of iodine (0.005 mol/L) VS and 1.5 ml of starch IS. The blue colour of the solution does not disappear completely.

Residue on ignition To 20 ml add 2 drops of sulfuric acid and evaporate to dryness. Carry out the test for residue on ignition (Appendix VIII N); not more than 2 mg (0.01%).

Iron Evaporate 20 ml to dryness on a water bath. To the residue add 25 ml of water, carry out the limit test for iron (Appendix VII G). Any colour produced is not more intense than that of a reference solution using 1.0 ml of iron standard solution (0.00005%).

Heavy metals Evaporate 10 ml to dryness on a water bath, add 2 ml of acetate BS (pH 3.5) and a quantity of water to produce a solution of 25 ml. Carry out the limit test for heavy metals (Appendix VIII H, method 1); not more than 0.0002%.

Arsenic Dilute 1.4 ml with 22 ml of water, add 5 ml of hydrochloric acid. Complies with the limit test for arsenic (Appendix VIII J, method 1) (0.00014%).

Assay Measure accurately 10 ml, dilute with 20 ml of water, add 2 drops of methyl red IS and titrate with sodium hydroxide (1 mol/L) VS. Each ml of sodium hydroxide (1 mol/L) VS is equivalent to 36.46 mg of HCl.

Category Pharmaceutical aid, acidifying agent.

Storage Preserve in tightly closed glass bottles.

Ethylcellulose

not less than 44.0% and not more than 51.0% of ethoxy ($-\text{OC}_2\text{H}_5$) groups, calculated on the dried basis.

Description A white granules or powder; odourless; tasteless. A 5% suspension exhibits neutrality to litmus paper; freely soluble in toluene and ether; insoluble in water.

Identification Dissolve 5 g in 100 ml of a mixture of ethanol-toluene (1 : 4) with shaking, a clear and slightly yellow solution is produced. Place a quantity of the solution on a glass plate. A thin and elastic film is formed after evaporating the solvent. The film is flammable.

Viscosity Weigh accurately 2.5 g calculated on the dried basis into a conical flask with stopper. Accurately add 50 ml of a mixture of ethanol-toluene (1 : 4) with shaking until the substance is completely dissolved. Allow to stand for 8 to 10 hours. Adjust the temperature of the solution to $20^\circ\text{C} \pm 0.1^\circ\text{C}$, and determine the kinetic viscosity (Appendix VI G, method 1, using a capillary tube with 2 mm internal diameter). Its viscosity is not less than 90.0% and not more than 110.0% when the labelled viscosity is 10 $\text{mPa} \cdot \text{s}$ or more; not less than 80.0% and not more than 120.0% when the labelled viscosity is less than 10 $\text{mPa} \cdot \text{s}$ but more than 6 $\text{mPa} \cdot \text{s}$; and not less than 75.0% and not more than 140.0% when the labelled viscosity is 6 $\text{mPa} \cdot \text{s}$ or less.

Loss on drying When dried at 105°C for 2 hours, loses not more than 3.0% of its weight (Appendix VIII L).

Residue on ignition Not more than 0.4% (Appendix VIII N), using 1.0 g.

Heavy metals Carry out the limit test for heavy metals (Appendix VIII H, method 2), using the residue obtained in the test for Residue on ignition; not more than 0.002%.

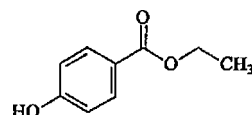
Arsenic Mix 0.67 g with 1.0 g of calcium hydroxide, add water and mix well. After dryness, heat gently until it is thoroughly charred, then ignite at $500-600^\circ\text{C}$ until the incineration is completed. Dissolve the cooled residue in a mixture of 8 ml of hydrochloric acid and 23 ml of water. Carry out the limit test for arsenic (Appendix VIII J, method 1); not more than 0.0003%.

Assay Carry out the method for determination of methoxyl (Appendix VII G) using a quantity equivalent to about 10 mg of ethoxy groups, adjust the temperature of oil bath to $150-160^\circ\text{C}$, extend the heating time for 1-2 hours longer. Each ml of sodium thiosulfate (0.1 mol/L) VS is equivalent to 0.7510 mg of ethoxy group.

Category Pharmaceutical aid.

Storage Preserve in tightly closed containers and stored in a dry place.

Ethylparaben



$\text{C}_9\text{H}_{10}\text{O}_3$ 166.18

[120-47-8]

Ethylparaben is ethyl *p*-hydroxybenzoate. It contains not less than 99.0% of $\text{C}_9\text{H}_{10}\text{O}_3$.

Description A white crystalline powder; odour, slight and characteristic, or odourless; taste, slightly bitter, burning

Freely soluble in ethanol or ether; sparingly soluble in chloroform; slightly soluble in glycerol; practically insoluble in water.

Melting range 114-118°C (Appendix VI C).

Identification (1) Dissolve about 0.1 g in 2 ml of ethanol, boil, add 0.5 ml of mercuric nitrate TS; a precipitate is produced gradually on standing and the supernatant liquid becomes red.

(2) The light absorption of a solution of 5 µg per ml in ethanol exhibits a maximum at 259 nm, the absorbance is about 0.48 (Appendix IV A).

(3) The infrared absorption spectrum (Appendix IV C) is concordant with reference spectrum of ethylparaben (Appendix XVI).

Acidity Heat 2.0 g with 50 ml of water to 80°C, cool, filter; pH 4.0-7.0 (Appendix VI H), using 20 ml of the filtrate.

Chloride Carry out the limit test for chlorides (Appendix VII A), using 5 ml of the filtrate obtained in the test for Acidity. Any opalescence produced is not more intense than that of a reference using 7.0 ml of sodium chloride standard solution (0.035%).

Sulfate Carry out the limit test for sulfates (Appendix VII B), using 25 ml of the filtrate obtained in Acidity. Any opalescence produced is not more intense than that of a reference using 2.4 ml of potassium sulfate standard solution (0.024%).

Salicylic acid Dissolve 0.10 g in 1 ml of ethanol in a Nessler cylinder, add water to produce 50 ml and add immediately 1 ml of freshly prepared dilute ferric ammonium sulfate solution [to 1 ml of hydrochloric acid (1 mol/L) add 2 ml of ferric ammonium sulfate IS, add water to produce 100 ml], mix well. Any colour produced within 30 seconds is not more intense than that of a reference (dissolve 0.1 g of salicylic acid, weighed accurately, in water in a 1000 ml volumetric flask, add 1 ml of glacial acid, dilute with water to volume, mix well; measure accurately 1.0 ml, add 1 ml of ethanol, 48 ml of water, and 1 ml of the freshly prepared dilute ferric ammonium sulfate solution) (0.10%).

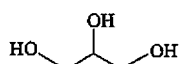
Residue on ignition Not more than 0.1% (Appendix VII N).

Assay Weigh accurately about 2 g to a conical flask, add 40 ml of sodium hydroxide (1 mol/L) VS, accurately measured, heat gently under reflux for 1 hour. Cool to room temperature, add 5 drops of bromothymol blue IS, titrate with sulfuric acid (0.5 mol/L) VS. To 40 ml of phosphate BS (pH 6.5) add 5 drops of bromothymol blue IS, the resulting solution is used as a reference for the endpoint. Perform a blank determination and make any necessary correction. Each ml of sodium hydroxide (1 mol/L) VS is equivalent to 166.2 mg of $C_3H_8O_3$.

Category Pharmaceutical aid, disinfectant.

Storage Preserve in tightly closed containers.

Glycerol for Injection



$C_3H_8O_3$ 92.09

[56-81-5]

Glycerol for Injection is 1, 2, 3-propanetriol. It contains not less than 98.0% of $C_3H_8O_3$.

hygroscopic; the aqueous solution (1 → 10) exhibits a neutral reaction.

Miscible with water or ethanol; slightly soluble in acetone; insoluble in chloroform or ether.

Relative density Not less than 1.257 at 25°C (Appendix VI A).

Refractive index 1.470-1.475 (Appendix VI F).

Identification The infrared absorption spectrum is concordant with the reference spectrum of glycerol (No. 77 in Spectra Atlas).

Acidity or alkalinity Dilute 25.0 g to 50 ml with water, add 0.5 ml of phenolphthalein IS, the solution is colourless. Then add 0.2 ml of 0.1 mol/L sodium hydroxide solution, the solution is pink.

Colour Transfer 50 ml to a Nessler cylinder; any colour produced is not more intense than that of a reference solution prepared by diluting 0.2 ml of potassium dichromate CS to 50 ml with water.

Chloride Carry out the limit test for chloride (Appendix VII A), using 5.0 g. Any opalescence produced is not more pronounced than that of a reference solution using 3.0 ml of sodium chloride standard solution (0.0006%).

Sulfate Carry out the limit test for sulfate (Appendix VII B), using 10 g. Any opalescence produced is not more pronounced than that of a reference solution using 2.0 ml of potassium sulfate standard solution (0.002%).

Aldehydes and reducing substances Transfer 3.75 g to a Nessler cylinder with stopper, dilute to 15 ml with water and mix. Add 1.0 ml of decolorized pararufuchsin (weigh 0.1 g of pararufuchsin hydrochloride ($C_{19}H_{18}ClN_3$) into a conical flask with stopper, add 60 ml of water and 10 ml of 7.5% sodium metabisulfite solution, then add 4.5 ml of dilute hydrochloric acid with gentle stirring. Insert the stopper and shake until completely dissolved, dilute to 100 ml with water and mix, allow to stand for 12 hours before use), mix, insert the stopper, and allow to stand for 1 hour. Any colour produced is not more intense than that of a reference solution operated in the similar manner using 7.5 ml of formaldehyde solution (containing 5.0 µg of formaldehyde (CH_2O) per ml) and 7.5 ml of water. (The test is not valid unless the reference solution is red)

Fatty acids and esters To 40 g add 40 ml of freshly boiled and cooled water, add 10 ml of sodium hydroxide (0.1 mol/L) VS, accurately measured, and mix well. Boil for 5 minutes and cool. Add several drops of phenolphthalein IS, titrate with hydrochloric acid (0.1 mol/L) VS until the pink colour disappears. Perform a blank determination and make any necessary correction. Not less than 2.0 ml of hydrochloric acid (0.1 mol/L) VS is required.

Readily carbonizable substances Carry out the limit test for readily carbonizable substances (Appendix VIII O), using 5.0 ml, allow to stand for 1 hour. Any colour produced is not more intense than that of an equal volume of a reference solution prepared by mixing 0.2 ml of cobaltous chloride CS, 1.6 ml of potassium dichromate CS and 8.2 ml of water.

Sugar Mix 5.0 g with 5 ml of water, add 1 ml of dilute sulfuric acid, warm on a water bath for 5 minutes. Add 3 ml of 2 mol/L carbonate-free sodium hydroxide solution and 1 ml of cupric sulfate TS dropwise, mix well. The solution is blue and clear, continue to warm on a water bath for 5 minutes, the solution is still blue and no precipitate is produced.

Residue on ignition Heat 20.0 g and stop heating when the substance ignites. After combustion, allow to cool; not

Iron Carry out the limit test for iron (Appendix VIII G), using 20.0 g. Any colour produced is not more intense than that of a reference solution using 1.0 ml of iron standard solution (0.00005%).

Heavy metals Carry out the limit test for heavy metals (Appendix VIII H, method 1), using 5.0 g; not more than 0.0002%.

Arsenic Mix 6.65 g with 23 ml of water and 5 ml of hydrochloric acid. Carry out the limit test for arsenic (Appendix VIII J, method 1); not more than 0.00003%.

Assay Mix about 0.1 g, accurately weighed, with 45 ml of water, add 25 ml of 2.14% (g/ml) sodium periodate solution, accurately measured, mix well, and allow to stand in a dark place for 15 minutes. Add 5 ml of 50% (g/ml) ethylene glycol and mix well, allow to stand in a dark place for 20 minutes. Add 0.5 ml of phenolphthalein IS, titrate with sodium hydroxide (0.1 mol/L) VS. Perform a blank determination and make any necessary correction. Each ml of sodium hydroxide (0.1 mol/L) VS is equivalent to 9.21 mg of $C_3H_5O_3$.

Category Pharmaceutical aid.

Storage Preserve in tightly closed containers, stored in a dry place.

Hydrochloric Acid

HCl 36.46 [7647-01-0]

Hydrochloric Acid contains not less than 36.0% and not more than 38.0% (g/g) of HCl.

Description A clear, colourless, fuming liquid; odour, pungent. It is strongly acidic.

Relative density About 1.18 at 25°C (Appendix IV A).

Identification Yields the reactions characteristic of chlorides (Appendix III).

Free chlorine or bromine Dilute 10 g (8.5 ml) to 20 ml with water, cool, add 0.2 ml of zinc starch-iodide IS, no blue colour is produced within 10 minutes.

Sulfate Mix 25 g (21 ml) with 2 drops of sodium carbonate TS, evaporate to dryness on a water bath, dissolve the residue in 20 ml of water. Carry out the limit test for sulfates (Appendix VIII B), any opalescence produced is not more pronounced than that of a reference using 1.25 ml of potassium sulfate standard solution (0.0005%).

Sulfite Mix 1 g of potassium iodide, 0.15 ml of iodine (0.005 mol/L) VS, and 1.5 ml of starch IS with 50 ml of freshly boiled and cooled water. The blue colour does not disappear on the addition of a mixture of 5 ml of the substance being examined and 50 ml of freshly boiled and cooled water.

Residue on ignition Add 2 drops of sulfuric acid to 100 g (85 ml), evaporate to dryness, and carry out the test for residue on ignition (Appendix VIII N); not more than 2 mg (0.002%).

Iron Evaporate 10 g (8.5 ml) on a water bath to dryness, add 25 ml of water to the residue, carry out the limit test for iron (Appendix VIII G). Any colour produced is not more intense than that of a reference solution using 1.0 ml of standard iron solution (0.0001%).

Heavy metals Evaporate 10 g (8.5 ml) on a water bath to

water to produce 25 ml. Carry out the limit test for heavy metals (Appendix VIII H, method 1); not more than 0.0002%.

Arsenic To 2 g (1.7 ml) add 22 ml of water and 5 ml of hydrochloric acid, carry out the limit test for arsenic (Appendix VIII J, method 1); not more than 0.0001%.

Assay Transfer about 3 ml to a tared glass-stoppered flask containing about 20 ml of water and weigh accurately. Add 25 ml of water and 2 drops of methyl red IS, titrate with sodium hydroxide (1 mol/L) VS. Each ml of sodium hydroxide (1 mol/L) VS is equivalent to 36.46 mg of HCl.

Category Pharmaceutical aid, acidifying agent.

Storage Preserve in tightly closed containers.

Hyprollose

[9004-64-2]

Hyprollose is low substituted 2-hydroxypropyl cellulose. It contains not less than 7.0% and not more than 16.0% of hydroxypropyloxe group ($C_3H_7O_2$), calculated on the dried basis.

Description A white or almost white powder; odourless; tasteless.

Disperses and swells in water to produce a colloidal solution; insoluble in ethanol, acetone or ether.

Identification (1) To a quantity of 2% aqueous solution in a test tube add 1 ml of a solution of 0.035% anthrone in sulfuric acid slowly along the tube wall, a blue ring is produced at the interface of the two layers and changes to green gradually.

(2) Dissolve 0.5 g of sodium hydroxide in 5 ml of 2% aqueous solution of the substance being examined with shaking. Allow it to stand for 10 minutes, a creamy white viscous solution is produced, shake with 10 ml of methanol, a white flocculent precipitate is produced.

Acidity or alkalinity Dissolve 0.10 g in 10 ml of water, pH 5.0-7.5 (Appendix VI H).

Chloride To 0.10 g add 30 ml of hot water, heat in water bath for 10 minutes and filter while hot. Wash the residue with 4 quantities of 15 ml of hot water. Combine the filtrate and the washings in 100 ml volumetric flask, allow to cool, dilute with water to volume and shake well. Carry out the limit test for chlorides (Appendix VIII A), using 10 ml of the resulting solution. Any opalescence produced is not more pronounced than that of a reference using 2.0 ml of standard sodium chloride solution (0.20%).

Loss on drying When dried at 105°C to constant weight, loses not more than 8.0% of its weight (Appendix VIII L).

Residue on ignition Not more than 1.0% (Appendix VIII N); using 1.0 g.

Iron Ignite 1.0 g as described under Residue on ignition. Dissolve the residue with 5 ml of dilute hydrochloric acid by heat in a water bath, add water to 25 ml and mix well. Carry out the limit test for iron (Appendix VIII G), using 5 ml of the solution. The colour produced is not more intense than that of a standard using 2.0 ml of iron standard solution (0.010%).

Heavy metals Carry out the test for heavy metals (Appendix VIII H, method 2), using the residue obtained in Residue on ignition; not more than 0.002%.

ml of water, stir well and dry at 40°C. Ignite gently to carbonize and then at 500-600°C until free from carbon. Allow it to cool and dissolve the residue with a mixture of 8 ml of hydrochloric acid and 23 ml of water. Carry out the limit test for arsenic (Appendix VIII L, method 1), the resulting solution complies with the requirement (0.0003%).

Assay Carry out the determination of hydroxypropyloxy group (Appendix VII F), using about 0.1 g, accurately weighed. Calculate the content of $C_3H_7O_2$.

Category Pharmaceutical aid.

Storage Preserve in tightly closed containers, stored in dry place.

Hypromellose

[9004-65-3]

Hypromellose is 2-hydroxypropyl methyl cellulose. It contains not less than 19.0% and not more than 30.0% of methoxyl group ($-OCH_3$) and not less than 4.0% and not more than 12.0% of hydroxypropyloxy group ($-OCH_2CHOHCH_3$), calculated on dried basis.

Description A white or almost white fibrous or granular powder; odourless.

Disperses and swells in water to produce a clear or slightly opalescent colloidal liquid; insoluble in dehydrated ethanol, acetone or ether.

Identification (1) To 1 g add 100 ml of hot water (80-90°C) with constant stirring, allow it to cool in ice bath to produce a viscous liquid. Transfer 2 ml of the liquid to a test tube and add 1 ml of 0.035% anthrone solution in sulfuric acid slowly along the tube wall, a bluish-green ring is produced at the interface of the liquids after standing for 5 minutes.

(2) Pour a quantity of the viscous liquid obtained in test (1) on a glass plate and allow the moisture to evaporate, an elastic membrane is produced.

Acidity or alkalinity Dissolve 1.0 g in 100 ml of water, pH 4.0-8.0 (Appendix VI H).

Viscosity To a quantity, calculated on dried basis, add hot water of 90°C to produce a 2.0% (g/g) solution, stir thoroughly for about 10 minutes. Allow it to cool in ice bath with continuing stirring, remove any air bubbles and adjust the weight. Carry out the determination of viscosity (Appendix VI G, method 2), using a NDJ-1 type rotatory viscosimeter with No. 1 rotator and a speed of 60 cycles per minute at $20^\circ C \pm 0.1^\circ C$, the viscosity is 0.005-0.075 Pa · s.

Water-insoluble matter Disperse 1.0 g in 100 ml of hot water (80-90°C) in a beaker and allow it to swell for about 15 minutes. Cool in an ice bath, add 300 ml of water, stir well and filter with No. 1 sintered glass crucible previously dried at 105°C to constant weight. Wash the beaker with water and combine the washings to the crucible, filter and dry to constant weight at 105°C. The residue is not more than 5 mg (0.5%).

Loss on drying When dried at 105°C for 2 hours, loses not more than 5% of its weight (Appendix VIII L).

Residue on ignition Not more than 1.5% (Appendix VIII N), using 1.0 g.

Heavy metals Carry out the test for heavy metals (Appendix

ignition; not more than 0.002%.

Arsenic Mix 1.0 g with 1.0 g of calcium hydroxide, stir well with a small amount of water. Allow it to dry, ignite gently to carbonize and then ignite at 600°C until free from carbon, cool and dissolve the residue in a mixture of 5 ml of hydrochloric acid and 23 ml of water. Carry out the limit test for arsenic (Appendix VIII J, method 1), the resulting solution complies with the requirement (0.0002%).

Assay Methoxyl group Carry out the determination of methoxyl group (Appendix VIII G), using about 0.1 g, accurately weighed. Calculate the content of CH_3O from the following expression

$$\text{content of } CH_3O(\%) = A - (B \times 31/75 \times 0.93)$$

Where A is the assay value of methoxyl group (%);

B is the assay value of hydroxypropyloxy group (%).

Hydroxypropyloxy group Carry out the determination of hydroxypropyloxy group (Appendix VII F), using about 0.1 g, accurately weighed. Calculate the content of $-OCH_2CHOHCH_3$.

Category Pharmaceutical aid.

Storage Preserve in tightly closed containers.

Kaolin

Kaolin is a natural hydrated aluminium-silicate, freed from most of its impurities by elutriation with water, treated with dilute mineral acid, washed with water repeatedly and dried.

Description A fine, almost white powder. When moistened with water, it has an odour of clay and darkens in colour. Practically insoluble in water, dilute mineral acids or sodium hydroxide solutions.

Identification To 1 g in a porcelain evaporating dish add 10 ml of water and 5 ml of sulfuric acid, heat until white fumes of sulfur trioxide appear. Cool, add slowly 20 ml of water, boil for 2-3 minutes and filter; a gray residue remains on the filter. The filtrate yields the reactions characteristic of aluminium salts (Appendix III).

Chloride Boil 0.20 g with 25 ml of water and 1 drop of nitric acid for 5 minutes and filter. Carry out the limit test for chlorides (Appendix VIII A), using the filtrate. Any opalescence produced is not more intense than that of a reference using 6.0 ml of sodium chloride standard solution (0.03%).

Sulfate Boil 0.3 g with 40 ml of water and 2 ml of dilute hydrochloric acid for 5 minutes, cool and filter. Carry out the limit test for sulfates (Appendix VIII B), using the filtrate. Any opalescence produced is not more intense than that of a reference using 3.0 ml of potassium sulfate standard solution (0.1%).

Acid-soluble substances Boil 1.0 g with 50 ml of hydrochloric acid solution (18→1000) for 5 minutes, filter, evaporate the filtrate to dryness and ignite to constant weight; the residue weighs not more than 10 mg.

Loss on ignition When ignited to constant weight, loses not more than 15.0% of its weight.

Sand particles To 2 g in a beaker add 50 ml of water and stir thoroughly, pour to a moistened sieve No. 7. Wash the beaker several times with water until the substance being examined is completely transferred to the sieve. Wash the

fingers; no feeling of gritty particles of sand.

Iron Boil 0.42 g with 25 ml of each of dilute hydrochloric acid and water for 2 minutes, cool and filter. Add water to the filtrate to produce 100 ml and mix well. To 20 ml add 50 mg of ammonium persulfate, dilute with water to 35 ml. Carry out the limit test for iron (Appendix VIII G), any colour produced is not more intense than that of a reference using 5.0 ml of iron standard solution (0.06%).

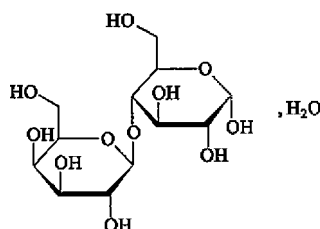
Heavy metals Boil 4.0 g with 4 ml of acetate BS (pH 3.5) and 46 ml of water, cool, filter, add water to the filtrate to produce 50 ml and mix well. Carry out the limit test for heavy metals (Appendix VIII H, method 1), using 25 ml; not more than 0.001%.

Arsenic To 1.0 g add 5 ml of hydrochloric acid and 23 ml of water. Carry out the limit test for arsenic (Appendix VIII J, method 1), complies with the requirements (0.0002%).

Category Pharmaceutical aid, excipient.

Storage Preserve in tightly closed containers.

Lactose



$C_{12}H_{22}O_{11} \cdot H_2O$ 360.31 [10039-26-6]

Lactose is 4-O- β -D-galactopyranosyl-D-glucose, monohydrate.

Description White crystalline granules or a crystalline powder; odourless; taste, slightly sweet. Freely soluble in water; insoluble in ethanol, chloroform or ether.

Specific optical rotation +52.0° to +52.6°, in a solution of 0.10 g of lactose (dried at 80°C for 2 hours) and 0.02 ml of ammonia TS per ml in water (Appendix VI E).

Identification (1) To 0.2 g add 5 ml of sodium hydroxide TS and heat gently, the colour of the solution becomes yellow, then reddish-brown and a red precipitate of cuprous oxide is produced on addition of a few drops of copper sulfate TS.

(2) The infrared absorption spectrum (Appendix IV C) is concordant with the reference spectrum of lactose (Appendix XVI).

Acidity Dissolve 1.0 g in 20 ml of water, pH 4.0-7.0 (Appendix VI H).

Clarity of solution Dissolve 3.0 g in 10 ml of boiling water, the resulting solution is clear.

Protein Dissolve 5.0 g in 25 ml of hot water, cool. Add 0.5 ml of mercuric nitrate TS; no flocculent precipitate is produced in 5 minutes.

Residue on ignition Not more than 0.1% (Appendix VIII N).

Heavy metals Dissolve 3.0 g in 20 ml of warm water, add 2 ml of acetate BS (pH 3.5) and sufficient water to produce

VIII H, method 1); not more than 0.0005%.

Microbial limit Comply with the test for microbial limit (Appendix XI J), except that number of bacterial is not more than 1000 and that of fungi is not more than 100 per g, *Escherichia coli* is not detected.

Category Pharmaceutical aid, excipients.

Storage Preserve in tightly closed containers.

Lanolin

Description A pale-yellow or brownish-yellow substance with the consistency of an ointment; odour, slight and characteristic. Freely soluble in chloroform or ether, soluble in hot ethanol, very slightly soluble in ethanol, insoluble in water but mix with about twice its weight of water without difficulty.

Melting range 36-42°C (Appendix VI C, method 2).

Acid value Not greater than 1.5 (Appendix VII H).

Saponification value 92-106 (Appendix VII H) (heat under reflux for 2 hours).

Iodine value 18-35 (Appendix VII H) (allow to stand in the 'ar' for 4 hours).

Identification Dissolve 0.5 g in 5 ml of chloroform, add 1 ml of acetic anhydride and 2 drops of sulfuric acid; a deep green colour is produced.

Acidity or alkalinity Melt 10 g with 50 ml of water on a water bath, stir continuously, cool, remove the separated fat, the aqueous solution is clear. To 10 ml of this solution add 1 drop of phenolphthalein IS, no red colour is produced. To another 10 ml, add 1 drop of methyl red IS, no red colour is produced.

Chloride To 0.2 g in a conical flask add 27 ml of ethanol, heat under reflux for several minutes, cool, add 0.5 ml of nitric acid and filter. To the filtrate add 5 drops of ethanolic silver nitrate solution (1→50). Any opalescence produced is not more pronounced than that of a reference solution [to 20 ml of ethanol, add 7.0 ml of sodium chloride standard solution, 0.5 ml of nitric acid and 5 drops of ethanolic silver nitrate solution (1→50)] (0.035%).

Readily oxidizable substances To 10 ml of the aqueous solution obtained in test for Acidity or alkalinity, add 1 drop of potassium permanganate solution (0.02 mol/L), the red colour does not completely disappear within 5 minutes.

Ethanol-insoluble substances Boil 0.5 g with 40 ml of dehydrated ethanol, the solution is clear or very slightly turbid.

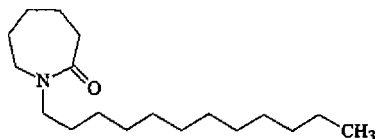
Loss on drying When dried with frequent stirring to constant weight at 105°C, loses not more than 0.5% of its weight (Appendix VIII L).

Residue on ignition Not more than 0.15% (Appendix VIII N).

Category Pharmaceutical aid, ointment base.

Storage Preserve in tightly closed containers, stored in a cool place.

Laurocapram



$C_{18}H_{35}NO$ 281.48

[59227-89-3]

Laurocapram is 1-dodecylhexahydro-2*H*-azepin-2-one. It contains not less than 97.0% and not more than 102.0% of $C_{18}H_{35}NO$.

Description A clear colourless viscous liquid; almost odourless; tasteless.

Very soluble in dehydrated ethanol, ethyl acetate, ether, benzene or cyclohexane; insoluble in water.

Relative density 0.906-0.926 (Appendix VI A).

Refractive index 1.470-1.473 (Appendix VI F).

Viscosity Kinematic viscosity (Appendix VI G, method 1, internal diameter of capillary is $1.2\text{ mm} \pm 0.05\text{ mm}$) is 32-34 mm^2/s at 25°C .

Identification (1) To 2 ml add 2 ml of methanol and 1 ml of freshly prepared 1 mol/L hydroxylamine hydrochloride solution, and 1 granule of potassium hydroxide, heat on a water bath, cool, and add 1 drop of ferric chloride TS, mix well. Heat on a water bath again, a brownish violet colour is produced.

(2) The infrared absorption spectrum (Appendix IV C) is concordant with the reference spectrum of laurocapram (Appendix XVI).

Acidity or alkalinity To 5 ml add 5 ml of neutral ethanol, heat gently to dissolve laurocapram, cool, the litmus paper moistened by the solution exhibits a neutral reaction.

Hexalactam and related substances Carry out the method for thin-layer chromatography (Appendix V B), using silica gel G as the coating substance and a mixture of carbon tetrachloride-acetone (1 : 1) as the mobile phase. Apply separately to the plate $10\text{ }\mu\text{l}$ each of three solutions in acetone containing (1) 100 mg per ml and (2) 20 mg of the substance being examined per ml; (3) 0.5 mg of hexalactam CRS per ml. After developing and removal of the plate, dry in air, spray with glacial acetic acid, and put in a warm air current until no acetic acid odour perceived. Fumigate the plate in chlorine [place a small beaker containing 1 g of potassium permanganate and 10 ml of hydrochloric acid solution (1→4) in a suitable size glass chamber, put the lid on chamber tightly for 5 minutes] for a few seconds, remove the plate, expel the chlorine with a current of cool air, spray with potassium iodide-starch TS. The colour of the spot obtained with solution (1) corresponds to and is not more intense than the principal spot obtained with solution (3). No any secondary spot other than the principal spot obtained with solution (2) in the chromatogram is observed.

Bromide Shake well 1.0 g with 10 ml of water, add 3 drops of hydrochloric acid and 1 ml of chloroform, then add freshly prepared 2% chloroamine T solution dropwise with shaking. Any colour produced in the chloroform layer is not more intense than that of a chloroform layer prepared using 1 ml of potassium bromide standard solution (weigh accurately and dissolve 0.1489 g of potassium bromide previously dried to constant weight at 105°C in water to produce 100 ml, mix

manner (0.1%).

Residue on ignition Not more than 0.1% (Appendix VII N); using 2.0 g.

Heavy metals Carry out the limit test for heavy metals (Appendix VIII H, method 2), using the residue obtained in the test for Residue on ignition; not more than 0.001%.

Assay Carry out the method for gas chromatography (Appendix V E), using a column packed with 10% methylvinylpolysiloxane (SE-30) as the stationary phase, and maintain the column temperature at $240^\circ\text{C} \pm 10^\circ\text{C}$. The number of theoretical plates of the column is not less than 1000, calculate with reference to the peak of laurocapram and the resolution factor between the peaks of laurocapram and internal standard substance complies with the related requirements.

Dissolve a quantity of tetracosane, accurately weighed, in hexane, dilute with *n*-hexane to produce a solution of 2 mg per ml as internal standard solution. Dissolve about 20 mg of laurocapram CRS, accurately weighed, in internal standard solution and dilute to 10 ml, mix well, inject $1\text{ }\mu\text{l}$ into the column, calculate the correction factor.

Dissolve about 20 mg, accurately weighed, in internal standard solution in a 10 ml volumetric flask, dilute to volume and mix well. Inject each $1\text{ }\mu\text{l}$ for 3-5 times, calculate the content of laurocapram ($C_{18}H_{35}NO$).

Category Pharmaceutical aid, skin osmotic penetrant.

Storage Preserve in tightly closed containers, protected from light.

Macrogol 400

Macrogol 400 is a mixture of polymer of ethylene oxide and water, represented by the general molecular formula $\text{HO}(\text{CH}_2\text{CH}_2\text{O})_n\text{H}$, where *n* is the average number of ethylene oxide groups.

Description A colourless or almost colourless viscous liquid; odour, slightly characteristic.

Freely soluble in water or ethanol; insoluble in ether.

Relative density 1.110-1.140 (Appendix VI A).

Viscosity Kinematic viscosity at 40°C , 37-45 mm^2/s (Appendix VI G, method 1), using a capillary tube of 0.8 mm in inner diameter.

Average molecular weight Place about 1.2 g, accurately weighed, in a dry 250 ml conical flask with stopper, add 25 ml, accurately measured, of a solution of phthalic anhydride in pyridine, prepared by dissolving 14 g of phthalic anhydride in 100 ml of anhydrous pyridine and allow it to stand over night. Shake well and heat for 30-60 minutes in a boiling water bath. Allow it to cool after removal, add 50 ml of sodium hydroxide VS (0.5 mol/L), accurately measured, and a solution of phenolphthalein in pyridine (1→100) as indicator and titrate with sodium hydroxide (0.5 mol/L) VS until a pink colour is produced, carry out a blank determination and make any necessary correction. Multiply the weight (g) of substance being examined by 4000 and divide by the volume (ml) of sodium hydroxide (0.5 mol/L) VS consumed, the average molecular weight is 380-420.

Acidity Dissolve 1.0 g in 20 ml of water, pH 4.0-7.0 (Appendix VI H).

Clarity and colour of solution Dissolve 5.0 g in 50 ml of

produced is not more pronounced than that of reference suspension No. 2 (Appendix IX B). Any colour produced is not more intense than that of reference solution Y₂ (Appendix IX A, method 1).

Ethylene glycol and diglycol To 50 mg each of ethylene glycol and diglycol add water in a 100 ml volumetric flask, dilute to volume and shake thoroughly, use as reference solution. To 4.0 g in a 10 ml volumetric flask add water to volume, shake thoroughly and use as test solution. Carry out the method for gas chromatography (Appendix V E), using kieselguhr as the carrier, sorbitol as stationary phase and keep the column temperature at 160°C; not more than 0.25% (g/g) of ethylene glycol and diglycol, respectively.

Residue on ignition Not more than 0.2% (Appendix VIII N).

Heavy metals Dissolve 4.0 g in 5 ml of hydrochloric acid solution (9→1000) and a quantity of water, adjust to pH 3.0-4.0 with dilute acetic acid or ammonia TS, then dilute with water to 25 ml. Carry out the limit test for heavy metals (Appendix VIII H, method 1); not more than 0.0005%.

Arsenic To 0.67 g in a kjeldahl flask add 5 ml of sulfuric acid, digest gently at a temperature not exceeding 120°C, add sulfuric acid if necessary, keep the total quantity not more than 10 ml. Add cautiously, in dropwise, of concentrate hydrogen peroxide solution until the reaction goes to completion. Continue to heat the reaction mixture and add, in dropwise, concentrate hydrogen peroxide solution until the solution becomes colourless. Allow it to cool, add 10 ml of water, evaporate until the fume of excess hydrogen peroxide evolves completely. Add 5 ml of hydrochloric acid and a quantity of water to the resulting solution. Carry out the limit test for arsenic (Appendix VIII J, method 1), it complies with the requirement (0.0003%).

Category Pharmaceutical aid.

Storage Preserve in tightly closed containers.

Macrogol 600

Macrogol 600 is a mixture of polymer of ethylene oxide and water with the molecular formula represented by $\text{HO}(\text{CH}_2\text{CH}_2\text{O})_n\text{H}$, where n is the average number of ethyleneoxy groups.

Description Colourless or almost colourless viscous liquid, or translucent waxy soft substance; odour, slight and characteristic. Freely soluble in water or ethanol; insoluble in ether.

Relative density 1.115-1.145 (Appendix IV A).

Viscosity The kinematic viscosity at 40°C is 56-62 mm²/s, using a U-tube viscosimeter with a capillary tube of 1.5 mm in internal diameter (Appendix VI G, method 1).

Average molecular weight Weigh accurately about 1.6 g, carry out the determination described under Macrogol 400, the average molecular weight is 570-630.

Acidity, Clarity and colour of solution, Residue on ignition As described under Macrogol 400.

Category Pharmaceutical aid.

Storage Preserve in tightly closed containers, stored in a dry place.

Macrogol 1000

Macrogol 1000 is a mixture of polymers of ethylene oxide and water, represented by the general molecular formula $\text{HO}(\text{CH}_2\text{CH}_2\text{O})_n\text{H}$, where n is the average number of ethylene oxide groups.

Description White waxy solids; plates or granular powder; odour, slightly characteristic.

Freely soluble in water or ethanol; insoluble in ether.

Congealing point 33-38 °C (Appendix VI D).

Viscosity Kinematic viscosity at 40°C, 8.5-11.0 mm²/s (Appendix VI G, method 1), using a test solution, prepared by dissolving 25.0 g in water and diluting to volume in a 50 ml volumetric flask and U-tube viscosimeter with a capillary tube of 0.8 mm in inner diameter.

Average molecular weight Weight accurately about 3.0 g, carry out the determination described under Macrogol 400. The average molecular weight is 900-1100.

Acidity, Clarity and colour of solution, Residue on ignition As described under Macrogol 400.

Category Pharmaceutical aid.

Storage Preserve in tightly closed containers, stored in dry place.

Macrogol 1500

Macrogol 1500 is a mixture of polymers of ethylene oxide and water. It is represented by the molecular formula $\text{HO}(\text{CH}_2\text{CH}_2\text{O})_n\text{H}$, where n is the average number of ethyleneoxy groups.

Description White waxy solids, plates or granular powder; odour, slightly characteristic.

Freely soluble in water or ethanol; insoluble in ether.

Congealing point 41-46 °C (Appendix VI D).

Viscosity Dissolve 25.0 g in a 100 ml volumetric flask in water and dilute to volume, mix well. The kinematic viscosity at 40°C is 3.0-4.0 mm²/s, using a U-tube viscosimeter with a capillary tube of 0.8 mm in internal diameter (Appendix VI G, method 1).

Average molecular weight Weigh accurately about 4.5 g, carry out the determination described under macrogol 400, the average molecular weight is 1350-1650.

Acidity, Clarity and colour of solution, Residue on ignition As described under macrogol 400.

Category Pharmaceutical aid.

Storage Preserve in tightly closed containers, stored in dry place.

Macrogol 4000

Macrogol 4000 is a mixture of polymers of ethylene oxide and water. It is represented by the

the average number of ethyleneoxy groups.

Description White waxy solids, plates or granular powder; odour, slightly characteristic.

Freely soluble in water or ethanol; insoluble in ether.

Congealing point 50-54 °C (Appendix VI D).

Viscosity Dissolve 25.0 g in a 100 ml volumetric flask with water, dilute to volume and mix well. The kinematic viscosity at 40°C is 5.5-9.0 mm²/s using a U-tube viscosimeter with a capillary tube of 0.8 mm in internal diameter (Appendix VI G, method 1).

Average molecular weight Weigh accurately about 12 g to a 250 ml conical flask with stopper, add 25 ml of pyridine and heat to dissolve. Allow to cool, carry out the determination described under macrogol 400 beginning at the words "Add a solution, accurately measured, of phthalic anhydride in pyridine", the average molecular weight is 3400-4200.

Acidity, Clarity and colour of solution, Residue on ignition As described under Macrogol 400.

Category Pharmaceutical aid.

Storage Preserve in tightly closed containers, stored in a dry place.

Macrogol 6000

Macrogol 6000 is a mixtures of polymers of ethylene oxide and water. It is represented by the molecular formula $\text{HO}(\text{CH}_2\text{CH}_2\text{O})_n\text{H}$, where n is the average number of ethyleneoxy groups.

Description White waxy solids, plates or granular powder; odour, slightly characteristic.

Freely soluble in water or ethanol; insoluble in ether.

Congealing point 53-58 °C (Appendix VI D).

Viscosity Dissolve 25.0 g in a 100 ml volumetric flask with water and dilute to volume, mix well. The Kinematic viscosity at 40°C is 10.5-16.5 mm²/s using a U-tube viscosimeter with a capillary tube of 1.0 mm in internal diameter (Appendix VI G, method 1).

Average molecular weight Weigh accurately about 12.5 g to a 250 ml dry conical flask with stopper, add 25 ml of pyridine, heat to dissolve. Allow to cool, carry out the determination described under macrogol 400 beginning at the words "Add a solution, accurately measured, of phthalic anhydride in pyridine", the average molecular weight is 5400-7800.

Acidity, Clarity and colour of solution, Residue on ignition As described under Macrogol 400.

Category Pharmaceutical aid.

Storage Preserve in tightly closed containers, stored in a dry place.

Magnesium Stearate

Magnesium Stearate is a mixture consisted chiefly of magnesium stearate ($\text{C}_{35}\text{H}_{70}\text{MgO}_4$) and magnesium palmitate ($\text{C}_{32}\text{H}_{62}\text{MgO}_4$). It contains the equivalent of not less than 6.5% and not more than 7.5% of

Description A very fine, light, white powder, free from grittiness; odour faint; unctuous to the touch with skin. Insoluble in water, ethanol or ether.

Identification (1) Mix 10 g with 25 ml of dilute sulfuric acid and 100 ml of hot water, then heat the mixture with frequent stirring until the fatty acids separate as an oily layer. Separate the aqueous layer and retain it for Identification test (2). Wash the oily layer with boiling water to free from sulfate. Allow it to cool and discard the washing water. Heat to melt the oily layer, filter while hot, and dry at 105°C. Its congealing point is not lower than 54°C (Appendix VI D).

(2) The aqueous layer obtained in Identification test (1) yields the reactions characteristic of magnesium salts (Appendix III).

Chloride Boil 0.20 g with 1 ml of nitric acid and 24 ml of water and allow to cool until the oily layer solidifies. Filter, dilute the filtrate with water to 50 ml, carry out the limit test for chlorides (Appendix VIII A), using 5 ml of the resulting solution. Any opalescence produced is not more pronounced than that of a reference solution using 3.0 ml of sodium chloride standard solution (0.15%).

Sulfate Boil 0.10 g with 20 ml of water and 1 ml of hydrochloric acid solution (9→100), allow to cool until the oily layer solidifies. Filter, wash the residue with 4-5 successive quantities of water, dilute the combined filtrate and washings to 40 ml with water, carry out the limit test for sulfates (Appendix VIII B). Any opalescence produced is not more pronounced than that of a reference solution using 6.0 ml of potassium sulfate standard solution (0.6%).

Loss on drying When dried to constant weight at 80°C, loses not more than 5.0% of its weight (Appendix VIII L).

Iron Ignite 0.50 g and boil the residue with 5 ml of dilute hydrochloric acid and 10 ml of water. Allow to cool, and filter. To the filtrate add 50 mg of ammonium persulfate, dilute with water to 35 ml. Carry out the limit test for iron (Appendix VIII G). Any colour produced is not more intense than that of a reference solution using 5.0 ml of iron standard solution (0.01%).

Heavy metals Heat 2.0 g with 10 ml of dilute hydrochloric acid and 20 ml of water to boiling and allow to cool until the oily layer solidifies. Filter, evaporate the filtrate to dryness. Dissolve the residue in 10 ml of water and filter. Add 2 ml of acetate BS (pH 3.5) to the filtrate and add sufficient water to produce 25 ml, carry out the limit test for heavy metals (Appendix VIII H, method 1); not more than 0.0015%.

Assay Heat about 1.0 g, accurately weighed, with 50 ml of sulfuric acid (0.05 mol/L) VS, measured accurately, to boiling until the oily layer is clear and heat for 10 minutes more, cool to room temperature, add 1-2 drops of methyl orange IS, titrate with sodium hydroxide (0.1 mol/L) VS. Each ml of sulfuric acid (0.05 mol/L) VS, is equivalent to 2.016 mg of MgO.

Category Pharmaceutical aid, excipient.

Storage Preserve in tightly closed containers.

Methacrylic Acid Copolymer I

Methacrylic acid copolymer I is a copolymer of methyl methacrylate, ethyl acrylate and trimethyl ammonium chloride ethyl methacrylate in a ratio of

Description Slightly white, translucent or transparent solid with different shape and size.

Soluble in boiling water or acetone; practically insoluble in isopropanol.

Refractive index Dissolve 1.25 g in 10 ml of isopropanol-acetone (6 : 4), the refractive index is 1.380-1.385 (Appendix VI F).

Viscosity Dissolve 6.0 g in 100 ml of 75% ethanol solution, the kinematic viscosity at 20°C is not more than 0.015 Pa · s, using a rotating viscosimeter with a No. 0 rotator (Appendix VI F) at the speed of 30 rpm.

Alkaline value Dissolve 1 g, previously dried to constant weight at 110°C (for about 5 hours) and accurately weighed, in 25 ml of dichloromethane, add 50 ml of glacial acetic acid and 5 ml of mercuric acetate TS, mix well and add 3 drops of quinaldine red IS, titrate with perchloric acid (0.1 mol/L) VS until the colour of the solution changes from red to colourless. Perform a blank determination and make any necessary correction. Each ml of perchloric acid (0.1 mol/L) VS is equivalent to 5.61 mg of KOH. The value is 23.9-32.3 mg/g, calculated on the dried basis.

Identification The infrared absorption spectrum (Appendix IV C) is concordant with the spectrum of methacrylic acid copolymer I CRS.

Related substances Dissolve a quantity of the substance being examined, accurately weighed, in methanol to produce a solution of 1 mg per ml as test solution; Dissolve an accurately weighed quantity of methacrylic acid CRS, ethyl acrylate CRS and methyl methacrylate CRS in methanol to produce a reference solution of each 3 µg per ml. Carry out the method for high performance liquid chromatography (Appendix V D), using a column packed with octadecylsilane bonded silica gel and a mixture of methanol-phosphate buffer [dissolve 3.55 g of disodium hydrogen phosphate (Na_2HPO_4) and 3.40 g of potassium dihydrogen phosphate (KH_2PO_4) in 1000 ml of water, and adjust the pH value of the solution to 2.0 with phosphoric acid] (2 : 8) as the mobile phase. Detection wavelength is 202 nm and the number of the theoretical plates of the column is not less than 1000, calculated with reference to the peak of methacrylic acid and the resolution factor between the peaks of ethyl acrylate and methyl methacrylate complies with the related requirements. Inject separately 20 µl each of the test solution and the reference solution into the column, and record the chromatograms. Calculate the content of each monomer impurity separately with respect to the peak area obtained in the chromatogram by the external standard method. The sum of contents is not more than 0.3%.

Loss on drying When dried at 110°C for 6 hours, loses not more than 5.0% of its weight (Appendix VIII L).

Residue on ignition Not more than 0.3% (Appendix VIII N), using 1.0 g.

Heavy metals Carry out the limit test for heavy metals (Appendix VIII H, method 2), using the residue obtained in the test for residue on ignition; not more than 0.003%.

Arsenic Transfer 1.0 g to a 150 ml conical flask, add 5 ml of sulfuric acid, heat until the substance is thoroughly charred, add concentrated hydrogen peroxide solution dropwise (if a lot of foam is involved, stop heating and rotate the conical flask to prevent the unreacted substance conglomerating at the bottom) until the solution is colourless. Allow to cool, add cautiously 10 ml of water, heat again until sulfur trioxide is evolved, cool and add slowly 5 ml of hydrochloric acid and a quantity of water to

(Appendix VIII J, method 1); not more than 0.0002%.

Category Pharmaceutical aid.

Storage Preserve in tightly closed containers, and stored in a cool place.

Methacrylic Acid Copolymer II

Methacrylic acid copolymer II is a copolymer of methyl methacrylate, ethyl acrylate and trimethyl ammonium chloride ethyl methacrylate in a ratio of 65 : 30 : 5.

Description Slightly white, translucent or transparent solid with different shape and size.

Sparingly soluble in acetone; practically insoluble in boiling water or isopropanol.

Refractive index Dissolve 1.25 g in 10 ml of isopropanol-acetone (6 : 4), the refractive index is 1.380-1.385 (Appendix VI F).

Viscosity Dissolve 6.0 g in 100 ml of 75% ethanol solution, the kinematic viscosity at 20°C is not more than 0.015 Pa · s, using a rotating viscosimeter with a No. 0 rotator (Appendix VI F) at the speed of 30 rpm.

Alkaline value Dissolve 1 g, previously dried to constant weight at 110°C (for about 5 hours) and accurately weighed, in 25 ml of dichloromethane, add 50 ml of glacial acetic acid and 5 ml of mercuric acetate TS, mix well and add 3 drops of quinaldine red IS, titrate with perchloric acid (0.1 mol/L) VS until the colour of the solution changes from red to colourless. Perform a blank determination and make any necessary correction. Each ml of perchloric acid (0.1 mol/L) VS is equivalent to 5.61 mg of KOH. The value is 12.1-18.3 mg/g, calculated on the dried basis.

Identification The infrared absorption spectrum (Appendix IV C) is concordant with the spectrum of methacrylic acid copolymer II CRS.

Related substances Dissolve a quantity of the substance being examined, accurately weighed, in methanol to produce a solution of 1 mg per ml as test solution; Dissolve an accurately weighed quantity of methacrylic acid CRS, ethyl acrylate CRS and methyl methacrylate CRS in methanol to produce a reference solution of each 3 µg per ml. Carry out the method for high performance liquid chromatography (Appendix V D), using a column packed with octadecylsilane bonded silica gel and a mixture of methanol-phosphate buffer [dissolve 3.55 g of disodium hydrogen phosphate (Na_2HPO_4) and 3.40 g of potassium dihydrogen phosphate (KH_2PO_4) in 1000 ml of water, and adjust the pH value of the solution to 2.0 with phosphoric acid] (2 : 8) as the mobile phase. Detection wavelength is 202 nm and the number of the theoretical plates of the column is not less than 1000, calculated with reference to the peak of methacrylic acid and the resolution factor between the peaks of ethyl acrylate and methyl methacrylate complies with the related requirements. Inject separately 20 µl each of the test solution and the reference solution into the column, and record the chromatograms. Calculate the content of each monomer impurity separately with respect to the peak area obtained in the chromatogram by the external standard method. The sum of contents is not more than 0.3%.

Loss on drying When dried at 110°C for 6 hours, loses not more than 5.0% of its weight (Appendix VIII L).

N), using 1.0 g.

Heavy metals Carry out the limit test for heavy metals (Appendix VIII H, method 2), using the residue obtained in the test for residue on ignition; not more than 0.003%.

Arsenic Transfer 1.0 g to a 150 ml conical flask, add 5 ml of sulfuric acid, heat until the substance is thoroughly charred, add concentrated hydrogen peroxide solution dropwise (if a lot of foam is involved, stop heating and rotate the conical flask to prevent the unreacted substance conglomerating at the bottom) until the solution is colourless. Allow to cool, add cautiously 10 ml of water, heat again until sulfur trioxide is evolved, cool and add slowly 5 ml of hydrochloric acid and a quantity of water to produce 28 ml. Carry out the limit test for arsenic (Appendix VIII J, method 1); not more than 0.0002%.

Category Pharmaceutical aid.

Storage Preserve in tightly closed containers, and stored in a cool place.

Methylcellulose

Methylcellulose is methyl ether cellulose. It contains not less than 27.0% and not more than 32.0% of methoxyl ($-\text{OCH}_3$), calculated on the dried basis.

Description A white or almost white, fibrous or granular powder; odourless; tasteless.

Disperses and swells in water to produce a clear or slightly opalescent colloidal solution; insoluble in dehydrated ethanol, chloroform or ether.

Identification (1) To a quantity of 1% aqueous solution in a test tube add 2 ml of a solution of 0.035% anthrone in sulfuric acid cautiously along the inner wall of the tube and allow to stand. A bluish green ring is produced at the interface of the two layers.

(2) Heat 10 ml of 1% aqueous solution. The solution becomes cloudy or a flocculent precipitate is formed. The solution becomes clear again on cooling.

(3) Place a quantity of 1% aqueous solution on a glass plate. After evaporation of the water a thin and elastic film is formed.

Acidity or alkalinity Dissolve 1.0 g in 100 ml water, pH 4.0-8.0 (Appendix VI H).

Viscosity To a quantity of the substance being examined, calculated on the dried basis, add hot water of 90°C to produce a 2.0% (g/g) solution. Stir thoroughly for about 10 minutes, cool in ice bath and continue stirring, allow to remain in ice bath for 40 minutes. Adjust the weight of the solution, and stir evenly. Determine the viscosity (Appendix VI G, method 2) with a rotating viscometer at $20^\circ\text{C} \pm 0.1^\circ\text{C}$. The viscosity is not less than 80.0% and not more than 120.0% of that stated on the label for viscosity types of 100 mPa · s or less, and not less than 75.0% and not more than 140.0% of that stated on the label for viscosity types higher than 100 mPa · s.

Loss on drying When dried at 105°C for 2 hours, loses not more than 5.0% of its weight (Appendix VIII L).

Residue on ignition Not more than 1.0% (Appendix VIII N), using 1.0 g.

Heavy metals Carry out the limit test for heavy metals (Appendix VIII H, method 2), using the residue obtained in

Arsenic Mix 1.0 g with 1.0 g of calcium hydroxide, add water and mix well. After dryness, heat gently until it is thoroughly charred, and then ignite at 500-600°C until the incineration is completed. Dissolve the cooled residue in a mixture of 8 ml of hydrochloric acid and 23 ml of water. Carry out the limit test for arsenic (Appendix VIII J, method 1); not more than 0.0002%.

Assay Weigh accurately and carry out the method for determination of methoxyl (Appendix VII G). Calculate the content of $-\text{OCH}_3$.

Category Pharmaceutical aid.

Storage Preserve in tightly closed containers and stored in a dry place.

Microcrystalline Cellulose

Microcrystalline Cellulose is a powder prepared by hydrolysis of purified cotton cellulose. It contains not less than 97.0% and not more than 102.0% of cellulose, calculated on the dried basis.

Description A white or almost white powder; odourless; tasteless.

Insoluble in water, ethanol, acetone or toluene.

Identification Place about 10 mg on a watch glass, add 2 ml of zinc chloride-iodine TS, a blue colour is produced.

Particle size Transfer 20.0 g on a sieve No. 7, not more than 5.0% is retained on the screen; not less than 50.0% is passed through a sieve No. 9.

Acidity or alkalinity Shake 2.0 g with 100 ml of water for 5 minutes, filter. For the filtrate, pH 5.0-7.5 (Appendix VI H).

Water-soluble substances Shake 5.0 g with 80 ml of water for 10 minutes, filter and transfer the filtrate to an evaporating dish which is previously dried to constant weight, evaporate on a water bath to dryness and dry the residue at 105°C for 1 hour; not more than 0.2%.

Chloride Shake 0.10 g with 35 ml of water, filter. Carry out the limit test for chloride (Appendix VIII A), using the filtrate. Any opalescence produced is not more pronounced than that of a reference solution using 3.0 ml of sodium chloride standard solution (0.03%).

Starch Shake 0.1 g with 5 ml of water, add 0.2 ml of iodine TS, no blue colour is produced.

Loss on drying When dried to constant weight at 105°C, loses not more than 5.0% of its weight (Appendix VIII L).

Residue on ignition Not more than 0.2% (Appendix VIII N); using 1.0 g.

Heavy metals Carry out the limit test for heavy metals (Appendix VIII H, method 2), using the residue obtained in the test for Residue on ignition; not more than 0.001%.

Arsenic Mix 1.0 g with 1.0 g of calcium hydroxide and a quantity of water, stir and dry. Heat gently until it is thoroughly charred, and then ignite at 600 °C until the incineration is complete, allow to cool, add 5 ml of hydrochloric acid and 23 ml of water to dissolve the residue. Carry out the limit test for arsenic (Appendix VIII J, method 1); not more than 0.0002%.

Assay Weigh accurately about 0.125 g to a conical flask, add 25 ml of water and 50.0 ml of potassium dichromate

standard in water to produce 200 ml), accurately measured, carefully add 100 ml of sulfuric acid, heat rapidly to boil, cool and transfer to a 250 ml volumetric flask, dilute with water to volume, mix well. Measure accurately 50 ml of the solution, add 3 drops of o-phenanthroline IS, titrate with ferrous ammonium sulfate (0.1 mol/L) VS. Perform a blank determination and make any necessary correction. Each ml of ferrous ammonium sulfate (0.1 mol/L) VS is equivalent to 0.675 mg of cellulose.

Category Pharmaceutical aid, excipient.

Storage Preserve in tightly closed containers.

Oxystarch

Oxystarch is a sodium periodate oxidation product of corn starch, which has two aldehyde groups on each monomer. It contains not less than 96.0% of oxystarch, calculated on the dried basis.

Description A white or pale yellow powder; odourless; tasteless; very hygroscopic. Insoluble in water or ethanol.

Identification (1) To about 0.1 g add 5 ml of water, heat to boil, shake vigorously and filter. To the filtrate add 0.5 ml of 2,4-dinitrophenylhydrazine TS and heat, opalescence is produced. On cooling yellow crystals are formed which is soluble in ethanol.

(2) To about 10 mg add 1 ml of alkaline cupric tartrate TS and heat, a cuprous oxide precipitate is produced immediately.

Free starch Boil 0.1 g with 5 ml of water, cool; a sediment is deposited on the bottom without burning. Add 1 drop of iodine TS; no blue colour is produced.

Iodide Weigh 1 g into a beaker, add a small quantity of water, stir thoroughly, filter and wash with a small quantity of water. Combine the washings and filtrate, dilute to 10 ml with water. Add 0.5 ml of hydrogen peroxide TS, and mix well. Add 2 drops of sulfuric acid and heat to boil. Add 0.5 ml of starch IS after cooling; no blue colour is produced.

Acidity To 1 g add 10 ml of water, stir and filter. The pH of the filtrate is not less than 2.5 (Appendix VI H).

Loss on drying When dried to constant weight at 100°C, loses not more than 15.5% of its weight, using 0.5 g (Appendix VIII L).

Residue on ignition Not more than 0.1% (Appendix VIII N), using 1.0 g.

Heavy metals Carry out the limit test for heavy metals (Appendix VIII H, method 2), using the residue obtained in the test for Residue on ignition; not more than 0.002%.

Iron To 0.5 add 20 ml of dilute hydrochloric acid solution, shake for 5 minutes, filter and wash the residue with a small amount of water. Combine the washings and filtrate, carry out the limit test for iron (Appendix VIII G). Any colour produced is not more intense than that of a reference solution using 1.5 ml of iron standard solution (0.003%).

Other requirements Complies with the general requirements for powders (Appendix I P).

Assay To about 0.1 g, accurately weighed, add 15 ml of hydroxylamine hydrochloride solution (dissolve 7.5 g of hydroxylamine hydrochloride in 15 ml of water, add 200 ml

solution, and mix well. Add 2.5 ml of bromophenol blue IS, mix well, allow to stand over night, filter if necessary), accurately measured, and 10 ml of ethanol solution (1→2), heat gently under reflux for 10 minutes and cool. Titrate with hydrochloric acid (0.1 mol/L) VS until the solution becomes yellowish-green. Perform a blank determination and make any necessary correction. Each ml of hydrochloric acid (0.1 mol/L) VS is equivalent to 8.0 mg of oxystarch.

Category Pharmaceutical aid, urea nitrogen sorbent.

Strength 10 g

Storage Stored in a dry place and protected from light.

Paraffin

Paraffin is a mixture of solid hydrocarbons obtained from petroleum or shale oil.

Description Colourless or white translucent mass, usually exhibit a crystalline structure; odourless; tasteless; slightly greasy to the touch.

Soluble in chloroform or ether; practically insoluble in water or ethanol.

Melting range 50-65°C (Appendix VI C, method 2).

Identification (1) When strongly heated, it burns with a luminous flame to leave a carbonized residue.

(2) Heat about 0.5 g in a dry test tube with an equal quantity of sulfur; the mixture is carbonized with the evolution of hydrogen sulfide.

Acidity or alkalinity Melt about 5 g, add an equal volume of hot neutral ethanol and shake. Allow to separate, the solution is neutral to litmus paper.

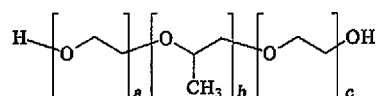
Readily carbonized substances Transfer 4.0 g to a test tube with stopper, heat in a water bath at 65-70°C. Add 5 ml of 95% sulfuric acid and maintain at this temperature for 10 minutes, shake the mixture thoroughly for a few seconds at intervals of every one minute. The paraffin remains unchanged in colour, any colour produced in the acid layer is not more intense than that of a reference solution (mix standard cobaltous chloride CS 0.8 ml, standard copper sulfate CS 0.3 ml, standard potassium dichromate CS 1.0 ml and water 2.9 ml).

Residue on ignition Not more than 0.05% (Appendix VIII H).

Category Pharmaceutical aid, ointment base.

Storage Preserve in tightly closed containers.

Poloxamer



Poloxamer is a block copolymer of ethylene oxide and propylene oxide, i.e., α -hydro- ω -hydroxypoly (oxyethylene)_a poly (oxypropylene)_b poly (oxyethylene)_c, where *a* and *c* is 2-130 and *b* is 15-67. The average content of oxyethylene units is

not less than 90.0% and not more than 110.0% of the labelled nominal value if the labelled nominal value is between 1000 and 7000. It is not less than 80.0% and not more than 120.0% of the labelled nominal value if the labelled nominal value is above 7000.

Description White or slightly yellow translucent waxy solids; odour, slightly characteristic.

Freely soluble in ethanol or water; soluble in dehydrated ethanol or ethyl acetate; practically insoluble in ether or petroleum benzin.

Identification The infrared absorption spectrum (Appendix IV C) is concordant with the reference spectrum of poloxamer (Appendix XVI).

Acidity or alkalinity Dissolve 1.0 g in 40 ml of water, pH 5.0-7.5 (Appendix VI H).

Heavy metals Dissolve 1.0 g in 23 ml of water, add 2 ml of acetate BS (pH 3.5). Carry out the limit test for heavy metals (Appendix VIII H, method 1); not more than 0.002%.

Arsenic To 1.0 g add 5 ml of hydrochloric acid and 23 ml of water, shake to dissolve. Carry out the limit test for arsenic (Appendix VIII J, method 1); not more than 0.0002%.

Weight percent of oxyethylene Transfer 0.5-1.0 ml of 10%-20% (g/ml) solution of the substance being examined in deuteriochloroform containing 1% of tetramethylsilane (or in deuterium oxide containing 1% of sodium 4,4-dimethyl-4-silapentane-5-sulfonate as internal standard) to an NMR sample tube, add 1 drop of deuterium oxide and shake well. Measure the resulting solution with NMR instrument by Relative Method for Quantitation and scan the region from 0×10^{-6} to 5×10^{-6} , calculate the EO value with the following equation:

$$EO = 3300\alpha / (33\alpha + 58)$$

Where α is $(A_2/A_1) - 1$;

A_1 is the average area of the doublet appearing at about 1.15×10^{-6} due to the methyl groups of the oxypropylene units;

A_2 is the average area of the composite band from 3.2 to 3.8×10^{-6} due to the CH_2O groups of both the oxyethylene and oxypropylene units and the CHO groups of the oxypropylene units;

EO is the percentage of oxyethylene units, by weight, in the poloxamer molecule (%).

Unsaturation Weigh accurately about 15.0 g of the powdered poloxamer, add accurately 50 ml of mercuric acetate solution, and mix on a magnetic stirrer until the poloxamer is dissolved completely. Allow to stand for 30 minutes with occasional shaking. Add 10 g of sodium bromide crystals, and stir on a magnetic stirrer for about 2 minutes, add 1 ml of phenolphthalein IS immediately, titrate with methanolic potassium hydroxide (0.1 mol/L) VS. Perform a blank determination and determine the initial acidity (Dissolve 15.0 g of poloxamer in 75 ml of neutral methanol (neutral to phenolphthalein IS), titrate with methanolic potassium hydroxide (0.1 mol/L) VS until the solution is neutral to phenolphthalein IS) to make any necessary correction. The unsaturation is 0.065 ± 0.035 . It is calculated, in mEq per g, with the following equation:

$$\text{Unsaturation} = (V_{\text{sample}} - V_{\text{blank}} - V_{\text{initial}}) N / W,$$

Where V_{sample} , V_{blank} and V_{initial} are the volumes, of methanolic potassium hydroxide (0.1 mol/L) VS consumed for titrating the substance being examined, the blank and the initial acidity, respectively, ml;
 N is the concentration, of the methanolic pota-

W is the weight of the substance being examined, g.

Average molecular weight Weigh accurately a quantity, calculated by multiplying the molecular weight by 0.002, of poloxamer, add accurately 25 ml of phthalic anhydride-pyridine solution and a few of glass beads. Heat under a reflux condenser for 1 hour, allow to cool and wash the reflux condenser with two 10 ml portions of pyridine. Add 10 ml of water, mix well, seal and allow to stand for 10 minutes. Add accurately 50 ml of 0.66 mol/L sodium hydroxide solution and 0.5 ml of a mixture of phenolphthalein-pyridine solution (1 \rightarrow 100), titrate with sodium hydroxide (0.5 mol/L) VS until the solution changes to a light pink colour that resists for 15 seconds. Perform a blank determination and make any necessary correction. Calculate the average molecular weight for the substance being examined using the following equation:

$$\text{average molecular weight} = 2000W / [(B - S)N]$$

Where W is the weight of the substance being examined, g;

B is the volume, of the sodium hydroxide (0.5 mol/L) VS consumed for titrating blank, ml;

S is the volume, of the sodium hydroxide (0.5 mol/L) VS consumed for titrating the substance being examined, ml;

N is the concentration, of the sodium hydroxide (0.5 mol/L) VS, mol/L.

Category Pharmaceutical aid (for oral).

Storage Preserve in tightly closed containers, protected from light.

Preparation of mercuric acetate solution Dissolve 50 g of mercuric acetate in 900 ml of methanol to which 0.5 ml of glacial acetic acid has been added, dilute with methanol to 1000 ml and mix. Discard the solution if it changes to yellow. If it is turbid, filter it. Discard it if it is still turbid or presents as yellow. The solution should be freshly prepared, and preserve in an amber glass bottle, stored in dark place.

Preparation of phthalic anhydride-pyridine solution

Preparation To 500 ml of pyridine containing less than 0.1% of water (or dissolve 30 g of phthalic anhydride in 500 ml of pyridine, distill and use the middle portion of the distillate.) add 72 g of phthalic anhydride, shake vigorously or heat on a water bath at 40°C until solution is effected, allow to stand overnight with protecting from light.

Standardization Mix 10 ml of the above resulting solution, accurately measured, with 25 ml of pyridine and 50 ml of water, allow to stand for 15 minutes, add 0.5 ml of a mixture of phenolphthalein-pyridine solution (1 \rightarrow 100), titrate with sodium hydroxide (0.5 mol/L) VS; it consumes between 37.6 ml to 40.0 ml.

Polyacrylic Resin II

Polyacrylic Resin II is a copolymer of methylacrylic acid and methyl methacrylate in a ratio of 50 : 50.

Description A white strip or powder, easy to conglomerate in ethanol. Soluble in warm ethanol within 1 hour (break the strip to 1 cm long, and the powder does not need to triturate); insoluble in water.

Viscosity To 6.0 g, add 100 ml of ethanol, warm to dissolve, the kinematic viscosity at 25°C is not more than

G, method 2).

Acid value Dissolve about 0.5 g, accurately weighed, in a 250 ml conical flask with 25 ml of 75% ethanol (neutral to phenolphthalein IS) by warming. Allow to cool; add dropwise 15 ml of sodium hydroxide (0.1 mol/L) VS, accurately measured, add 5 g of sodium chloride and 10 ml of water, continue the titration with sodium hydroxide (0.1 mol/L) VS until a pink colour persists for 30 seconds. The acid value is 300-330, calculated on the dried basis (Appendix VII H).

Identification The infrared absorption spectrum (Appendix IV C) is concordant with the reference spectrum of polyacrylic Resin II CRS.

Acidity Dissolve 3.0 g in 100 ml of 75% ethanol (pH value about 7) by warming and allow to cool, pH is 4.0-6.0 (Appendix VIII H).

Loss on drying When dried to constant weight at 110°C, loses not more than 10.0% (Appendix VIII L).

Heavy metals Carry out the limit test for heavy metals (Appendix VIII H, method 2), using 1.0 g; not more than 0.003%.

Arsenic Heat 1.0 g in a 150 ml conical flask with 5 ml of sulfuric acid, until it is completely charred, add concentrate hydrogen peroxide solution dropwise (if a lot of foam evolved, stop heating and rotate the conical flask to prevent conglomeration of the unreactant on the bottom) until the solution becomes colourless. Allow to cool, add cautiously 10 ml of water, heat again, the sulfur trioxide is evolved, cool and add slowly a quantity of water to 28 ml. It complies with the limit test for arsenic (Appendix VIII J) (0.0002%).

Category Pharmaceutical acid.

Storage Preserve in tightly closed containers, stored in cool place.

Polyacrylic Resin III

Polyacrylic Resin III is a copolymer of methylacrylic acid and methyl methacrylate in a ratio of 35 : 65.

Description A white strip or powder, easy to conglomerate in ethanol.

Soluble in warm ethanol within 1 hour (break the strip to 1 cm long and the powder does not need to triturate); insoluble in water.

Viscosity To 6.0 g add 100 ml of ethanol, warm to dissolve, the kinematic viscosity at 25°C is not more than 50×10^{-3} Pa · s, using a rotating viscosimeter (Appendix VI G, method 2).

Acid value Dissolve about 0.5 g, accurately weighed in a 250 ml conical flask with 25 ml of 75% ethanol (neutral to phenolphthalein IS) by warming. Allow to cool, add dropwise 15 ml of sodium hydroxide (0.1 mol/L) VS, accurately measured, 5 g of sodium chloride and 10 ml of water, continue the titration with sodium hydroxide (0.1 mol/L) VS until a pink colour persists for 30 seconds. The acid value is 210-240, calculated on the dried basis. (Appendix VII H).

Identification The infrared absorption spectrum (Appendix IV C) is concordant with the reference spectrum of polyacrylic Resin III CRS.

about 7) by warming, cool, pH is 4.0-6.0 (Appendix VI H).

Loss on drying When dried to constant weight at 110°C, loses not more than 10.0% (Appendix VIII L).

Heavy metals Carry out the limit test for heavy metals (Appendix VIII H, method 2), using 1.0 g; not more than 0.003%.

Arsenic Transfer 1.0 g to a 150 ml conical flask, add 5 ml of sulfuric acid, heat until it is completely charred, add concentrate hydrogen peroxide solution dropwise (If a lot of foam is evolved stop heating and rotate the conical flask to prevent the unreactant to conglomerate at the bottom) until the solution is colourless. Allow to cool, add cautiously 10 ml of water, heat again, until sulfur trioxide is evolved, cool and add slowly a quantity of water to 28 ml. It complies with the limit test for arsenic (Appendix VIII J) (0.0002%).

Category Pharmaceutical acid.

Storage Preserve in tightly closed containers, stored in cool place.

Polyacrylic Resin IV

Polyacrylic Resin IV is a copolymer of dimethylaminoethyl methacrylate and methylacrylic esters.

Description Pale yellow granule or flake solid; odour, characteristic.

Soluble in warm ethanol (within 1 hour); sparingly soluble in hydrochloric acid solution (9→1000) (within 1 hour); insoluble in water.

Relative density Dissolve 10.25 g with isopropanol-acetone (3 : 2) in a 100 ml volumetric flask and dilute to volume as the test solution. The relative density of the test solution is 0.810-0.820 (Appendix VI A).

Refractive index 1.380-1.395 (Appendix VI F), using the test solution obtained in the test for Relative density.

Viscosity Dissolve 12.00 g in a 100 ml volumetric flask with ethanol and dilute to volume, the kinematic viscosity at 30°C is 0.005-0.020 Pa · s, using a model NDJ-79 rotating viscosimeter (Appendix VI G, method 2).

Alkaline value Dissolve about 0.3 g, accurately weighed, with 25 ml of neutral ethanol (reveals yellow to bromophenol blue IS), add 20 ml of hydrochloric acid (0.1 mol/L) VS, accurately measured, and several drops of bromophenol blue IS, mix well. Titrate with sodium hydroxide (0.1 mol/L) VS until the solution becomes bluish-green. Perform a blank determination. Calculate the alkaline value with the following equation; the alkaline value is 162.0-198.0.

$$\text{Alkaline value} = \frac{(B-A) \times 5.61}{G}$$

where A is volume consumed of sodium hydroxide (0.1 mol/L) VS of the substance being examined;
B is volume consumed in blank determination;
G is the weight of the substance being examined.

Identification Apply about 10 µl of the solution obtained in the test for Viscosity to a blank potassium bromide disc of 13 mm in diameter, heat to evaporate the solvent. The infrared spectrum (Appendix IV C) is concordant with the spectrum of polyacrylic Resin IV CRS treated in the same manner.

Colour of solution The light absorbance at 420 nm is not

obtained in the test for Relative density.

Loss on drying When dried to constant weight at 110°C, loses not more than 4.0% (Appendix VIII L).

Residue on ignition Not more than 0.2% (Appendix VIII N, method 2), using 1 g.

Heavy metals Carry out the limit test for heavy metals (Appendix VIII H, method 2), using the residue obtained in the test for Residue on ignition; not more than 0.001%.

Arsenic Add 10 ml of sulfuric acid to 1.0 g, heat until it is completely charred, add hydrogen peroxide solution dropwise until the solution is colourless, allow to cool. Add 10 ml of water, heat until sulfur trioxide is evolved. Cool and add a quantity of water to 28 ml, the solution complies with the limit test for arsenic (Appendix VIII J, method 1) (0.0002%).

Category Pharmaceutical acid.

Storage Preserve in tightly closed containers, stored in cool place.

Polyoxyl (40) Stearate

[9004-99-3]

Polyoxyl (40) Stearate is polyethylene glycol monostearate. It is represented by the molecular formula $C_{17}H_{35}COO(CH_2CH_2O)_nH$, where n is about 40.

Description White or pale yellow waxy solids; odourless. Soluble in water, ethanol or ether; insoluble in ethylene glycol.

Melting range 46-51°C (Appendix VI C, method 2).

Acid value Not greater than 2 (Appendix VII H).

Saponification value 25-35 (Appendix VII H).

Hydroxyl value 22-38 (Appendix VII H).

Clarity and colour of solution A solution of 1.0 g in 20 ml of water is clear and colourless; any colour produced is not more intense than that of reference solution Y₆ (Appendix IX A).

Residue on ignition Not more than 0.3% (Appendix VIII N).

Heavy metals Carry out the limit test for heavy metals (Appendix VIII H, method 3), using 2.0 g; not more than 0.001%.

Category Pharmaceutical aid, surfactant.

Storage Preserve in tightly closed containers, stored in a dry and cool place.

Polysorbate 80

[9005-65-6]

Polysorbate 80 is polyoxyethylene (20) sorbitan monooleate.

Description A pale yellow to orange-yellow, viscous liquid; odour, faint and characteristic; taste, slightly bitter and astringent with a warm feeling. Freely soluble in water, ethanol, methanol or ethyl acetate.

Relative density 1.06-1.09 (Appendix VI A, hydrostatic method).

Kinematic viscosity 350-550 mm²/s (Appendix VI G, method 1), determined at 25°C, using a capillary tube of 3.4-4.2 mm in internal diameter.

Acid value Dissolve 10 g, accurately weighed, with 50 ml of ethanol neutralize to phenolphthalein IS in a 250 ml conical flask. Boil under reflux for 10 minutes, cool, add 5 drops of phenolphthalein IS, titrate with sodium hydroxide (0.1 mol/L) VS. The acid value is not more than 2.2 (Appendix VII H).

Saponification value 45-60 (Appendix VII H).

Hydroxyl value 65-80 (Appendix VII H).

Iodine value 18-24 (Appendix VII H).

Identification (1) To 5 ml of a solution (1→20) add 5 ml of sodium hydroxide TS. Boil for a few minutes, cool, and acidify with dilute hydrochloric acid; a creamy-white turbidity is produced.

(2) To a solution (1→20) add bromine TS dropwise; the bromine is decolourized.

(3) To 6 ml add 4 ml of water, mix well; a gelatinous mass is formed.

(4) To 10 ml of a solution (1→20) add 5 ml of ammonium cobalt thiocyanate solution (dissolve 17.4 g of ammonium thiocyanate and 2.8 g of cobalt nitrate in 100 ml of water), mix well. Add 5 ml of chloroform, shake, allow to stand, chloroform layer turns blue.

Acidity or alkalinity Dissolve 0.50 g in 10 ml of water, pH 5.0-8.0 (Appendix VI H).

Colour Not more intense than that of a reference solution prepared by mixing 8.0 ml of standard potassium dichromate CS and 0.8 ml of standard cobaltous chloride CS with sufficient water to produce 10 ml.

Freezing test Allow to stand for 24 hours in a glass container at 5°C ± 2°C, it is not frozen.

Water Not more than 3.0% (Appendix VIII M, method 1 A).

Residue on ignition Not more than 0.2% (Appendix VIII N); using 1.0 g.

Heavy metals Carry out the limit test for heavy metals (Appendix VIII H, method 2), using the residue obtained in the test for Residue on ignition; not more than 0.001%.

Category Pharmaceutical acid.

Storage Preserve in tightly closed containers, protected from light.

Polyvinyl Alcohol Resin

Polyvinyl alcohol resin is obtained by alcoholysis of polyvinyl acetate in methanol in the presence of alkali. It is represented by the formula $(CH_2CHOH)_n(CH_2CHOCOCH_3)_m$, in which $m+n$ represents the average polymerization degree.

Description White or pale yellow granules or powder; odourless; tasteless.

Freely soluble in hot water or boiling water; practically insoluble in anhydrous ethanol or benzene; insoluble in cold water.

Viscosity Dissolve by heating in a water bath 12 g, accurately weighed, in water to produce solutions of 3.8%.

G, method
Acid val
250
pH
viscosity

931

mPa · s.

Acidity To 2 g add 50 ml of water, heat in a water bath until dissolved, allow to cool, pH 4.5-6.5 (Appendix VI H).

Loss on drying When dried to constant weight at 105°C, loses not more than 6.0% of its weight (Appendix VIII L).

Residue on ignition Not more than 0.5% (Appendix VIII N), using 1.0 g.

Degree of alcohololysis Accurately weigh 1 g into a 500 ml iodine flask with a stopper, add 200 ml of water, heat on a water bath until dissolved. Allow to cool, add 2-3 drops of phenolphthalein TS, and sodium hydroxide (0.1 mol/L) VS dropwise until the colour of the solution turns pink. Add 20 ml of sodium hydroxide (0.1 mol/L) VS, accurately measure, titrate with sodium hydroxide (0.1 mol/L) VS. Perform a blank determination in the same manner and make any necessary correction. Each ml of sodium hydroxide (0.1 mol/L) VS is equivalent to 60.05 mg of acetic acid.

Category Pharmaceutical aid.

Storage Preserve in tightly closed containers.

Pregelatinized Starch

Pregelatinized Starch is mechanically processed starch to improve its flowability and compressibility.

Description A white powder; odourless; tasteless.

Identification (1) Boil about 1 g with 15 ml of water, cool, a semitransparent white gelatinous substance is produced. (2) Mix about 0.1 g with 20 ml of water, add a few drops of iodine TS, a blue or bluish black colour is produced which gradually disappears on heating and reappears on cooling. (3) Mix the sample and glycerine-acetic acid TS on a slide and examine under microscope; aggregates of original starch and remainders are observed, the spheroidal particulates are no longer exist, changing to irregular granules on surface. (4) Examine under polarization microscope; polarized cross of some of the granules disappears completely.

Acidity Shake 10.0 g with 10 ml of neutral ethanol, add 100 ml of boiled and cooled water, mechanically stir for 5 minutes, the pH value of the supernatant liquid is 4.5-7.0 (Appendix VI H).

Loss on drying When dried at 120°C for 4 hours, loses not more than 14.0% of its weight (Appendix VIII L).

Ash Weigh accurately about 1.0 g in a crucible, previously ignited to constant weight, ignite gently until completely carbonized. Incinerate completely to constant weight at 600-700°C which is raised gradually. The remaining ash is not more than 0.3% of its weight.

Iron To 0.50 g add 4 ml of dilute hydrochloric acid and 16

ml of water, combine the filtrate and washings, add 50 mg of ammonium persulfate and dilute with water to 35 ml. Carry out the limit test for iron (Appendix VIII G). Any colour produced is not more intense than that of a reference solution using 1.0 ml of iron standard solution (0.002%).

Sulfur dioxide To 20 g add 200 ml of water in a conical flask with stopper, shake thoroughly, filter. To 100 ml of the filtrate add 2 ml of starch IS, titrate with iodine (0.01 mol/L) VS. Not more than 2.50 ml of iodine (0.01 mol/L) VS is required (0.008%).

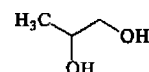
Oxidizing substances To 5 g add 20 ml of a mixture of methanol and water (1 : 1), and 1 ml of 6 mol/L acetic acid solution, stir until a homogenized suspension is obtained. Add 0.5 ml of a freshly prepared and saturated potassium iodine solution, mix well, allow to stand for 5 minutes; no distinct bluish brown or violet colour is produced (0.002%).

Category Pharmaceutical aid, excipient.

Storage Stored in a dry place.

Storage Stored in a dry place.

Propylene Glycol



C₃H₈O₂ 76.09

[57-55-6]

Propylene glycol is 1,2-propanediol.

Description A viscous, clear, colourless liquid; odourless; taste, slightly sweet; hygroscopic. Miscible with water, ethanol or chloroform.

Relative density 1.035-1.037 at 25°C (Appendix VI A).

Identification The infrared absorption spectrum (Appendix IV C) is concordant with the reference spectrum of Propylene glycol (Appendix XVI).

Acidity Dissolve 10.0 ml in 50 ml of freshly boiled and cooled water and add 3 drops of bromothymol blue IS, titrate with sodium hydroxide (0.01 mol/L) VS until the colour changes to blue. Not more than 0.50 ml of sodium hydroxide (0.01 mol/L) VS is required.

Chloride Carry out the limit test for chloride (Appendix VIII A), using 1.0 ml. Any opalescence produced is not more pronounced than that of a reference solution using 7.0 ml of sodium chloride standard solution (0.007%).

Sulfate Carry out the limit test for sulfate (Appendix VIII B), using 5.0 ml. Any opalescence produced is not more pronounced than that of a reference solution using 3.0 ml of potassium sulfate standard solution (0.006%).

Oxidizing substances To 5.0 ml add 1.5 ml of potassium iodide TS and 2 ml of dilute sulfuric acid, allow to stand in a ground-glass-stoppered flask protected from light for 15 minutes and add 2 ml of starch IS, any blue colour produced requires not more than 0.2 ml of sodium thiosulfate (0.005 mol/L) VS to disappear.

Water Not more than 0.2% (Appendix VIII M, method 1 A).

Residue on ignition Heat 50 g until it ignites and allow it to burn without further application of heat in a place free from drafts. Ignite to constant weight at 700-800°C; the weight of the residue dose not exceed 3.5 mg.

Heavy metals To 4.0 ml add 19 ml of water and 2 ml of acetate buffer (pH 3.5) and mix well. Carry out the limit

more than 0.0005%.

Category Pharmaceutical aid, medicinal adjuvant solvent.

Storage Preserve in tightly closed containers, stored in a dry place.

Purple Ferric Oxide

Fe_2O_3 159.69

Purple Ferric Oxide contains not less than 98.0% of Fe_2O_3 , calculated with reference to the substance freshly ignited to constant weight.

Description A dark purple powder; odourless; tasteless. Insoluble in water; freely soluble in boiling hydrochloric acid.

Identification Boil about 0.1 g with 5 ml of dilute hydrochloric acid, allow to cool, the solution yields the reactions characteristic of ferric salts (Appendix III).

Water soluble substances To 2.0 g add 100 ml of water, heat under reflux on a water bath for 2 hours and filter. Wash the residue with a quantity of water, evaporate the combined filtrate and washings to dryness in an evaporating dish previously dried to constant weight at 105°C, dry the residue to constant weight at 105°C; not more than 10 mg (0.5%).

Acid insoluble substances Dissolve 2.0 g in 25 ml of hydrochloric acid by heating in a water bath, add 100 ml of water, filter through a sintered glass crucible (No. 4) previously dried to constant weight at 105°C, wash the residue with hydrochloric acid solution (1→100) until the washings become colourless, then wash the residue with water until the washings give no reaction of chlorides, dry the residue to constant weight at 105°C; not more than 20 mg (1.0%).

Loss on ignition When ignited to constant weight at 700–800°C, loses not more than 4.0% of its weight, using 1.0 g.

Barium To 0.2 g add 5 ml of hydrochloric acid, heat until dissolved. Add 1 drop of hydrogen peroxide TS and 20 ml of 10% sodium hydroxide solution, filter, wash the residue with 10 ml of water. Combine the filtrate and washings, add 10 ml of sulfuric acid solution (2→10), no opalescence is produced.

Lead To 0.5 g add 10 ml of hydrochloric acid, heat until dissolved. Add 3 ml of nitric acid, boil for 1 minute, allow to cool. Extract with anhydrous ether for 4 times (30 ml, 20 ml, 20 ml and 20 ml), discard the ether layer. Heat the acid solution to expel the remaining ether, add ammonia TS to make the solution alkaline, add 1 ml of potassium cyanide TS and sufficient water to produce 50 ml. Add a few drops of sodium sulfide TS and mix well. Any colour produced is not more intense than that of a reference solution prepared in the same manner using 1.5 ml of lead standard solution (0.003%).

Arsenic To 0.2 g add 7 ml of hydrochloric acid, heat until dissolved. Add 21 ml of water, and add acid stannous chloride TS dropwise until the yellow colour disappears. Carry out the limit test for arsenic (Appendix VIII J, method 1); not more than 0.001%.

Assay Add to about 0.15 g, accurately weighed, in a conical flask with stopper 2.5 ml of hydrochloric acid, heat until dissolved on a water bath. Add 1 ml of hydrogen

water, allow to cool. Add 1.5 g of potassium iodide and 2.5 ml of hydrochloric acid, stopper and shake thoroughly, allow to stand in a dark place for 15 minutes. Titrate with sodium thiosulfate (0.1 mol/L) VS, add 2.5 ml of starch TS towards the end of titration, continue the titration until the blue colour disappears. Each ml of sodium thiosulfate (0.1 mol/L) VS is equivalent to 7.985 mg of Fe_2O_3 .

Category Pharmaceutical aid, colouring agent.

Storage Preserve in tightly closed containers.

Red Ferric Oxide

Fe_2O_3 159.69

[1309-37-1]

Red Ferric Oxide contains not less than 98.0% of Fe_2O_3 , calculated with reference to substance freshly ignited to constant weight.

Description A dark red powder; odourless; tasteless. Insoluble in water; freely soluble in boiling hydrochloric acid.

Identification Boil about 0.1 g with 5 ml of dilute hydrochloric acid, allow to cool, the solution yields the reactions characteristic of ferric salts (Appendix III).

Water soluble substances To 2.0 g add 100 ml of water, reflux on a water bath for 2 hours and filter. Wash the residue with a quantity of water, evaporate the combined filtrate and washings to dryness in a tared evaporating dish, dry the residue to constant weight at 105°C; not more than 10 mg (0.5%).

Acid insoluble substances Dissolve 2.0 g in 25 ml of hydrochloric acid by heating in a water bath, add 100 ml of water, filter through a sintered glass crucible (No. 4) previously dried to constant weight at 105°C, wash the residue with hydrochloric acid solution (1→100) until the washing becomes colourless, then wash the residue with water until the washing gives no reaction of chlorides, dry the residue to constant weight at 105°C; not more than 20 mg (1.0%).

Loss on ignition When ignited to constant weight at 700–800°C, loses not more than 4.0% of its weight, using 1.0 g.

Barium To 0.20 g add 5 ml of hydrochloric acid heat to dissolve red ferric oxide. Add 1 drop of hydrogen peroxide TS and 20 ml of 10% sodium hydroxide solution, filter, wash the residue with 10 ml of water, combine the filtrate and the washings. Add 10 ml of sulfuric acid solution (2→10), no opalescence is produced.

Lead To 0.50 g add 10 ml of hydrochloric acid, and heat to dissolve. Add 3 ml of nitric acid, boil for 1 minute, allow to cool. Extract with dehydrated ether for 4 times (30 ml, 20 ml, 20 ml and 20 ml), discard the ether layer, heat the acid solution to expel the remaining ether, add ammonia TS to make the solution alkalize, add 1 ml of potassium cyanide TS and sufficient water to produce 50 ml. Add a few drops of sodium sulfide TS and mix well. Any colour produced is not more intense than that of a reference solution prepared in the same manner using 1.5 ml of lead standard solution (0.003%).

Arsenic To 0.20 g add 7 ml of hydrochloric acid, heat to dissolve, add 21 ml of water and stannous chloride TS dropwise until the yellow colour disappears. Carry out the limit test for arsenic (Appendix VIII J, method 1); not more than 0.001%.

Assay To about 0.15 g, accurately weighed, in a conical

dissolve red ferric oxide on a water bath. Add 1 ml of hydrogen peroxide TS, heat to boil for a few minutes, add 25 ml of water, allow to cool. Add 1.5 g of potassium iodide and 2.5 ml of hydrochloric acid, stopper and shake thoroughly, allow to stand in dark place for 15 minutes. Titrate with sodium thiosulfate (0.1 mol/L) VS, add 2.5 ml of starch IS towards the end of the titration, continue the titration until the blue colour disappears. Each ml of sodium thiosulfate (0.1 mol/L) VS is equivalent to 7.985 mg of Fe_2O_3 .

Category Pharmaceutical aid, colouring agent.

Storage Preserve in tightly closed containers.

Refined Corn Oil

Refined Corn Oil is fat oil made from seed embryo of maize using the method of hot-pressing.

Description A clear pale yellow oily liquid; odour, slightly characteristic; taste, mild.

Miscible with ether, chloroform, petroleum ether or acetone; slightly soluble in ethanol.

Relative density 0.915-0.923 (Appendix VI A).

Refractive index 1.472-1.475 (Appendix VI F).

Acid value Not more than 0.6 (Appendix VII H).

Saponification value 187-195 (Appendix VII H).

Iodine value 108-128 (Appendix VII H).

Composition of fatty acids Transfer 8-10 drops (about 150-200 mg) to a 10 ml volumetric flask (w/ out touching inner wall of the flask when adding), add 4 ml of 0.5 mol/L methanolic potassium hydroxide solution, and heat under reflux in a water bath at 65°C until oil droplets dissolved. Cool, add 15 ml of 15% methanolic boron trifluoride solution, and heat under reflux for 2 minutes in a water bath at 65°C. Cool, add 1-4 ml of hexane, and heat for 1 minute in a water bath at 65°C. Cool, add saturated solution of sodium chloride to the neck of the flask, mix well, allow to separate. Carry out the method for gas chromatography (Appendix V E), using a column coated with 10%-15% polyethylene glycol succinate as the stationary phase, nitrogen as carrier gas at a flow rate of 30 ml/min, the flow rate of hydrogen is 30 ml/min, the flow rate of air is 300 ml/min. Maintain the injection temperature at 250°C, the detection temperature at 250°C, and the column temperature at 185°C. Inject 1-2 µl of the supernatant into the column, and record the chromatogram. The order of elution of the peaks is methyl esters of palmitic acid, stearic acid, oleic acid, linoleic acid and linolenic acid, and the content is 8%-19%, 1%-4%, 19%-50%, 34%-62%, 0-2% respectively, calculated by the area normalization method with respect to the peak area obtained in the chromatogram.

Water and Volatile Substances Not more than 0.2% (Appendix VII H).

Microbial limit Carry out the microbial limit tests (Appendix XI J), not more than 100 bacteria per ml and not more than 100 fungi per ml, no growth of *Escherichia coli* is detected.

Category Pharmaceutical aid.

Storage Preserve in tightly closed containers, stored in a cool place and protected from light.

Simple Syrup

Simple Syrup is an almost saturated solution of sucrose in water.

Formula	Sucrose Water	850 g sufficient quantity
	To make	1000 ml

Processing Heat 450 ml of water to boiling, add the sucrose and agitate until it is dissolved. Continue to heat at 100°C and filter through absorbent cotton, wash the cotton with sufficient hot water to produce 1000 ml at room temperature and mix well.

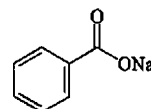
Description A colourless or pale yellow, viscous liquid; taste, sweet; becomes rancid on exposure to undue heat.

Relative density Not lower than 1.30 (Appendix VI A).

Category Pharmaceutical aid, excipient, flavouring agent.

Storage Preserve in tightly closed containers, protected from light and stored at a temperature below 30°C.

Sodium Benzoate



$\text{C}_7\text{H}_5\text{NaO}_2$ 144.11

[532-32-1]

Sodium Benzoate contains not less than 99.0% of $\text{C}_7\text{H}_5\text{NaO}_2$, calculated on the dried basis.

Description A white granular powder or crystalline powder; odourless or almost odourless; taste, sweetish and salty. Freely soluble in water and sparingly soluble in ethanol.

Identification (1) The infrared absorption spectrum (Appendix IV C) is concordant with the reference spectrum of sodium Benzoate (Appendix XVI).

(2) Dissolve about 0.5 g in 10 ml of water, the solution yields the reactions characteristic of sodium salts and benzoates (Appendix III).

Acidity or alkalinity Dissolve 1.0 g in 20 ml of water, add 2 drops of phenolphthalein IS. Not more than 0.25 ml of either sulfuric acid (0.05 mol/L) VS or sodium hydroxide (0.1 mol/L) VS is required to change the colour of the solution.

Loss on drying When dried to constant weight at 105°C, loses not more than 1.5% of its weight (Appendix VIII L).

Heavy metals To 2.0 g add 45 ml of water, stir continuously, add dropwise 5 ml of dilute hydrochloric acid and filter. Carry out the limit test for heavy metals (Appendix VIII H, method 1), using 25 ml of the filtrate; not more than 0.001%.

Arsenic Spread 1 g of anhydrous sodium carbonate on the bottom and inner wall of a crucible, add 0.40 g of the substance being examined and moisten with a small quantity of water. Dry and carbonize thoroughly with a small flame then ignite at 500-600°C until completely incinerated. Allow it to cool, dissolve the residue in 5 ml of hydrochloric acid

(Appendix VIII J, method 1); not more than 0.0005%.

Assay Transfer about 1.5 g, accurately weighed, to a separator, add 25 ml of water, 50 ml of ether and 2 drops of methyl orange IS, titrate with hydrochloric acid (0.5 mol/L) VS with constant shaking until the colour of the aqueous phase changes to reddish orange. Transfer the aqueous layer to a conical flask with stopper, wash the ether layer with 5 ml of water, add the washing to the conical flask. Add 20 ml of ether, complete the titration with hydrochloric acid (0.5 mol/L) VS, with constant shaking until a persistent reddish orange colour is obtained in the aqueous layer. Each ml of hydrochloric acid (0.5 mol/L) VS is equivalent to 72.06 mg of $C_7H_5NaO_2$.

Category Pharmaceutical aid and preservative.

Storage Preserve in tightly closed containers.

Sodium Bisulfite

$NaHSO_3$ 104.06

[7631-90-5]

Sodium Bisulfate is a mixture of sodium bisulfite and sodium pyrosulfite. It contains not less than 58.5% and not more than 67.4%, calculated as sulfur dioxide (SO_2).

Description A white crystalline powder or granules; odour resembling sulfur dioxide.

Freely soluble in water; practically insoluble in ethanol or ether.

Identification (1) The aqueous solution (1→20) exhibits acidic and yields the reactions characteristic of bisulfite (Appendix III).

(2) Yields the reactions characteristic of sodium (Appendix III).

Clarity and colour of solution Dissolve 1.0 g in 10 ml of water, the solution is clear and colourless.

Thiosulfate Dissolve 1.0 g in 15 ml of water, add 5 ml of dilute hydrochloric acid, shake, and allow to stand for 5 minutes. No turbidity is produced.

Iron To 1.0 g add 2 ml of hydrochloric acid, evaporate to dryness on a water bath and dissolve the residue in a quantity of water. Carry out the limit test for iron (Appendix VIII G), using the resulting solution. Any colour produced is not more intense than that of a reference solution using 2.0 ml iron standard solution (0.002%).

Heavy metals Carry out the limit test for heavy metals (Appendix VIII H, method 1), using 1.0 g; not more than 0.002%.

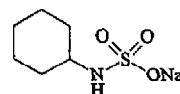
Arsenic Dissolve 0.5 g in 10 ml of water, add 1 ml of sulfuric acid, evaporate on a sand bath until white fumes are evolved, cool. Dissolve the residue in 21 ml of water and add 5 ml of hydrochloric acid. Carry out the limit test for arsenic (Appendix VIII J, method 2); not more than 0.0004%.

Assay To about 0.15 g, accurately weighed, add 50 ml of iodine (0.05 mol/L) VS, accurately measured, stopper and shake until dissolved. Allow to stand in dark for 5 minutes. Titrate with sodium thiosulfate (0.1 mol/L) VS, add 1 ml of starch IS towards the end of the titration and continue the titration until the blue colour disappears. Perform a blank determination and make any necessary correction. Each ml of iodine (0.05 mol/L) VS is equivalent to 3.203 mg of SO_2 .

Category Pharmaceutical aid.

from light.

Sodium Cyclamate



$C_6H_{12}NNaO_3S$ 201.22

[139-05-9]

Sodium Cyclamate is sodium *N*-cyclohexylsulfamate. It contains not less than 98.0% of $C_6H_{12}NNaO_3S$, calculated on the dried substance.

Description A white, crystalline powder; odourless; taste, sweet.

Freely soluble in water, very slightly soluble in ethanol; practically insoluble in chloroform or ether.

Identification (1) Dissolve 0.1 g in 10 ml of water, add 1 ml of hydrochloric acid and 1 ml of barium chloride solution (1→10); the solution is clear. Add 1 ml of sodium nitrite solution (1→10); a white precipitate is produced.

(2) The infrared absorption spectrum (Appendix IV C) is concordant with the reference spectrum of Sodium Cyclamate (Appendix XVI).

(3) The aqueous solution yields the reactions characteristic of sodium salts (Appendix III).

Acidity or alkalinity The pH of a 100 mg per ml solution in water is 5.5–7.5 (Appendix VI H).

Light absorption The absorption of a 100 mg per ml solution in water at 420 nm is not more than 0.022 (Appendix IV A).

Sulfate Carry out the limit test for sulfates (Appendix VIII B), using 0.5 g. Any opalescence produced is not more pronounced than that of a reference using 1.2 ml of preparation 0.024%.

Cyclohexylamine Reference preparation Place 0.1 g of cyclohexylamine CRS, accurately weighed, in 100 ml volumetric flask, add 50 ml of hydrochloric acid solution (1→100) to dissolve and dilute to volume with water, mix well. Dilute a quantity of the solution, accurately measured, with water to produce the reference solution of 2.5 µl per ml.

Test preparation Weigh accurately 10 g to a 100 ml volumetric flask, add water to dissolve and dilute to volume with water, shake well.

Procedure Transfer 10 ml each of the two preparations, accurately measured, to two 60 ml separators, add 3.0 ml of the alkaline solution of disodium edetate (dissolve 10 g of disodium edetate and 3.4 g of sodium hydroxide in 100 ml of water) and 15.0 ml of chloroform-*n*-butanol (20 : 1), shake for 2 minutes and allow it to stand until separation takes place. Separate the chloroform layer, and then measure accurately 10 ml each of the chloroform extracts to other two separators, add 2.0 ml of methyl orange-boric acid solution (dissolve 200 mg of methyl orange CRS and 3.5 mg of boric acid CRS in 100 ml of water, heat in water bath to dissolve and allow to stand for 24 hours; filter before use); shake for 2 minutes and allow to stand. Separate the chloroform layer, add 1 g of anhydrous sodium sulfite CRS, shake and allow to stand. Measure accurately 5 ml each of the chloroform extracts to two cylinders, add 0.5 ml of methanol-sulfuric acid and shake well, any colour produced

measure separately the absorbances at 520 nm (Appendix IV A), the absorbance of the test solution is not greater than that of the reference solution (0.0025%).

Loss on drying When dried to constant weight at 105°C, loses not more than 1.0% of its weight (Appendix VIII L).

Heavy metals Dissolve 1.0 g in 23 ml of water, add 2 ml of acetate BS (pH 3.5). Carry out the limit test for heavy metals (Appendix VIII H, method 1); not more than 0.001%.

Arsenic Dissolve 2.0 g in 22 ml of water, add 5 ml of hydrochloric acid CRS. Carry out the limit test for arsenic (Appendix VIII J, method 1); not more than 0.0001%.

Assay To 0.16 g, accurately weighted, add 40 ml of glacial acetic acid, heat gently to dissolve and cool. Add two drops of crystal violet IS and titrate with perchloric acid (0.1 mol/L) VS until the solution becomes green. Perform a blank determination and make any necessary correction. Each ml of perchloric acid (0.1 mol/L) VS is equivalent to 20.12 mg of $C_6H_{12}NNaO_3S$.

Category Pharmaceutical aid and sweetening agent.

Storage Preserve in tightly closed containers.

Sodium Hydroxide

NaOH 40.00 [1310-73-2]

Sodium Hydroxide contains not less than 96.0% of total alkali, calculated as sodium hydroxide (NaOH); and not more than 2.0% of sodium carbonate (Na_2CO_3), calculated on the basis of total alkali.

Description White, fused pellets, cubes, sticks or flakes; dry, hard, brittle and showing a crystalline fracture; very hygroscopic; rapidly absorbs carbon dioxide in the air. Very soluble in water, freely soluble in ethanol.

Identification The aqueous solution yields the reactions characteristic of sodium salts (Appendix III).

Chloride Carry out the limit test for chlorides (Appendix VIII A), using 0.50 g. Any opalescence produced is not more pronounced than that of a reference solution using 5.0 ml of sodium chloride standard solution (0.01%).

Sulfate Carry out the limit test for sulfates (Appendix VIII B), using 1.0 g. Any opalescence produced is not more pronounced than that of a reference solution using 2.0 ml of potassium sulfate standard solution (0.02%).

Potassium Dissolve 0.25 g in 5 ml of water, acidify with acetic acid; allow to cool in an ice bath and add a few drops of sodium cobaltinitrite TS. No opalescence is produced.

Aluminum and iron Dissolve 5.0 g in 50 ml of dilute hydrochloric acid, boil, allow to cool, make alkaline with ammonia TS and filter. Wash the residue with water thoroughly and ignite to constant weight, the residue is not more than 5 mg.

Heavy metals Dissolve 1.0 g in 5 ml of water and 11 ml of dilute hydrochloric acid, boil, allow to cool. Add 1 drop of phenolphthalein IS and a quantity of ammonia TS until the solution becomes pink. Add 2 ml of acetate BS (pH 3.5) and a quantity of water to produce 25 ml. Carry out the limit test for heavy metals (Appendix VIII H, method 1); not more than 0.003%.

volumetric flask in a quantity of freshly boiled and cooled water, allow to cool, dilute to volume with water and mix well. To 25 ml of the resulting solution, accurately measured, add 3 drops of phenolphthalein IS, titrate with sulfuric acid (0.1 mol/L) VS until the pink colour disappears. Read the volume (ml) of sulfuric acid (0.1 mol/L) VS consumed; add 2 drops of methyl orange IS, continue the titration with sulfuric acid (0.1 mol/L) VS until a persistent orange-red colour is produced. Each ml of sulfuric acid (0.5 mol/L) VS used in the combined titrations is equivalent to 8.00 mg of total alkali, calculated as NaOH. Each ml of sulfuric acid (0.1 mol/L) VS used in the second titration is equivalent to 21.20 mg of Na_2CO_3 .

Category Pharmaceutical aid, alkalizing agent.

Storage Preserve in tightly closed containers.

Sodium Lauryl Sulfate

Sodium Lauryl Sulfate is a mixture of sodium alkyl sulfates consisting chiefly of sodium lauryl sulfate ($C_{12}H_{25}NaO_4S$).

Description A white or pale yellow powder or crystals with a slight characteristic odour.

Freely soluble in water; practically insoluble in ether.

Identification (1) The aqueous solution (1→10) yields the reactions characteristic of sodium salts (Appendix III). (2) Acidify the aqueous solution (1→10) with hydrochloric acid, gently heat to boiling for 20 minutes. The solution gives the reactions characteristic of sulfate (Appendix III).

Alkalinity Dissolve 1.0 g in 100 ml of water, add 2 drops of phenol red IS. Not more than 0.60 ml of hydrochloric acid (0.1 mol/L) VS is required to change the colour of the indicator.

Sodium chloride Dissolve about 5 g, accurately weighed, in 50 ml of water. Add diluted nitric acid until the solution is neutral (adjust pH to 6.5-10.5), add 2 ml of potassium chromate IS, and titrate with silver nitrate (0.1 mol/L) VS. Each ml of silver nitrate (0.1 mol/L) VS is equivalent to 5.844 mg of NaCl.

Sodium sulfate Dissolve about 1 g, accurately weighed, in 10 ml of water. Add 100 ml of ethanol, heat to nearly boiling for 2 hour, filter while still hot. Wash the residue with 100 ml of boiling ethanol, then dissolve the residue in 150 ml of water and wash the container. To this solution add 10 ml of hydrochloric acid, heat to boiling, add 10 ml of 25% barium chloride, allow to stand overnight, filter. Wash the residue with water until the washings yield no reactions characteristic of chloride, then ignite to constant weight at 500-600°C. The combined content of the residue and sodium chloride is not more than 8.0%.

Non-esterified alcohols Dissolve about 10 g, accurately weighed, in 100 ml of water. Add 100 ml of ethanol and extract the solution with three quantities, each of 50 ml, of *n*-hexane, adding sodium chloride, if necessary, to promote separation of the two layers. Wash the combined *n*-hexane layers with three quantities, each of 50 ml, of water, dry with anhydrous sodium sulfate, filter and evaporate on a water bath. Heat the residue at 105°C for 30 minutes and cool. The weight of residue is not more than 4.0% of the weight of Sodium Lauryl Sulfate taken.

Total alcohols Dissolve about 5 g, accurately weighed, in 150 ml of water. Add 50 ml of hydrochloric acid, boil

the solution with two quantities, each of 75 ml, of ether, evaporate the combined ether layers on a water bath, heat the residue at 105°C for 30 minutes, cool and weigh. The residue represents the total alcohols, and is not less than 59.0% of the weight of Sodium Lauryl Sulfate taken.

Category Pharmaceutical aid.

Storage Preserve in tightly closed containers.

um Py sulf te

$\text{Na}_2\text{S}_2\text{O}_5$ 190.10

Sodium pyrosulfite contains not less than 95.0% of $\text{Na}_2\text{S}_2\text{O}_5$.

Description Colourless prismatic crystals or a white powder; odour, sulfurous; taste, sour and saline, changes gradually to yellow colour on standing; aqueous solution yields an acidic reaction.

Freely soluble in water; very slightly soluble in ethanol.

Identification (1) A solution in water decolourizes iodine TS and the resulting solution yields the reactions characteristic of sulfates (Appendix III).

(2) Yields the flame test characteristic of sodium salts (Appendix III).

Thiosulfate Dissolve 1.1 g in 10 ml of dilute hydrochloric acid and heat on a water bath for 10 minutes. Allow it to cool, transfer to a Nessler cylinder and dilute with water to 20 ml. Any opalescence produced is not more pronounced than that of a reference solution using 0.20 ml of sodium thiosulfate (0.1 mol/L) VS (0.2%).

Iron Dissolve 1.0 g in 5 ml of water and 2 ml of hydrochloric acid and evaporate to dryness on a water bath. Dissolve the residue in 15 ml of water and 2 ml of hydrochloric acid, add a quantity of bromine TS until the pale yellow colour is produced, heat to remove the excess of bromine, cool and dilute with water to 25 ml. Carry out the limit test for iron (Appendix VIII G). Any colour produced is not more intense than that of a reference solution using 2.0 ml of iron standard solution (0.002%).

Heavy metals Dissolve 1.0 g in 10 ml of water, add 5 ml of hydrochloric acid, evaporate to dryness on a water bath. To the residue add 15 ml of water, boil gently for 2 minutes and filter. To the filtrate add a quantity of bromine TS to make the solution clear, heat to remove the excess of bromine and cool. Add 1 drop of phenolphthalein IS and a quantity of ammonia TS until the solution turns to pink colour, add 2 ml of sodium acetate BS (pH 3.5) and a quantity of water to 25 ml. Carry out the limit test for heavy metals (Appendix VIII H, method 1); not more than 0.002%.

Arsenic Dissolve 1.0 g in 4 ml of water, add 3 ml of nitric acid and evaporate to dryness on a water bath. To the residue add a few ml of water, shake and filter. Wash the residue with water, combine the washings and filtrate, evaporate to dryness. Dissolve the residue in 5 ml of hydrochloric acid and 23 ml of water. Carry out the limit test for arsenic (Appendix VIII J, method 1); not more than 0.0002%.

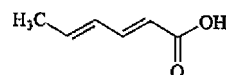
Assay To about 0.15 g, accurately weighed, in an iodine flask add 50 ml of iodine (0.05 mol/L) VS, accurately measured, stopper the flask and shake, add 1 ml of hydrochloric acid and titrate the excess of iodine with sodium thiosulfate (0.1 mol/L) VS, add 2 ml of starch IS towards the end of titration and continue the titration until the blue

any necessary correction. Each ml of iodine (0.05 mol/L) VS is equivalent to 4.752 mg of $\text{Na}_2\text{S}_2\text{O}_5$.

Category Pharmaceutical aid, antioxidant.

Storage Preserve in tightly closed containers, protected from light.

Sorbic Acid



$\text{C}_6\text{H}_8\text{O}_2$ 112.13

[22500-92-1]

Sorbic Acid is (E, E)-2,4-hexadienoic acid. It contains not less than 98.5% of $\text{C}_6\text{H}_8\text{O}_2$, calculated on the dried basis.

Description A white or pale yellowish white crystalline powder; odour characteristic.

Freely soluble in ethanol; soluble in ether; very slightly soluble in water.

Melting range 132-136°C (Appendix VI C).

Identification (1) Dissolve about 0.2 g in 2 ml of ethanol, add a few drops of bromine TS, the colour of bromine disappears immediately.

(2) The light absorption of a solution of 2.5 µg per ml in hydrochloric acid solution (0.1 mol/L) exhibits a maximum at 264 nm (Appendix IV A).

(3) The infrared absorption spectrum (Appendix IV C) is concordant with the reference spectrum of sorbic acid (Appendix XVI).

Clarity and colour of ethanol solution A solution of 1.0 g in 50 ml of ethanol is clear and colourless.

Water Carry out the determination of water, not more than 0.5% (Appendix VIII M, method 1 A).

Residue on ignition Not more than 0.1% (Appendix VIII N); use 1.0 g.

Heavy metals Carry out the limit test for heavy metals (Appendix VIII H, method 2), using the residue obtained in the test for Residue on ignition; not more than 0.001%.

Assay Dissolve about 0.25 g, accurately weighed, in 25 ml of neutral ethanol (neutral to phenolphthalein IS), add a few drops of phenolphthalein IS, titrate with sodium hydroxide (0.1 mol/L) VS. Each ml of sodium hydroxide (0.1 mol/L) VS is equivalent to 11.21 mg of $\text{C}_6\text{H}_8\text{O}_2$.

Category Pharmaceutical aid, Antiseptic.

Storage Preserve in tightly closed containers, protected from light, and stored in a cool place.

Soybean Oil

Soybean Oil is the refined fixed oil obtained from the seeds of the soya plant *Glycine soya* Bentham.

Description A pale yellow, clear liquid; odourless or almost odourless.

Miscible with ether or chloroform; very slightly soluble in ethanol; practically insoluble in water.

Refractive index 1.472-1.476 (Appendix VI F).

Acid value Not more than 0.2 (Appendix VII H).

Saponification value 188-200 (Appendix VII H).

Iodine value 126-140 (Appendix VII H).

Peroxide Dissolve 10.0 g in 30 ml of acetic acid-chloroform (60 : 40) in a 250 ml iodine flask with shaking. Add accurately 0.5 ml of saturated potassium iodide solution, stopper the flask, shake thoroughly for 1 minute and add 30 ml of water. Titrate with sodium thiosulfate (0.01 mol/L) VS Add 0.5 ml of starch TS towards the end point and continue the titration until the blue colour disappears. Perform a blank determination and make any necessary correction. Not more than 10.0 ml of sodium thiosulfate (0.01 mol/L) VS is consumed.

Unaponifiable matter Place 5.0 g in a 250 ml conical flask, add 50 ml of potassium hydroxide solution in ethanol (dissolve 12 g of potassium hydroxide in 10 ml of water, dilute to 100 ml with ethanol). Reflux the mixture for 1 hour, cool to below 25°C. Transfer the solution to a separator, wash the flask with two portions of water, each of 50 ml, and combine the washings to the separator. Extract with three portions of ether, each of 100 ml, combine the ether layer to another separator, wash with three portions of water, each of 40 ml, discard the washings. Wash the ether layer with 3% sodium hydroxide solution and water three times respectively, each of 40 ml, then wash with water for several times until no red colour is produced when dropping two drops of phenolphthalein IS, each of 40 ml. Transfer the ether extract to a evaporating dish, previously dried to constant weight, wash the separator with 10 ml of ether, transfer the washing to the evaporating dish, evaporating ether on a 50°C water bath, dissolve the residue with 6 ml of acetone, expel the acetone with current air. Dry at 105°C until the variation between two continuous weight is less than 1 mg, the content of the unaponifiable matter is not more than 1.0%.

Dissolve the residue with 20 ml of neutralized ethanol, add a few drops of phenolphthalein IS and titrate with ethanolic sodium hydroxide (0.1 mol/L) VS until a pink colour last 30 seconds, the test is invalid if more than 0.2 ml ethanolic sodium hydroxide (0.1 mol/L) VS is consumed, and the test must be done again.

Note : Ethanolic sodium hydroxide (0.1 mol/L) VS

Preparation Measure 2 ml of 50% sodium hydroxide solution, add 250 ml of ethanol (allow to stand over night if the solution is opalescence, and using the supernatant for standardization).

Standardization Dissolve about 0.2 g of benzoic acid, weighed accurately, in 10 ml of ethanol and 2 ml of water, add 2 drops of phenolphthalein IS and titrate with ethanolic sodium hydroxide (0.1 mol/L) VS until a persistent pink colour is produced. Each ml of ethanolic sodium hydroxide (0.1 mol/L) VS is equivalent to 12.21 mg of benzoic acid.

Heavy metals Transfer 4.0 g to a 50 ml porcelain evaporating dish, add 4 ml of sulfuric acid, mix well, heat gently until the sulfuric fumes are no longer evolved, add 2 ml of nitric acid and 5 drops of sulfuric acid, heat until nitrous oxide fumes are no longer evolved and ignite at 500-600°C until the incineration is complete. Cool, carry out the limit test for heavy metals (Appendix VIII H, method 2); not more than 0.0005%.

Cottonseed oil Mix 5 ml in a test tube with a mixture of equal volumes of pentanol and 1% solution of sulfur in carbon disulfide. Place the test tube in a saturated sodium chloride water bath, warm the mixture carefully, when no

it for 15 minutes, no red colour develops.

Fatty acid composition Carry out the method for gas chromatography (Appendix V B), using a column packed with 12% polyethylene-glycol succinate as the stationary phase, and maintain the column temperature at 175°C, the number of the theoretical plates of the column is not less than 1300, calculated with reference to the peak of linoleate.

Test solution Place 20 mg in a 10 ml test tube with stopper. Add 2 ml of 0.5 mol/L methanolic potassium hydroxide solution, saponify the fatty acid for about 15 minutes in the water bath at 65°C until the oleosome is dissolved. Cool, add 2 ml of 15% methanolic boron trifluoride, esterify the fatty acid for 2 minutes in the water bath at 65°C. Cool, add 2 ml of *n*-hexane, shake well, add 2 ml of saturated sodium chloride solution. use the upper layer.

Procedure Inject 1 µl of the upper layer into the column, measure the 5 main peak areas of the methyl esters of the fatty acid. The order of elution is palmitate, stearate, oleate, linoleate and linolenate, and their relative areas, expressed as percentages of the total area of the 5 main peaks, are in the ranges 7.0-14.0, 1.0-6.0, 18.0-30.0, 44.0-62.0 and 4.0-11.0.

Category Pharmaceutical aid.

Storage Preserve in tightly closed containers, protected from light, and stored in cool and dark place.

Starch

Starch is polysaccharide granules obtained from the caryopsis of maize (*Zea mays* L.) or from the tuber root of cassava (*Manihot utilisima* Pohl.)

Description A white powder; odourless; tasteless. Insoluble in cold water or ethanol.

Identification (1) Boil about 1 g with 15 ml of water, cool. A translucent whitish gelatinous substance is produced. (2) Mix about 0.1 g with 20 ml of water, add a few drops of iodine TS. A blue or dark blue colour is produced which gradually disappears on heating and reappears on cooling. (3) Examine under microscope with glycerine-acetic acid TS (Appendix II C, Volume I):

Maize starch: Simple grains, polygonal or ovoid, 5-30 µm in diameter. Central hilum, rounded or star-shaped. Striations indistinct.

Cassava starch: Simple grains, rounded or elliptical, 5-35 µm in diameter, consisting of a cavity on the side. Central hilum, rounded or star-shape. Striations indistinct.

(4) Under polarised microscope: both with polarized cross, intersecting at the hilum.

Acidity Shake 20.0 g with 100 ml of water for 5 minutes, determine the pH value immediately (Appendix VI H): pH 4.5-7.0.

Loss on drying When dried at 105°C for 5 hours, loses not more than 14.0% of the weight of maize starch and not more than 15.0% of the weight of cassava starch (Appendix VIII L).

Ash Weigh accurately about 1 g into a crucible, previously ignited to constant weight, ignite slowly until the substance being examined is completely carbonized. Raise the temperature gradually to 600-700°C, incinerate completely to constant weight. The remaining ash is not more than 0.2% of the weight of maize starch and not more than 0.3% of the

Iron To 0.50 g add 4 ml of dilute hydrochloric acid and 16 ml of water, shake for 5 minutes, filter and wash the residue with small quantity of water. Combine the filtrate and washings, add 50 mg of ammonium persulfate and dilute with water to 35 ml. Carry out the limit test for iron (Appendix VIII G). Any colour produced is not more intense than that of a reference solution using 1.0 ml of iron standard solution (0.002%).

Sulfur dioxide To 20.0 g in a conical flask with stopper add 200 ml of water, shake thoroughly and filter. To 100 ml of filtrate add 2 ml of starch IS and titrate with iodine (0.005 mol/L) VS. Perform a blank determination and make any necessary correction. The iodine (0.005 mol/L) VS consumed does not exceed 1.25 ml (0.004%).

Oxidizing substance Transfer 4.0 g of the substance being examined to a conical flask with stopper, add 50.0 ml of water, cover the stopper and shake for 5 minutes, transfer to a 50 ml centrifuge tube with stopper, centrifuge until the solution is clear. Transfer 30.0 ml of the supernatant liquid to a iodine flask, add 1 ml of acetic acid glacial and 1.0 g of potassium iodide, cover the stopper, shake, allow to stand for 30 minutes in a dark place. Add 1 ml of starch IS, and titrate with sodium thiosulfate (0.002 mol/L) VS until the blue colour disappears. Perform a blank determination and make any necessary correction. Each ml of sodium thiosulfate (0.002 mol/L) VS is equivalent to 34 µg of oxidized substance (calculated as H_2O_2), not more than 1.4 ml of sodium thiosulfate (0.002 mol/L) VS is consumed (0.002%).

Microbial limit Comply with test for microbial limit (Appendix XI J), except that number of bacterial is not more than 1000 and that of fungi is not more than 100 per g, *Escherichia coli* is not detected.

Category Pharmaceutical aid, expient.

Storage Preserve in a dry place.

Stearic Acid

Stearic Acid is a mixture of solid fatty acid obtained from fats and oils of animal or botanical resources. Its principal components are stearic acid ($C_{18}H_{36}O_2$) and palmitic acid ($C_{16}H_{32}O_2$).

Description A white or almost white creamy powder of crystalline mass. Its cross section shows needle crystals slightly lustrous; odour, slight; tasteless. Freely soluble in chloroform or ether; soluble in ethanol; practically insoluble in water.

Congeeing point Not lower than 54°C (Appendix VI D).

Iodine value Not greater than 4 (Appendix VII H).

Acid value 203-210 (Appendix VII H).

Water soluble acids Heat 5.0 g to melt, add an equal volume of boiling water, shake for 2 minutes, allow to cool and filter. Add 1 drop of methyl red IS to the filtrate, no red colour is produced.

Neutral fats or waxes Boil 1.0 g with 0.5 g of anhydrous sodium carbonate and 30 ml of water. The solution is clear.

Residue on ignition Not more than 0.1% (Appendix VIII N); use 4.0 g.

Heavy metals Carry out the limit test for heavy metals (Appendix VIII H, method 2), using the residue obtained in

Category Pharmaceutical aid, excipient.

Storage Preserve in tightly closed containers.

Steviosin

Steviosin is a mixed glucoside containing mainly steviosin ($C_{38}H_{60}O_{18}$). It contains not less than 95.0% of steviosin ($C_{38}H_{60}O_{18}$), calculated on the dried basis.

Description A white or almost white powder; odourless; taste, very sweet with light bitter. Soluble in ethanol; slightly soluble in water.

Identification Carry out the method for thin-layer chromatography (Appendix V B), using silica gel G as the coating substance and the lower layer of a mixture of chloroform-methanol-water (65 : 35 : 10) as the mobile phase. Apply separately to the plate 2 µl each of the two solutions in dehydrated ethanol containing (1) 10 mg of the substance being examined per ml and (2) 10 mg of steviosin CRS per ml. After developing and removal of the plate, dry in air and spray with 30% ethanolic sulfuric acid solution, heat at 110°C for about 15 minutes. The colour and position of the principal spot in the chromatogram obtained with solution (1) correspond to the principal spot obtained with solution (2).

Acidity To 0.5 g add 20 ml of ethanol (neutral to phenolphthalein IS), shake to dissolve steviosin, add 1 drop of phenolphthalein IS, titrate with sodium hydroxide (0.1 mol/L) VS. Not more than 0.5 ml of sodium hydroxide (0.1 mol/L) VS is required to change the colour of the solution which lasts at least 10 seconds.

Loss on drying When dried to constant weight at 105°C, loses not more than 5.0% of its weight (Appendix VIII L).

Residue on ignition Not more than 0.1% (Appendix VIII N); use 1.0 g.

Heavy metals Carry out the limit test for heavy metals (Appendix VIII H, method 2), using the residue obtained in the test for Residue on ignition; not more than 0.002%.

Assay To about 0.3 g, accurately weighed, in a 250 ml conical flask add 25 ml each of dilute sulfuric acid TS and water. Shake to dissolve steviosin, hydrolyze by heat to slightly boiling for 30 minutes, cool and filter. Wash the residue with water until the washing exhibits neutral reaction. Dissolve it in 50 ml of ethanol (neutral to phenolphthalein IS), add 2 drops of phenolphthalein IS, titrate with ethanolic potassium hydroxide (0.05 mol/L) VS until the colour changes to red which lasts at least 10 seconds. Each ml of ethanolic potassium hydroxide (0.05 mol/L) VS is equivalent to 40.24 mg of $C_{38}H_{60}O_{18}$.

Category Pharmaceutical aid, flavouring agent.

Storage Preserve in tightly closed containers.

Strong Ammonia Solution

(Concentrated Ammonia Solution)

Strong Ammonia Solution contains 25.0%-28.0% (g/g) of ammonia (NH_3).

Description A clear, colourless liquid; odour, strongly pungent and characteristic; volatile; strongly alkaline.

Relative density 0.900-0.908 (Appendix VI A).

Identification Dip a glass rod into hydrochloric acid, and hold it above the surface of the substance being examined, dense white fumes are produced.

Readily oxidizable substance Boil 2.0 ml with 3 ml of water, 40 ml of diluted sulfuric acid and 0.10 ml of potassium permanganate solution (0.02 mol/L) for 5 minutes, the pink colour does not disappear completely.

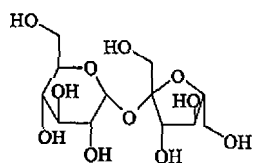
Heavy metals Evaporate 20 g (22 ml) to dryness on a water bath, add 1 ml of hydrochloric acid and evaporate to dryness again. Dissolve the residue in 2 ml of acetate BS (pH 3.5) and 23 ml of water. Carry out the limit test for heavy metals (Appendix VIII H, method 1); not more than 0.0001%.

Assay Transfer 2 ml, accurately weighed, to a tared stoppered conical flask containing 25 ml of water, add 2 drops of methyl red IS and titrate with sulfuric acid (0.5 mol/L) VS. Each ml of sulfuric acid (0.5 mol/L) VS is equivalent to 17.03 mg of NH_3 .

Category Pharmaceutical aid.

Storage Preserve in tightly closed containers, stored at a temperature below 30°C.

Sucrose



$\text{C}_{12}\text{H}_{22}\text{O}_{11}$ 342.30

[57-50-1]

Sucrose is β -D-fructofuranosyl- α -D-glucopyranoside.

Description Colourless crystals or a white, loose crystalline powder; odourless; taste, sweet. Very soluble in water; slightly soluble in ethanol; insoluble in chloroform or ether.

Specific optical rotation Not less than +66°, in a solution of 0.1 g per ml in water (Appendix VI E).

Identification (1) Heat the substance being examined with a direct flame. It melts and swells, then burns with an odour of caramel, leave a large amount of charcoal.

(2) Boil with sulfuric acid (0.05 mol/L) solution, neutralize with sodium hydroxide (0.1 mol/L) solution and add alkaline cupric tartrate TS. A red precipitate of cuprous oxide is produced on heating.

Colour of solution Dissolve 5 g in 5 ml of water. Any colour produced is not more intense than that of reference solution Y_6 (Appendix IX A, method 1).

Sulfate Carry out the limit test for sulfates (Appendix VIII B), using 1.0 g. Any opalescence produced is not more pronounced than that of a reference using 5.0 ml of potassium sulfate standard solution (0.05%).

Reducing sugar Place 5.0 g in a 250 ml conical flask, dissolve it with 25 ml of water, add accurately 25 ml of alkaline cupric citrate TS and a few pieces of glass beads. Allow to boil under reflux within 3 minutes and kept boiling for 5 minutes. Cool rapidly to room temperature, take care to avoid the contact of cuprous oxide with air. Add 15 ml of

Add slowly 25 ml of sulfuric acid solution (1→5) with constant swirling until no more carbon dioxide is evolved. Titrate immediately with sodium thiosulfate (0.1 mol/L) VS. Add 2 ml of starch IS when the end point is nearly approached, continue the titration until the blue colour disappears. Perform a blank determination and make any necessary correction. The difference of amounts of sodium thiosulfate (0.1 mol/L) VS consumed between the determination and the blank determination does not exceed 2.0 ml (0.10%).

Residue on ignition Not more than 0.1% (Appendix VIII N), using 2.0 g.

Calcium Dissolve 1.0 g in 25 ml of water, add 1 ml of ammonia TS and 5 ml of ammonium oxalate TS, mix well and allow to stand for 1 hour. Any opalescence produced is not more pronounced than that of a reference using 5.0 ml of calcium standard solution (place 0.125 g of calcium carbonate, accurately weighed, in a 500 ml volumetric flask, add 5 ml of water and 0.5 ml of hydrochloric acid to effect dissolution, add water to volume, mix well. Each ml of the solution is equivalent to 0.10 mg of Ca) (0.05%).

Heavy metals Carry out the limit test for heavy metals (Appendix VIII H, method 2), using the residue obtained in the test for Residue on ignition; not more than 0.0005%.

Category Pharmaceutical aid, sweetener and excipient.

Storage Preserve in tightly closed containers, stored in a dry place.

Sucrose Stearate S-3, S-7, S-11, S-15

Sucrose Stearate S-3, S-7, S-11, S-15 are a mixture of sucrose stearates.

Description A white to slightly yellowish brown block solid or powder; odourless or with a slight odor; tasteless. Soluble in hot *n*-butanol, chloroform or tetrahydrofuran.

Identification Shake to dissolve 0.5 g in a mixture of 20 ml of *n*-butanol and 20 ml of a 5% solution of sodium chloride, previously heated to 40-60°C, allow to separate, discard the aqueous layer, wash the *n*-butanol phase with 40 ml of a 5% solution of sodium chloride in two portions, previously heated to 40-60°C. To about 2 ml of the *n*-butanol phase in an inclined test tube, add slowly about 3 ml of anthrone TS along the wall until two layers are produced, heat on a water bath at 60°C for 3 minutes; a blue to green colour between the two phases is produced.

Loss on drying When dried in vacuum over phosphorous pentoxide to constant weight at 60°C, loses not more than 3.0% of its weight (Appendix VIII L).

Acidity value Dissolve 4 g, accurately weighed, in 40 ml of tetrahydrofuran and 20 ml of water by gently heating, cool. Carry out the method of potentiometric titration (Appendix VII A), titrate with sodium hydroxide (0.1 mol/L) VS to pH 8.20. Perform a blank determination and make any necessary correction. Acidity value is not more than 5.0 (Appendix VII H).

Free sucrose Remove the silica gel zone at the origin of the plate obtained under Content of monoester and carry out the test beginning at the words "to a 10 ml centrifuge test tube...". The absorbance is not greater than 0.105 (5.0%).

Water Not more than 3.0%, using about 0.5 g, accurately

Residue on ignition Not more than 1.5% (Appendix VIII N), using 1.0 g.

Heavy metals Carry out the limit test for heavy metals (Appendix VIII H, method 2), using the residue obtained in the test for Residue on ignition: not more than 0.002%.

Arsenic To 2.0 g, add 5 ml of each of sulfuric acid and nitric acid, heat gently to boiling; add dropwise nitric acid, 2-3 ml each time, until the colour of the solution changes to colourless or pale yellow. Cool, add 15 ml of saturated ammonium oxalate solution, heat until heavy smoke is produced, condense the solution to 2-3 ml, cool and dilute with water to 25 ml. Carry out the limit test for arsenic (Appendix VIII J, method 1): not more than 0.0001%.

Content of monoester Sucrose Stearates are divided into Sucrose Stearate S-3, S-7, S-11 and S-15 according to the relative content of monoester in total esters. The contents of monoester of Sucrose Stearate S-3, S-7, S-11, and S-15 are 0%-24%, 25%-44%, 45%-64% and not less than 65%, respectively.

Dissolve about 0.2 g, accurately weighed, in chloroform in a 10 ml volumetric flask, dilute to volume and mix well. Carry out the method for thin-layer chromatography (Appendix V B), using silica gel G as the coating substance and the mixture of chloroform-methanol-glacial acetic acid-water (80 : 10 : 8 : 2) as the mobile phase. Apply to the plate 20 μ l of the above solution. After developing and removal of the plate, dry it in air, heat at 100°C for 30 minutes, cool and spray with moric acid solution (dissolve 50 mg of moric acid in methanol and dilute to 100 ml). Examine under ultraviolet light at 365 nm and identify the spots of monoester (M; the first one nearest to the origin), diester (D; the second-fourth one in the middle) and triester (T; the first-fourth one farthest to the origin) in the chromatogram (the distance between the three groups of spots is relatively larger). Remove separately the M, D and T zone from the plate to three separate 10 ml centrifuge test tubes, add 1 ml of ethanol and 7 ml of anthrone TS, both accurately measured, and mix well. Heat on a water bath at 60°C for 20 minutes, cool, centrifuge at a speed of 2500 rpm for 15 minutes and use the supernatant liquid as a test solution. Remove the silica gel zone of similar size at the blank of the plate and prepare a blank solution in the same manner. Measure the absorbances of the resulting solutions at 625 nm (Appendix IV A). Calculate the content of monoester as follows (taking the total esters as 100%).

$$\begin{aligned} & \text{Sucrose monostearate\%} \\ &= \frac{1.754A_M}{1.754A_M + 2.508A_D + 3.261A_T} \times 100\% \end{aligned}$$

Category Pharmaceutical aid.

Storage Preserve in tightly closed containers, stored in a dry place.

Titanium Dioxide

TiO₂ 79.88 [13463-67-7]

The content of TiO₂ is not less than 98.0%, calculated on the dried basis.

Description A white powder; odourless; tasteless. Insoluble in water, hydrochloric acid, nitric acid or dilute sulfuric acid.

Identification To about 0.5 g add 5 g of anhydrous sodium sulfate and 10 ml of water, shake thoroughly, add 10 ml of sulfuric acid, heat to boiling, until the solution is clear.

slowly, dilute with water to 100 ml and mix well. Proceed the test of Identification as follows.

(1) To 5 ml of the solution add several drops of hydrogen peroxide TS; an orange-red colour is produced.

(2) To 5 ml of the solution add several granules of zinc granule, allow to stand for 45 minutes; a blueish-violet colour is produced.

Water-soluble substances To 10.0 g add 0.5 g of ammonium sulfate and 150 ml of water, heat to boiling for 5 minutes, cool, dilute with water to 200 ml, mix well, filter through double layer of quantitative filter paper, discard the initial filtrate. Measure accurately 100 ml of the successive filtrate, evaporate to dryness, ignite the residue at 600°C to constant weight. The residue is not more than 12.5 mg (0.25%).

Acid-soluble substances To 5.0 g add 100 ml of 0.5 mol/L hydrochloric acid solution, heat on a water bath for 30 minutes with stirring occasionally, filter through three layers of quantitative filter paper, wash the residue with hydrochloric acid solution (0.5 mol/L). Combine the filtrate and washings, evaporate to dryness, ignite the residue at 600°C to constant weight. The residue is not more than 25 mg (0.5%).

Barium To 1 ml of the solution obtained in the Assay add 1 ml of dilute sulfuric acid, allow to stand; no opalescence or precipitate is produced.

Loss on drying When dried at 105°C for 3 hours to constant weight, loses not more than 0.5% of its weight (Appendix VIII L).

Loss on ignition Weigh accurately about 2.0 g on dried basis, ignite at about 800°C to constant weight, loses not more than 0.5% of its weight.

Heavy metals To 2.0 g add 3 ml of hydrochloric acid, shake for 1 minute, add 10 ml of water, heat to boiling and filter. Wash the residue with water, combine the filtrate and washings to a 20 ml volumetric flask, dilute with water to volume, mix well. Measure accurately 10 ml, neutralized it to phenolphthalein IS by adding ammonia TS, then add 2 ml of dilute acetic acid, dilute with water to 25 ml. Carry out the limit test for heavy metals (Appendix VIII H, method 1): not more than 0.002%.

Arsenic Place 0.25 g in a 250 ml conical flask, add 35 ml of water, 0.3 g of hydrazine sulfate, 0.3 g of potassium bromide, 13 g of sodium chloride and 17 ml of sulfuric acid, insert a stopper fitted with a thermometer and a glass conduit, dip the other end of glass conduit into 23 ml of water in a conical flask for determination of arsenic. Heat the conical flask to 90-100°C for 15 minutes. Remove the conical flask for determination of arsenic, cool, add 5 ml of hydrochloric acid. Carry out the limit test for arsenic (Appendix VIII J, method 1): not more than 0.0008%.

Assay Place about 1.0 g, accurately weighed, in a platinum crucible, add 2 g of potassium carbonate, mix well, ignite at 900°C for 30 minutes, cool. Transfer the residue with a mixture of 20 ml of water and 30 ml of hydrochloric acid in divided portions to a 100 ml volumetric flask, heat on a water bath until the solution is clear. Allow to cool, dilute with water to volume, mix well. Measure accurately 10 ml, add 200 ml of water and 4 ml of concentrate hydrogen peroxide solution, mix well. Add 50 ml of disodium edetate (0.05 mol/L) VS, accurately measured, allow to stand for 5 minutes, add 1 drop of methylred IS, neutralize the solution with 20% sodium hydroxide solution, add 5 g of urotropine, shake to dissolve, then add 1 ml of 0.1% xylenol solution IS, titrate with zinc (0.05 mol/L) VS, until the solution turns from

disodium edetate (0.05 mol/L) VS is equivalent to 3.995 mg of TiO_2 .

Category Pharmaceutical aid, excipient.

Storage Preserve in tightly closed containers, stored in a dry place.

White Vaseline

White Vaseline is a semisolid mixture of hydrocarbons obtained from petroleum.

Description A white or yellowish homogeneous soft mass, odourless or almost odourless; unctuous to the touch on skin.

Freely soluble in benzene at about 35°C ; soluble in chloroform at about 35°C ; slightly soluble in ether; practically insoluble in ethanol or water.

Melting range $45\text{--}60^\circ\text{C}$ (Appendix VI C, method 3).

Colour Melt 10 g on a water bath by heating in a beaker. Pour it into a Nessler cylinder, compare with the same volume of the reference solution prepared by mixing well 7.8 ml of potassium dichromate standard solution CS with 0.2 ml of copper sulfate standard solution CS and diluting 2.5 ml of the resulting solution with water to 25 ml. Any colour produced is not more intense than that of the reference solution observed under reflexed light against a white background without the interference of fluorescence.

Absorbance of impurities Measure the absorbance of a solution of 0.50 mg per ml in trimethylpentane at 290 nm (Appendix IV A), not more than 0.50.

Penetrativity, Acidity or alkalinity, Organic acid, Foreign organic compounds, Residue on Ignition, Sulfide Complies with the respective requirements described under Yellow Vaseline.

Category Pharmaceutical aid, lubricant and ointment base.

Storage Preserve in tightly closed containers.

Yellow Vaseline

Yellow Vaseline is a mixture of semi-solid hydrocarbons obtained from petroleum.

Description An unctuous mass of pale yellow or yellow colour; odourless or almost odourless; when contact with skin have a satiny feeling.

Freely soluble in benzene at 35°C ; soluble in chloroform at 35°C slightly soluble in ether; practically insoluble in ethanol or water.

Melting range $45\text{--}60^\circ\text{C}$ (Appendix VI C, method 3).

Penetrativity Melt a quantity of vaselin at $85^\circ\text{C} \pm 2^\circ\text{C}$, pour it into a metallic round cylinder of $100\text{ mm} \pm 5\text{ mm}$ in diameter and not less than 65 mm in height, fill it to a volume of 6 mm below the top of container, allow to stand for 16–18 hours at $25^\circ\text{C} \pm 2^\circ\text{C}$. Before the examination, the container is immersed in a water bath at $25.0^\circ\text{C} \pm 0.5^\circ\text{C}$ for 2 hours. Place a standard cone (total weight is $102.50\text{ g} \pm 0.05\text{ g}$ with a smooth outer surface and a detachable tip, the tip of the cone having an angle of 30° with the upper part being truncated to a diameter of $0.38\text{ mm} \pm 0.02\text{ mm}$; the base of tip is $8.40\text{ mm} \pm 0.02\text{ mm}$ in diameter, $15.00\text{ mm} \pm$

angle of $90^\circ 0' \pm 15'$, $32.1\text{ mm} \pm 0.2\text{ mm}$ in height, and a maximum diameter of $69.3\text{ mm} \pm 0.1\text{ mm}$ at the base) into a water bath and adjust the temperature to $25.0^\circ\text{C} \pm 0.5^\circ\text{C}$. Take off, put on a penetrometer platform adjusted to horizontal level beforehand, with the tip of instrument at 25–38 mm apart from the wall of container to touch the top surface of the sample. Adjust the dial indicator to zero. Quickly push the “start” button, let the cone falls down freely for 5.0 ± 0.1 seconds. Adjust the level of the cone to stop the cone continuing to fall. Read the value of penetrativity from the dial. If the value is less than 200 Units, it may be determined 3 times successively, make sure that the areas of testing do not overlap. When the value is more than 200 Units, repeat the test in the center of the container. The mean deviation of 3 testing values is within $\pm 3\%$. The average value of the three determinations is taken as the penetrativity (penetrativity represents the depth of the cone reached in vaselin in 5 seconds, calculated in depth of 0.1 mm as 1 Unit), which is 130–230 Units.

Acidity or alkalinity To 35.0 g add 100 ml of water, heat to gentle boiling, stir for 5 minutes, allow to stand and cool. Separate the aqueous layer, add 1 drop of phenolphthalein IS, the solution is colourless; add 0.10 ml of methyl orange IS, no pink colour is produced.

Colour Melt 10 g in a beaker on a water bath. Pour it into Nessler cylinder, the colour is not more intense than that of a reference solution (2.0 ml of standard cobaltous chloride CS and 6.0 ml of standard potassium dichromate CS, diluted to 10 ml with water). Compare the colour against a white background to avoid fluorescence under reflected light.

Organic acids To 20.0 g add 100 ml of neutral dilute ethanol, stir and heat to boiling, add 1 ml of phenolphthalein IS and 0.40 ml of sodium hydroxide (0.1 mol/L) VS, stir vigorously; a red colour is produced.

Absorbance of impurity Dissolve a quantity in trimethylpentane to produce a solution of 0.50 mg per ml, the absorbance at 290 nm (Appendix IV A) is not greater than 0.75.

Foreign organic matter and residue on ignition Heat 2.0 g with a direct flame, no characteristic pungent odour is produced; ignite, the residue on ignition is not more than 1 mg (0.05%).

Sulfide Carry out the limit test for sulfide (Appendix VII C), using 3.0 g; not more than 0.00017%.

Category Pharmaceutical aid, lubricant and base for ointments.

Storage Preserve in tightly closed containers.

Yellow Ferric Oxide

$\text{Fe}_2\text{O}_3 \cdot \text{H}_2\text{O}$ 177.70

Yellow Ferric Oxide is ferric oxide monohydrate. It contains not less than 97.5% of Fe_2O_3 , calculated with reference to the substance freshly ignited to constant weight.

Description A ochreous powder; odourless; tasteless. Insoluble in water; freely soluble in boiling hydrochloric acid.

Identification Boil about 0.1 g with 5 ml of dilute hydrochloric acid, allow to cool, and the solution yields the reactions characteristic of ferric salts (Appendix III).

heat under reflux on a water bath for 2 hours and filter. Wash the residue with a quantity of water, evaporate the combined filtrate and washings to dryness in an evaporating dish previously dried to constant weight at 105°C, dry the residue to constant weight at 105°C: not more than 20mg (1.0%).

Acid insoluble substances Dissolve 2.0 g in 25 ml of hydrochloric acid by heating in a water bath, add 100ml of water, filter through a sintered glass crucible (No.4) previously dried to constant weight at 105°C, wash the residue with hydrochloric acid solution (1→100) until the washings become colourless, then wash the residue with water until the washings give no reaction of chlorides, dry the residue to constant weight at 105°C: not more than 20 mg (1.0%).

Loss on ignition When ignited to constant weight at 700-800°C, loses not more than 12.0% of its weight, using 1.0g.

Barium To 0.2 g add 5 ml of hydrochloric acid, heat until dissolved. Add 1 drop of hydrogen peroxide TS and 20 ml of 10% sodium hydroxide solution, filter, wash the residue with 10ml of water. Combine the filtrate and washings, add 10 ml of sulfuric acid solution (2→10), no opalescence is produced.

Lead To 0.5 g add 10 ml of hydrochloric acid, heat to dissolved. Add 3 ml of nitric acid, boil for 1 minute, allow to cool. Extract with anhydrous ether for 4 times (30 ml, 20 ml, 20 ml and 20 ml), discard the ether layer. Heat the acid solution to expel the remaining ether, add ammonia TS to make the solution alkaline, add 1 ml of potassium cyanide TS and sufficient water to produce 50 ml. Add a few drops of sodium sulfide TS and mix well. Any colour produced is not more intense than that of a reference solution prepared in the same manner using 1.5 ml of lead standard solution (0.003%).

Arsenic To 0.2 g add 7 ml of hydrochloric acid, heat until dissolved. Add 21 ml of water, and add acid stannous chloride TS dropwise until the yellow colour disappears. Carry out the limit test for arsenic (Appendix VII J, method 1): not more than 0.001%.

Assay Add to about 0.15 g, accurately weighed, in a conical flask with stopper 2.5 ml of hydrochloric acid, heat to dissolve on a water bath. Add 1 ml of hydrogen peroxide TS, heat to boiling for a few minutes, add 25 ml of water, allow to cool. Add 1.5 g of potassium iodide and 2.5 ml of hydrochloric acid, stopper and shake thoroughly, allow to stand in a dark place for 15 minutes. Titrate with sodium thiosulfate (0.1 mol/L) VS, add 2.5 ml of starch TS towards the end of titration, continue the titration until the blue colour disappears. Each ml of sodium thiosulfate (0.1 mol/L) VS is equivalent to 7.985mg of Fe₂O₃.

Category Pharmaceutical aid, colouring agent.

Storage Preserve in tightly closed containers.

Identification Dissolve about 20 mg in 90% ethanol, add a few drops of 10% lead acetate solution, a white precipitate is produced immediately.

Ether soluble substances Transfer about 1 g, calculated on the dried basis, to a Soxhlet's extractor, add 80-100 ml of anhydrous ether, heat under reflux for 6 hours, evaporate ether and dry to constant weight at 80°C. The residue is not more than 2.0%.

Loss on drying When dried to constant weight at 105°C, loses not more than 10.0% of its weight (Appendix VIII L).

Residue on ignition Not more than 0.3% (Appendix VIII N), using 1.0 g.

Heavy metals Carry out the limit test for heavy metals (Appendix VIII H, method 2), using the residue obtained in the test for Residue on ignition: not more than 0.002%.

Microbial limit Carry out the microbial limit tests (Appendix XI J): bacteria count is not more than 1000 per g, fungi count is not more than 100 per g, and no growth of *Escherichia coli* is detected.

Assay Weigh accurately 0.2 g and carry out the method for determination of Nitrogen (Appendix VII D, method 1).

Category Pharmaceutical aid.

Storage Preserve in tightly closed containers, stored in a dry place.

Zein

Zein is a prolamine derived from corn gluten. It contains not less than 14.0% of N, calculated on the dried basis.

Description Yellow or pale yellow flakes, moderately lustrous on one side; odourless; tasteless. Freely soluble in 80%-92% ethanol or 70%-80% acetone;

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Appendix I General Requirements for Preparations

I A Tablets

Tablets are solid preparations of various shapes, round or heteromorphic, and obtained by compressing uniform volumes of particles containing medicaments with suitable excipients.

They are mainly conventional oral tablets, also include lozenges, sublingual tablets, dental patches, chewable tablets, dispersible tablets, soluble tablets, effervescent tablets, vaginal tablets, effervescent vaginal tablets, sustained-release tablets, controlled-release tablets, and enteric-coated tablets, etc.

Lozenges Lozenges are tablets intended to be placed in the mouth where they dissolve slowly to exert prolonged local action.

The medicaments in lozenges should be freely soluble in water. Lozenges are intended mainly for local antiphlogistic, antimicrobial, apocrustic, analgetic or local anesthetic action. Unless otherwise stated, lozenges disintegrate completely within 30 minutes when examined by the test for disintegration (Appendix X A).

Sublingual Tablets Sublingual Tablets are tablets, intended to be inserted beneath the tongue, where they dissolve rapidly and the medicaments are absorbed directly through mucosa to obtain a systemic effect.

The medicaments and excipients are freely soluble in water. Sublingual tablets are intended mainly for treatment of emergency.

Unless otherwise stated, sublingual tablets disintegrate within 5 minutes when examined by the test for disintegration (Appendix X A).

Dental Patches Dental Patches are preparations that are intended for adhesion to the mucous membrane of mouth for local or systemic effect.

They comply with the requirements for tests of dissolution or drug release.

Chewable Tablets Chewable Tablets are tablets intended to be chewed or sucked to disintegrate and then swallowed to effect in gastrointestinal track, or to be absorbed by gastrointestinal track for systemic action.

Mannitol, sorbitol, or sucrose, which are excipients freely soluble in water, are usually utilized as fillers and binders. The hardness of chewable tablets should be suitable.

Dispersible Tablets Dispersible Tablets are tablets which are intended to be dispersed rapidly in water giving a uniform dispersion before administration.

The medicaments in the dispersible tablets are usually insoluble in water. Dispersible tablets may be administered after being dispersed in water or sucked in the mouth or swallowed whole. Dispersible tablets comply with the requirements for the tests of dissolution and uniformity of dispersion.

Soluble Tablets Soluble Tablets are film-coated or uncoated tablets which are dissolved in water before administration. Soluble tablets are freely soluble in water, and their solutions may be slightly opalescent and are intended for oral administration, external application or gargling.

Effervescent Tablets Effervescent Tablets are tablets containing sodium bicarbonate and organic acids which release carbon dioxide in effervescent appearance when dissolved in water.

The medicaments in effervescent tablets are freely soluble in water as well as in the effervescent solution. Organic acids such as citric acid, tartaric acid and fumaric acid are usually used.

Vaginal Tablets and Effervescent Vaginal Tablets They are tablets intended for administration to the vagina. Their shape should be suitable for vaginal administration, and they may be inserted into the vagina with a suitable device. They are conventional tablets and may readily dissolve, disperse, melt, or disintegrate and the medicaments are released in the vagina to obtain a local antiphlogistic and antimicrobial effect. Sexual hormones can also be administered in this way while those medicaments with local irritant effect should not be prepared in such a way.

Vaginal tablets comply with the test for disintegration (Appendix X B).

Effervescent vaginal tablets comply with the requirements for the test of effervescent volume.

Sustained-release tablets Sustained-release tablets are tablets which release medicaments in a gradual, non-constant rate way in water or a prescriptive release medium. They comply with the related requirements for sustained-release preparations (Appendix XX D) and the test for drug release.

Controlled-release tablets Controlled-release tablets are tablets which release medicaments in a gradual, constant rate way or nearly constant rate way in water or a prescriptive release medium. They comply with the related requirements for controlled-release preparations (Appendix XX D) and the test for drug release.

Enteric-coated tablets Enteric-coated tablets are tablets coated with enteric-coating material.

Tablets may be coated with gastro-resistant coating to prevent the medicaments from decomposition and failing to effectiveness or irritation to stomach, or to control the targeted release of the medicaments in the intestinal fluid. Tablets may be coated with colon-specific film for treatment of colon diseases.

Enteric-coated tablets, unless otherwise stated, comply with the test for drug release.

The production and storage of tablets comply with the following requirements.

1. The medicaments should be mixed with the excipients thoroughly. Tablets containing medicaments toxic or potent in nature or those administered in small dosage are dispersed uniformly in a way appropriate for the substances concerned.
2. Tablets containing volatile, thermolabile or photosensitive substances are processed in a way to avoid loss and failing to effectiveness or heating or to avoid decomposition by

protecting from light.

3. The moisture content of the drug substances or granules used in the process should be controlled to meet the requirements of processing and to prevent mold contamination or deterioration during storage.

4. Excipients such as flavouring, aromatic and colouring agents may be added to lozenges, dental patches, chewable tablets, dispersible tablets and effervescent tablets, if necessary.

5. Tablets may be coated with sugar or film for a variety of reasons, including enhancement of stability, masking of unpleasant tastes, and improvement of appearance.

6. Tablets have a clean, smooth appearance and uniformly coloured surface. They possess suitable hardness and wearability. The uncoated tablets should comply with the test for tablet friability to protect them from wearing or cracking during transportation.

7. Tablets comply with the requirements for the tests of dissolution, drug release, content uniformity and microbial limit. If necessary, film-coated tablets should be examined for residue of organic solvents.

8. Unless otherwise stated, tablets should be stored in tightly closed containers.

Unless otherwise stated, tablets comply with the following requirements.

Weight variation Suppositories comply with the following requirements.

Average weight or labelled weight	Weight variation limit
Less than 0.30 g	$\pm 7.5\%$
Not less than 0.30 g	$\pm 5.0\%$

Procedure Weigh accurately 20 tablets and calculate the average weight; then weigh individually each of the 20 tablets and compare the weight of each tablets with the average weight (if assay is not required, the weight of each tablet should be compared with the labelled weight). Not more than 2 of the individual weights deviate from the average weight by more than the weight variation limit shown in the table, and none deviations by more than twice the limit.

Before being coated with sugar, the tablet cores comply with the test for weight variation. Sugar coated tablets are not required to carry out the test for weight variation which film coated tablets are required to comply with.

Where the test for content uniformity is specified, the test for weight variation may not be required.

Disintegration Unless otherwise stated, tablets comply with the Determination of Disintegration (Appendix X A). Vaginal tablets comply with the Disintegration Test for Suppositories and Vaginal Tablets (Appendix X B). Chewable tablets may not be required to comply with the test for disintegration.

Where dissolution test or drug release test is specified, disintegration test may not be required.

Effervescence volume Effervescent vaginal tablets comply with the following requirements.

Procedure Add 2 ml each of water, accurately measured, to ten 25 ml graduated test tubes with stopper (the internal diameter is about 1.5 cm) separately, place on a water bath at $37^{\circ}\text{C} \pm 1^{\circ}\text{C}$ for 5 minutes. Add 1 tablet each to the ten test tubes respectively, stopper the test tubes for 20 minutes. Examine the maximum volume of effervescence, the average volume of effervescence is not less than 6 ml, and not more than 2 tablets lower than 3 ml.

Uniformity of disintegration Dispersible tablets comply with the

following requirements.

Procedure Place 2 tablets in 100 ml water at $20^{\circ}\text{C} \pm 1^{\circ}\text{C}$ and shake, they should disintegrate within 3 minutes. A smooth dispersion is produced, which passes through No. 2 sieve.

Microbial limit Dental patches, vaginal tablets, effervescent vaginal tablets and soluble tablets, which are all for local use, comply with the requirements of Microbial Limit Tests (Appendix XI J).

I B Injections

Injections are sterile products prepared using medicaments with suitable solution or disperse medium as solutions, emulsions, or suspensions which are intended for administration by injection into the body, and as sterile preparations, such as powders or concentrated solutions, which, should be dispensed or diluted as solutions or suspensions before use.

Injections are classified as liquid for injection, sterilized powders for injection and concentrated solutions for injection.

Liquid for injection Liquid for injection are sterile aqueous solutions, emulsions and suspensions which are intended for parenteral administration into the body, which can be applied to intramuscular injection, intravenous injection and intravenous infusion. The large volume injections (unless otherwise specified, the volume is not less than 100 ml) for intravenous infusion are also called intravenous transfusions.

Sterilized powders for injection Sterilized powders for injection are sterilized powders or sterilized nubby materials containing medicaments, which should be dispensed as clear solutions or uniform suspensions using suitable sterile solution before use. They should be prepared by addition of a suitable sterile solvents for Injection before injection, or be prepared by addition of intravenous transfusion before intravenous infusion. The sterilized powders may be prepared by menstruum crystallization, spray-drying process or lyophilization, and other methods.

Concentrated solutions for injection Concentrated solutions for injection are sterile solutions containing medicaments which are intended for injection or intravenous infusion after dilution. The production and storage of injections should comply with the following requirements.

1. Aqueous solutions for injection should be clear; Unless otherwise specified, particles contained in suspensions for injection should not exceed $15\ \mu\text{m}$ in diameter, particles of $15\text{--}20\ \mu\text{m}$ in diameter should not be more than 10% (rarely up to $20\text{--}50\ \mu\text{m}$ in diameter). If a sediment appears, the suspensions for injection should be readily dispersed on shaking. Suspensions for injection can not be used by intravenous or vertebral canula injection. Emulsions for injection should be stable and do not show any evidence of phase separation. They can not be used by vertebral canula injection. Over 90% of the globules in the emulsions for intravenous infusion should be less than $1\ \mu\text{m}$, and none is greater than $5\ \mu\text{m}$ in diameter. Intravenous infusions should be isotonic with blood as far as possible.

2. The solvents for injections should be safe and innocuous, and not affect the therapeutic efficacy and drug quality. Aqueous solvents and non-aqueous solvents are generally used as vehicles for injections.

(1) Water for injection is the most commonly used aqueous solvents. A 0.9% Sodium Chloride solution or the aqueous

solutions of other suitable substance may also be used.

(2) Vegetable oil is the most commonly used non-aqueous solvents. Soya-bean oil for injection is commonly used as oil solvents. Provided it complies with the requirements for Soya-bean Oil (for injection). Non-aqueous solvents also include solutions of ethanol, propanediol and polyethylene glycol.

3. Suitable additives may be added according to the nature of the medicaments in the manufacturing of injections. The common additives include the substances which are used for regulating the osmotic pressure, adjusting the pH, and enhancing the solubility of the medicaments, and antioxidants, anti-microbial preservatives, and emulsifying agents, suspending agents, etc. The additives should not affect the therapeutic efficacy, not interfere with quality testing. The concentration used should not cause toxicity or excessive stimulation. Antioxidants commonly used are Sodium Sulfite, Sodium Bisulfite and Sodium Pyrosulfite, etc, the concentration used is generally 0.1%-0.2%; Antimicrobial preservatives commonly used are 0.5% of Phenol, 0.3% of Cresol, 0.5% of Chlorobutanol, etc. Multi-dose injections may contain an appropriate concentration of suitable anti-microbial preservatives. The concentration of anti-microbial preservatives should be enough to prohibit the growth of micro-organisms in the injections. Sterilization should be conducted for those injections with added anti-microbial preservatives. It is not allowed to use anti-microbial preservatives for the injections to be administered by intravenous infusion, intracisternal injection, extradural injection, or vertebral canula injection. Unless otherwise specified, no anti-microbial preservative is added when the volume to be injected in a single dose exceeds 15 ml.

4. Containers commonly used for injections include glass ampoules, glass bottles, plastic ampoules and plastic bottles, etc. The tightness of the containers should be ensured by suitable means. Unless otherwise specified, containers should comply with the related requirements of the National Standards for glass and plastic containers for injections. The rubber closures, especially the closures for multi-dose containers, should be sufficiently firm and elastic, should comply with the related requirements of the National Standards.

5. The time for manufacturing the injections should be reduced as far as possible. Injections are prepared by methods designed to avoid the contamination of microorganism, pyrogens and to prevent the medicaments from deterioration. In the manufacture of intravenous infusions, it should be controlled more strictly. In the manufacture of emulsions for injection and suspensions for injection, the necessary measures should be taken to ensure that the particle size complies with the requirement of standards. Sterilized powders for injection should be manufactured under aseptic conditions.

6. Each container of injection is filled with a volume in slight excess of the labelled quantity if labelled volume of injection is 50 ml or less. The excess quantities are recommended in the accompanying table. A container may contain medicaments of multiple doses. Unless otherwise specified, it should not contain more than 10 doses, and the excess quantity in such containers should be sufficient to permit withdrawal and administration of the labelled quantity of each doses.

Labelled quantity/ml	Excess quantity/ml	
	Mobile liquid	Viscous liquid
0.5	0.10	0.12
1	0.10	0.15
2	0.15	0.25

continue

Labelled quantity/ml	Excess quantity/ml	
	Mobile liquid	Viscous liquid
5	0.30	0.50
10	0.50	0.70
20	0.60	0.90
50	1.0	1.5

The containers for filling the medicaments which are readily deterioration on exposure to air should be evacuated and displaced by carbon dioxide or nitrogen, etc, during filling, and then they are sealed by fusion or hermetic close.

7. After being sealed by fusion or hermetic seal, injections are sterilized by appropriate method according to the nature of the medicaments to ensure the sterility of the finished products. Containers of injections should undergo a leakage test under reduced pressure or by other suitable methods during or after the sterilizing process.

8. Unless otherwise stated, the storage of injections should be protected from light.

9. Where the injections contain a suitable anti-microbial preservative, the label should states the name and concentration of the anti-microbial preservative added. For sterilized powders for injection, the label should states the vehicle used.

Unless otherwise specified, injections should comply with the following requirements.

Filling The volume of injections and liquid concentrates for injection should comply with the following requirement.

Procedure Take 5 containers (the labelled quantity is not more than 2 ml); 3 containers (the labelled quantity is more than 2 ml and less than 50 ml); Open the containers with caution to avoid any loss of the contents. Take up individually the contents of each container into a dry syringe, then discharge the contents of the syringe into a calibrated cylinder (of such size that volume to be measured occupies at least 40% of its rated volume), and measure the volume at room temperature. For injections of oily liquids or suspensions, warm and thoroughly shake the containers before removing the contents, then process as mentioned above. Cool to room temperature before measuring the volume. The content in each container is not less than the labelled quantity of the injection.

If the labelled volume is over 50 ml, carry out the test for Minimum Fill (Appendix X F), the result should comply with the requirements.

Weight variation Unless otherwise specified, the weight variation of powders for injection should comply with the following requirements.

Procedure Take 5 containers, remove any adherent label and the aluminium cover from the sealed container, wash the outside with ethanol and dry thoroughly, weigh accurately each container as soon as possible, open the container with caution to avoid foreign matter such as glass bits falling into container, and weigh accurately the whole container immediately, remove the contents, wash the container with water or ethanol, dry it in a suitable condition and weigh accurately, calculate the weight of each container and the average weight of 5 containers. The weight variation of each container does not deviate from the average weight by a percentage greater than that shown in the table. If the weight variation of contents of one container does not comply with the above requirements, repeat the operation with another 10 containers, all of them should comply with the requirements.

Average weight	Weight variation limit
0.05 g or less	±15%
More than 0.05 g to 0.15 g	±10%
More than 0.15 g to 0.50 g	±7%
More than 0.50 g	±5%

If the test for uniformity of content is specified for a sterilized powder for injection, the test for weight variation is generally not required.

Visible particles Unless otherwise specified, comply with the requirements of the Test for Visible particles in Injections (Appendix IX H).

Particulate matter Unless otherwise specified, aqueous intravenous infusions, sterilized powders for infusion and liquid concentrates for injection, should comply with the requirements of the Test for Particulate matter in Injections (Appendix IX C).

Sterility Comply with the requirements of the Test for Sterility (Appendix XI H).

Bacterial Endotoxin or Pyrogens Unless otherwise specified, the injections for intravenous infusions should comply with the requirements of the Test for Bacterial Endotoxin (Appendix XI E) or the Test for Pyrogens (Appendix XI D) as specified in individual monograph.

I C Tinctures

Tinctures are clear liquid preparations of medicinal substances macerated or dissolved in ethanol of specified concentration or made by diluting the fluid extracts. They are intended for oral administration or external application. The production and storage of tinctures comply with the following requirements.

1. Unless otherwise stated, tinctures containing poisonous or potent drugs are generally equivalent to 10 g of the drug in 100 ml of the tincture; most of other tinctures represent 20 g of the drug in 100 ml of the tincture.

2. The active ingredients of a tincture containing poisonous or potent drugs may be determined by an assay of intermediate product and then the potency adjusted to produce a finished product that complies with the requirements stated in the monograph concerned.

3. Tinctures may be prepared by dissolution, dilution, maceration or percolation.

(1) *Dissolution or dilution* Dissolve a quantity of drug powder or dilute the liquid extracts with a quantity of ethanol of specified concentration, allow to stand, filter if necessary.

(2) *Maceration* Macerate the powdered drugs with a quantity of solvent in a closed vessel for 3-5 days or a specified time, stirring or shaking occasionally. Separate the supernatant liquid, to the residue add a quantity of the solvent and continue maceration in the same way until the active ingredients are completely extracted. Combine the extracts and add solvent to the required volume, allow to stand for 24 hours and filter.

(3) *Percolation* Percolate with a quantity of solvent as described under Extracts and Liquid Extracts (Volume I of this Pharmacopoeia, Appendix I O), until sufficient quantity of the percolate is obtained as required, allow to

stand and filter.

4. Precipitates produced after prolonged standing of the tincture may be removed by filtration provided that the content of active ingredients and ethanol still comply with the requirements stated in the monograph concerned.

5. Tinctures should be preserved in light-resistant, tightly closed containers and preserved in a cool place. Tinctures comply with the following requirements, unless otherwise stated.

Filling Comply with the test for Minimum Fill (Appendix X F).

Microbial limit Unless otherwise stated, tinctures comply with Microbial Limit Tests (Appendix XI J).

I D Suppositories

Suppositories are preparations made by incorporating medicaments in suitable bases, intended for administration to cavities.

Based on the different cavities they are intended to apply to, suppositories may be classified as rectal suppositories, vaginal suppositories and urethral suppositories. Rectal suppositories have the shape of torpedo, cone or cylinder, etc. Vaginal suppositories have the shape of drawing pen, ball or oval. Urethral suppositories are usually rodlike.

Suppositories may be classified into conventional and sustained-release suppositories.

The production and storage of suppositories comply with the following requirements.

1. Semi-synthetic fatty glycerides, cocoa butter, polyoxyethylene stearate, polyoxyethylene sorbitan fatty esters, hydrogenated vegetable oil, glycerogelatin, poloxamers, polyethylene glycol and other suitable materials may be used as suppository bases.

2. Bases which are soluble in water or able to mix with water are usually used for preparation of vaginal suppositories.

3. Solid drug substances, unless otherwise specified, should be finely powdered, and all the particles should pass through No. 6 sieve beforehand. Suppositories may be made in different shapes according to their usage and the cavities they are intended to apply to.

4. Surfactants, diluents, absorbents, lubricants and preservatives, etc. may be added, if necessary.

5. The drug substances and bases in suppositories should be thoroughly mixed. The suppositories should look intact and smooth. Suppositories are non-irritating and able to melt, soften or dissolve when inserted in the cavities and are miscible with body fluid to release the medicament gradually thus exert local or systemic effects. Suppositories are sufficiently hard to withstand packaging or storing without deformation.

6. Suppositories comply with the requirements for test of drug release and may not be necessary for test of disintegration.

7. Unless otherwise stated, suppositories should be preserved in well closed containers and preserved at a temperature below 30°C to protect from deformation, mould contamination or deterioration due to excessive heat and moisture. Unless otherwise specified, suppositories comply with the following requirements.

Weight variation Suppositories comply with the following

requirements.

Average weight	Weight variation limit
1.0 g or less	$\pm 10\%$
More than 1.0 to 3.0 g	$\pm 7.5\%$
More than 3.0 g	$\pm 5.0\%$

Procedure Weigh accurately together 10 suppositories and determine the average weight; then weigh individually each of the 10 suppositories. Not more than one of the individual weight deviates from the average weight by more than the weight variation limit shown in the table and none deviates from twice of the limit.

Where the test for content uniformity is specified, the test for weight variation may not be required.

Disintegration test Suppositories comply with the requirements of Disintegration Test for Suppositories and Vaginal Tablets (Appendix X B).

Microbial limit Suppositories comply with the requirements of Microbial Limit Tests (Appendix XI J).

I E Capsules

Capsules are solid preparations consisting of medicaments with or without excipients, filled in hollow hard capsules or sealed in soft shells.

Capsules may be classified into hard, soft, sustained-release, controlled-release, and enteric-coated capsules. They are mainly intended for oral administration.

Hard capsules (usually known as capsules) Hard capsules are capsules made of a quantity of powders, granules, minitabets or pellets of medicaments, with or without suitable excipients, which are produced by suitable preparative technology and enclosed in a hollow capsule shell.

Soft capsules Soft capsules are capsules prepared by enclosing directly a quantity of liquid medicament, or by enclosing a solution, suspension, emulsion and semi-solid, which are made by dissolving or dispersing solid medicaments, into spherical or elliptical soft capsule shells. The soft capsule shells are made of gelatin, glycerin or/and other suitable materials.

Sustained-release capsules Sustained-release capsules are capsules which release medicaments in a gradual, non-constant rate way in water or a prescriptive release medium. Sustained-release capsules comply with the related requirements for sustained-release preparations and the test for drug release.

Controlled-release capsules Controlled-release capsules are capsules which release medicaments in a gradual, constant rate way or nearly constant rate way in water or a prescriptive release medium. They comply with the related requirements for controlled-release preparations and the test for drug release.

Enteric-coated capsules Enteric-coated capsules are hard or soft capsules of which the shell is prepared by suitable enteric-coating material, or are capsules filled with granules or pills coated with enteric-coating material. Enteric-coated capsules are insoluble in gastric fluid, but can disintegrate in intestinal fluid to release active ingredients. Unless otherwise specified, enteric-coated capsules comply with the requirements for the test of drug release (Appendix X D).

The production and storage of capsules comply with the following requirements.

1. The active ingredients or excipients enclosed in capsules should not cause the deterioration of the shells.
2. Hard capsules may be enclosed with the following contents according to different preparative technologies.
 - (1) uniform powders, granules or minitabets made of a quantity of medicaments and suitable excipients such as diluents, lubricants and disintegrating agents;
 - (2) pills, fast-release pills, sustained-release pills, controlled-release pills or enteric-coated pills, in either simple form or compound form, and a quantity of blank pills may be added as the filler if necessary;
 - (3) medicinal powders without any excipients;
 - (4) inclusion complexes, solid dispersion, microcapsules or microspheres of medicaments;
 - (5) solutions, suspensions, emulsions, etc., filled with a special machine, and sealed if necessary.
3. Potent medicaments given in small doses are usually mixed thoroughly with a suitable diluent before filling.
4. Capsules should have a clean, smooth surface and well shaped without adhesion, deformation, leakage or breakage. Capsules should not have foreign odour.
5. Capsules comply with the requirements for tests of dissolution, drug release, content uniformity and microbial limit. If necessary, capsules with coated films should be examined for the residues of organic solvents.
6. Unless otherwise stated, capsules should be preserved in tightly closed containers at temperatures not exceeding 30°C and suitable humidity to protect from moisture, mold contamination or deterioration.

Unless otherwise stated, capsules comply with the following requirements.

Weight variation Capsules comply with the following weight variation limit.

Average weight	Weight variation limit
Less than 0.3 g	$\pm 10\%$
0.3 g or more	$\pm 7.5\%$

Procedure Weigh accurately each of 20 capsules, unless otherwise specified, and open each capsule without loss of shell material, remove the content as completely as possible; for hard capsules, clean the shell with a small brush; for soft capsules, wash the shell with ether or other volatile solvents, and allow to stand until the odour of the solvents is no longer perceptible. Weigh the shell of each capsule. The difference between the weights represents the weight of the content of each capsule and calculate the average weight of the capsule content. Not more than 2 of the individual weights deviate from the average weight by more than the weight variation limit shown in the table, and none deviates by more than twice of the limit.

Weight variation test may not be required if the capsules have proceeded content uniformity test.

Disintegration test Unless otherwise specified, capsules comply with the test for Determination of Disintegration (Appendix X A).

Where dissolution test or drug release test is specified, disintegration test may not be required.

I F Ointments, Creams and Pastes

Ointments Ointments are uniform semi-solid preparations made of medicaments and oleaginous or water-soluble bases and are intended for external application to the skin. Ointments may be divided into solution or suspended ointments according to different dispersion states of the medicaments in the bases. Solution ointments are the ointments of which the medicaments dissolve or melt into the simple or compound bases; suspended ointments are the ointments in which the fine powders of the medicaments are dispersed into the bases evenly.

Creams Creams are uniform semi-solid preparations made of emulsified bases in which medicaments are dissolved or dispersed. Creams are intended for external application to the skin. According to different bases, ointments may be divided into two types, oil-in-water and water-in-oil.

Pastes Pastes are semi-solid preparations which contain a large amount (usually more than 25%) of medicament powders uniformly dispersed in suitable bases. Pastes may be divided into homogeneous hydrogel and oleaginous pastes. The production and storage of the ointments, creams and pastes comply with the following requirements.

1. Bases utilized for ointments, creams and pastes are selected based on the characteristics of the preparation formulation, properties of the medicaments, therapeutic effect of the preparation and stability of the product. Mixed bases of different types can also be used.

Bases for ointments are divided into oleaginous and water-soluble bases. Oleaginous bases usually include vaseline, paraffin, liquid paraffin, silicone oil, beeswax, stearic acid, wool fat, etc.; water-soluble bases mainly include polyethylene glycols. Emulsifiers for creams are usually divided into two types, oil-in-water and water-on-oil. Oil-in-water emulsifiers include sodium soaps, triethanolamine soaps, sodium fatty alcohol sulphate (sodium lauryl sulphate) and tweens; water-in-oil emulsifiers include calcium soaps, wool fat, mono glycerides, fatty alcohols, etc.

2. The bases of ointments, creams and pastes should be uniform, fine and smooth without any irritation for use on skin or mucous membranes. Insoluble solid medicaments in suspended ointments and solid components in pastes should be powdered finely in advance with suitable method to ensure the specified particle size.

3. If necessary, wetting agents, preservatives, thickening agents, antioxidants and the transdermal accelerants may be added to the ointments and creams.

4. Ointments, creams and pastes should be applied easily to the skin or mucous membrane with proper consistency (pastes usually have larger consistency) but should not be melt, the consistency should only change a little with different temperatures.

5. Ointments, creams and pastes should show no evidence of deterioration such as rancidity, foreign odour, discolouration, hardening and creams no evidence of flatulence and separation of oil and water.

6. Unless otherwise specified, ointments, creams and pastes should be preserved in well closed containers, protected from light; creams should be preserved below 25°C but not frozen.

Unless otherwise specified, ointments, creams and pastes comply with the following requirements.

Particle size For suspended ointments, unless otherwise specified, spread a quantity of the ointments onto three microscope slides separately to form a thin layer whose area is equivalent to the cover-glass. Examine them according to the test for Particle Size and Its Distribution (Appendix IX E, method 1), no particle of greater than 180 μm in dimension is observed.

Filling Comply with the test of Minimum Fill (Appendix X F).

Sterility Ointments and creams for use on burns or grievous injuries comply with the Test for Sterility (Appendix XI H).

Microbial limit Unless otherwise specified, they comply with the requirements of Microbial Limit Tests (Appendix XI J).

I G Eye Preparations

Eye Preparations are preparations intended for direct application to the eye to display therapeutic effect. Eye preparations may be classified into liquid eye preparations (eye drops, eye lotions, ophthalmic injections), semi-solid eye preparations (eye ointments, eye creams, eye gels), solid eye preparations (eye pellicles, eye pilules, ophthalmic inserts), etc. They can also be packed in a solid form with a separate solvent, from which solutions or suspensions are prepared before use.

Eye Drops Eye Drops are sterile liquid eye preparations in the form of aqueous or oily, clear solutions, suspensions or emulsions made of medicaments and suitable excipients, intended for instillation onto the eye. The medicaments can be packed in the form of powder, granules, masses or tablets with a separate solvent, from which clear solutions or suspensions are prepared before use.

Eye Lotions Eye Lotions are sterile aqueous solutions intended for use in washing or bathing the eye to wash off the foreign matter or secretion or to neutralize foreign chemical materials.

Ophthalmic Injections Ophthalmic Injections are sterile liquid eye preparations in the form of clear solution prepared from medicaments and suitable excipients, intended for injection into the tissues around the eye (including subconjunctival injection, subtenon injection, and retrobulbar injection, etc.) or into the eye (including anterior chamber injection, anterior chamber washing, intravitreal injection and intravitreal perfusion, etc.).

Eye Ointments Eye Ointments are semi-solid eye preparations in the pasty form of sterile solution or suspension made of medicaments with suitable bases.

Eye Creams Eye Creams are semi-solid eye preparations in the form of sterile cream made of medicaments with suitable bases.

Eye Gels Eye Gels are semi-solid eye preparations in the form of sterile gel made of medicaments with suitable bases. Eye gels have large viscosity and mix easily with tears.

Eye Pellicles Eye Pellicles are solid eye preparations in the form of sterile film made of medicaments with suitable high polymer excipients, intended for use in the conjunctiva sac for slow release of medicaments.

Eye Pilules Eye Pilules are solid eye preparations in the

form of sterile sphere, almost sphere shape or ring made of medicaments with suitable excipients.

Ophthalmic Inserts Ophthalmic Inserts are sterile solid eye preparations of suitable size and shape, made of medicaments and suitable excipients, intended to be inserted in the conjunctiva sac for slow release of medicaments.

The production and storage of eye preparations comply with the following requirements.

1. Eye preparations may contain auxiliary substances to adjust the tonicity, pH value and viscosity, or excipients to increase the solubility of the medicaments or to stabilize the preparation, or bacteriostatics and antioxidants of suitable concentration. Such additives do not adversely affect the medicinal action, nor cause undue local irritation.

2. Unless otherwise stated, eye drops should be isotonic with tears and their osmolarity determined. Suspended eye drops may show a sediment which is readily dispersed on shaking and should not be a cake mass; their ratio of sedimental volume should be determined. Unless otherwise stated, each container of eye drops should not hold more than 10 ml.

3. Eye lotions are used in large amount and should be basically isotonic with tears and have a close pH value. Eye lotions packaged in multi-dose should contain suitable bacteriostatic which displays bacteriostatic effect during the period of use. Unless otherwise stated, each container of eye lotions should not hold more than 200 ml.

4. The selected bases of semi-solid eye preparations should be filtered and sterilized, and the insoluble medicaments should be finely powdered in advance. Eye ointments, eye creams and eye gels should be homogenized, fine and smooth. They should be applied easily to the eye for easy dispersion and absorption of the medicaments without any irritation. Each container should not hold more than 5 g.

5. Ophthalmic injections, ophthalmic inserts and eye preparations for injuries, surgical procedures or corneal perforation should not contain bacteriostatics, antioxidants or unsuitable buffering agents. They should be packaged in sterile containers of single dose.

6. The container should be cleaned and sterilized, and not break easily. Unless otherwise stated, the wall of the containers should be transparent enough to carry out the test for Visible Particles in Injections.

7. Unless otherwise stated, eye preparations comply with the general requirements for preparations of the dosage forms concerned. For example, eye gels should comply with the requirements of gels.

8. The content uniformity of eye preparations comply with the requirements.

9. Unless otherwise stated, eye preparations should be preserved in tightly closed containers protected from light.

10. Eye preparations must not be used for exceeding 4 weeks after opening.

Unless otherwise stated, eye preparations comply with the following requirements.

Visible particles Unless otherwise stated, eye drops comply with the test for Visible particles in Injections (Appendix IX H) of eye drops; ophthalmic injections comply with the test for Visible particles in Injections (Appendix IX H).

Particle size Unless otherwise stated, suspended eye preparations comply with the following test.

Procedure for suspended eye drops Shake the test sample

of the medicament onto the slide, carry out the test for determination of particle size and its distribution (Appendix IX E, method 1), not more 2 particles greater than 50 μm and no particle greater than 90 μm in dimension are allowed.

Procedure for suspended semi-solid eye preparations Take 10 tubes and extrude the content of each tube as completely as possible into a suitable container, stir thoroughly, and on each of three slides, spread a quantity of the content (equivalent to about 10 μg of the medicament) to form a thin layer with an area approximately corresponding to that of the cover-glass. Carry out the test for determination of particle size and its distribution (Appendix IX E, method 1), not more 2 particles greater than 50 μm and no particle greater than 90 μm in dimension are allowed.

Ratio of sedimental volume The ratio of sedimental volume of suspended eye drops should be not less than 0.90.

Procedure Unless otherwise stated, shake vigorously 50 ml of the test sample in a stoppered cylinder for 1 minute, and record highness H_0 in the beginning. Allow to stand for 3 hours, record the final highness H . Calculate the ratio of sedimental volume according to the following equation:

$$\text{Ratio of sedimental volume} = H/H_0$$

Metal particles Unless otherwise specified, semi-solid eye preparations comply with the following requirements.

Procedure Take 10 tubes, extrude the content of each tube, individually, as completely as possible into culture dishes which are 6 cm in diameter with flat bottom, free from gas bubbles and visible particles. Cover the dishes, heat at 85°C for 2 hours, unless otherwise stated, and allow the test sample to distribute uniformly, cool at room temperature until the ointment is congealed and invert each dish on the stage of a suitable microscope. Each dish is illuminated from above direction by a spotlight placed at an angle of 45° to the bottom of the plate. Examine at a 30 magnification and count the lustrous metal particles not less than 50 μm in dimension. Not more than one tube is found to contain more than 8 metal particles, and not more than 50 particles are totally found in the 10 tubes. If the test does not comply with the requirements above, repeat the test with another 20 tubes. The requirements are met if not more than 3 tubes in the 30 tubes are found to contain more than 8 metal particles in each tube, and not more than 150 particles are totally found.

Weight variation Unless otherwise stated, solid eye preparations comply with the following requirements.

Procedure Weigh accurately together 20 test samples (or their contents) and calculate the average weight; then weigh individually each of the 20 samples. Not more than 2 of the individual weight deviate from the average weight by more than $\pm 10\%$ and none more than $\pm 20\%$.

Where the test for content uniformity is specified, the test for weight variation may not be required.

Filling Semi-solid and liquid eye preparations comply with the test of Minimum Fill (Appendix X F).

Sterility Ophthalmic injections, ophthalmic inserts and eye preparations for injuries, surgical procedures or corneal perforation comply with Test for Sterility (Appendix XI J).

Microbial limit

Procedure for liquid eye preparations Unless otherwise stated, carry out the test of film filtration and direct inoculation (Appendix XI H). Take prescribed amount of at least 2 test samples (2 samples inoculated in one type of culture dishes, 1 ml each sample), inoculate in fluid thioglycollate medium or modified Martin medium, directly or with pre-treatment, then culture for 7 days. No evidence

of microbial growth is found. Should any fungi have grown, repeat the test using twice the number of samples. No evidence of microbial growth is found in any one of the tubes.

Procedure for semi-solid and solid eye preparations
Unless otherwise specified, they comply with the Microbial Limit Tests (Appendix XI J).

I H Pills

Pills are the solid preparations in spherical or almost spherical shape made of the uniform mixture of the medicaments and suitable excipients. Pills may be classified into dripping pills, sugar pills and pellets, etc.

Dripping Pills Dripping Pills are the preparations made of dripping a uniformly melted, emulsified or suspended mixture of solid or liquid medicaments and appropriate bases into an immiscible and non-interacting cooling liquid and congealing to pill form due to the action of surface tension. They are mainly intended for oral administration.

Sugar Pills Sugar Pills are the preparations made of appropriate sugar granules or base pills as the cores, sugar powder or the mixture of other excipients as the powdering materials, and suitable materials as adhesive or wetting agents, and the medicaments are encapsulated with an appropriate method in divided quantities.

Pellets Pellets are solid preparations in spherical or almost spherical shape prepared with suitable method from a uniform mixture of medicaments and suitable excipients with suitable adhesive or wetting agents. The diameter of pellets is usually 0.5-3.5 mm.

The production and storage of pills comply with the following requirements.

1. The bases used for the preparation of dripping pills consist of water-soluble and water-insoluble bases. Commonly used bases include polyethylene glycols (such as polyethylene glycol 6000, polyethylene glycol 4000, etc), poloxamers, polyoxyl (40) stearate, gelatin, stearic acid, glycerin monostearate, hydrogenated vegetable oil, etc. The cooling liquid for dripping pills must be innocuous and does not interact with the medicaments. Liquid paraffin, vegetable oil, methylsilicone oil and water are commonly used for this purpose.

Pills should be uniform in size and colour without adhesion.

2. Pills comply with the requirements for the tests of content uniformity and microbial limit, etc.

3. The surface cooling liquid of dripping pills should be removed after preparation.

4. Oral dripping pills or pellets may be sugar-coated or film-coated as required to suit for the properties of the medicaments and for the clinical usage and storage.

5. Unless otherwise stated, sugar pills and pellets should be dried under a suitable condition before packing. They should be sieved with sieves of suitable sieve number according to the dimensions of the pills.

6. Unless otherwise specified, pills should be kept in tightly closed containers, protected from moisture, mold and prevented from deterioration.

Unless otherwise stated, the following examinations should be carried out for pills.

Weight variation The limit of weight variation for pills complies with the following requirements.

Average weight	Weight variation limit
0.03 g or less	±15%
More than 0.03 g to 0.30 g	±10%
More than 0.3 g	±7.5%

Procedure Unless otherwise stated, weigh accurately 20 pills and calculate the average weight, then weigh each of them accurately. Compare the weight of each pill with the average weight. Not more than 2 pills deviate from the limit of weight variation, and none deviates from twice of the limit.

For pills packed in single dose, examine 20 doses, the limit of weight variation should comply with the above requirements.

The core weight variation of coating pills should be examined before coating, and comply with the requirements in the table mentioned above. The examination for weight variation is not required for sugar pills after coating, but required for film-coated pills.

Dispersion limit Unless otherwise specified, carry out the disintegration test (Appendix X A), pills comply with the requirements.

I J Implants

Implants are the sterile solid preparations containing medicaments and excipients, which will be implanted into the body. Implants are commonly implanted with the special syringe, or embedded by surgical open. They can continuously release the active substances over an extended period of time. Implants should comply with the requirements of the test for drug release.

The production and storage of implants should comply with the following requirements.

1. The excipients of the implants should be biological consistent, the material can be unbiodegradable, such as silica gel, also can be biodegradable. For unbiodegradable, it should be taken out when reached the designed time.

2. Implants should comply with the requirements of Drug Release Test.

3. Implants should be packaged in a single-dose sterilized container.

4. Implants should be preserved in tightly closed container, protected from light.

Unless otherwise stated specified, implants should comply with the following requirements.

Weight variation Unless otherwise specified, the weight variation of implants should comply with the following requirements.

Procedure Take 5 containers, remove any adherent label and the aluminium cover from the sealed container, wash the outside with ethanol and dry thoroughly, open the container with caution to avoid foreign matter such as glass bits falling into container, and weigh accurately each of the whole containers immediately, remove the contents, wash the container with water or ethanol, dry it in a suitable condition and weigh accurately, calculate the weight of each container and the average weight of 5 containers. The weight variation of each container does not deviate from the average weight by a percentage greater than that shown in the table. If the weight variation of contents of one container does not comply with the above requirements, repeat the operation with another 10 containers, all of them should comply with the requirements.

Average weight	Weight variation limit
0.05 g or less	±15%
More than 0.05 g to 0.15 g	±10%
More than 0.15 g to 0.50 g	±7%
More than 0.50 g	±5%

Sterility Comply with the requirements of the test for sterility (Appendix XI H).

I K Syrups

Syrups are concentrated aqueous solutions of sucrose containing medicaments. They are intended for oral administration. The production and storage of syrups comply with the following requirements.

1. Syrups should contain not less than 45% (g/ml) of sucrose.
2. Unless otherwise specified, syrups are generally prepared by dissolving the medicaments with freshly boiled-water and adding simple syrup. If prepared by direct addition of sucrose, they should be boiled, and filtered, if necessary, and a quantity of freshly boiled-water is added through the filter to prescribed amount.
3. Additives may be added to syrups if necessary. If preservatives are added in need, not more than 0.3% of sorbic acid or benzoic acid (potassium or sodium salts are calculated to their equivalent amount of corresponding acid), or not more than 0.05% of *p*-hydroxybenzoic acid esters, may be used. If other additives are added, the varieties and amount being used should comply with the related requirements of the National Standards, and they do not affect the stability of the product and quality control of the preparation concerned. Suitable amount of ethanol, glycerol or other polyhydric alcohols may be added if necessary.
4. Syrups should be clear, unless otherwise specified. Syrups should not be moldy or rancid, or generate gases and other deteriorations during storage.
5. Syrups should be kept in tightly closed containers and preserved at the temperature not exceeding 30°C. Unless otherwise specified, syrups should comply with the following requirements.

Filling Syrups comply with the test of Minimum Fill (Appendix X F).

Microbial limit Syrups comply with the Microbial Limit Tests (Appendix XI J).

I L Aerosols, Powders for Spray and Sprays

Aerosols, powders for spray and sprays are intended for application by special devices for the deep respiratory tract, mucosa of various body cavities or the skin to obtain a local or systemic effect. They can be classified as the preparations for inhalation, non-inhalation and for topical use according to the route of administration. Inhalation aerosols, powders for spray for inhalation and sprays for inhalation are presented as single-dose or multi-dose preparations. They should be manufactured according to the following requirements.

respiratory tract and various body cavities or their cilia.

Aerosols

Aerosols are solutions or emulsions or suspensions of one or more medicaments in suitable propellants that are packed in pressure resistant containers fitted with a specified valve system. Upon actuation of the valve the preparations are released from the container and inhaled into the lung, on mucosa of the respiratory tract, on skin, or specially for the purpose of sterilization of the space. Aerosols may be inhalation aerosols, non-inhalation aerosols and topical aerosols according to the route of administration. Aerosols may be two phase aerosols (gas and liquid) or three phase aerosols (gas, liquid, and solid or liquid) according to the formulation. Aerosols may be metered-dose aerosols and non-metered dose aerosols according to the delivery device. The manufacturing and storage of aerosols should comply with the following requirements.

1. In the processing of aerosols, suitable auxiliary substances may be added such as solvents, cosolvents, antioxidants, antiseptics and surfactants or other ingredients. The added substances to aerosols (inhalation, non-inhalation and topical) should be nonirritating to skin or mucosa.
2. Two phase aerosol is prepared according to the formula as a clear solution, which is filled in the containers with the required content. Three phase aerosol is a stable suspension or emulsion prepared by mixing and triturating the micronized powders or emulsifying the active ingredients and added substances thoroughly, if necessary, filled in the containers after quality control of the preparation. Strict control of water content of active ingredients, propellants, containers and apparatus is needed to prevent them from water infiltration. The hygroscopic drugs should be dispensed rapidly. The particle and droplet size of inhalation aerosols must be not more than 10 μm , most of them should be not more than 5 μm .
3. The propellants commonly used are liquids with low-boiling range. Mixtures of appropriate proportions of two or more propellants may be used to obtain the required pressure.
4. The containers are resistant to the internal pressure. Component units of the container should be compatible with the active substances and additives, and their precision of sizes and solubilizing or swelling properties should comply with the relevant requirements. Uniform and fine mist particles, and accurate emitted dose should be released in an actuation.
5. Appropriate method should be adopted to monitor the pressure and any leakage for safety use.
6. Aerosols should be stored in dark, cool place, not to be exposed to heat or sunlight. The container should not be punctured.
7. For metered-dose aerosols the following contents should be stated on the label: (1) the weight of the content in the container; (2) the quantity of active ingredient; (3) the total number of deliveries; and (4) the content of actives ingredient in an actuation. Unless otherwise specified, carry out the tests as follows.

Leakage rate The leakage rate per year of aerosols should comply with the following requirements.

Select 12 aerosol containers in random, wash the surfaces with ethanol, allow the containers to stand in an upright position at room temperature for 24 hours, and weigh accurately each container (W_1). Stand again for 72 hours (accuracy required ± 30 minutes) and weigh accurately (W_2). Cool them at $-4-20^\circ\text{C}$, drill quickly a hole in the

temperature until the propellants are expelled completely. Remove each of the valves from the containers, rinse with ethanol and dry at room temperature. Weigh accurately (W_3) and calculate the leakage rate according to the following formula. The average leakage rate per year is less than 3.5% and no one is not more than 5%.

$$\text{Leakage rate per year} = \frac{365 \times 24 \times (W_1 - W_2)}{[72 \times (W_1 - W_3)] \times 100\%}$$

Total number of deliveries per container The total number of deliveries per container of metered-dose aerosols should comply with the following requirements.

Select 4 aerosol containers, remove the caps and covers. Weigh each container accurately (W_1), shake thoroughly, and delivery the contents for ten times to a container containing a quantity of absorbent solution in a fume hood. Wash the mouthpieces with a suitable solvent, dry, and weigh each container accurately (W_2). Shake, and again delivery the contents for another ten times to the container. Wash the mouthpieces with a suitable solvent, dry and weigh each container accurately (W_3). Punch a small hole in the aluminium cap of the container, after the propellant has completely evaporated, discharge the contents, wash each container with a suitable solvent, dry, and weigh each container accurately (W_4). Calculate the total number of delivery per container by the formula: $10 \times (W_1 - W_4) / (W_2 - W_3)$, they are not less than the labelled number of delivery.

Content of active ingredient in an actuation The Content of active ingredient in an actuation of metered-dose aerosols should comply with the following requirements.

Procedure Select 1 aerosol container, shake thoroughly, and remove the cap and cover. Discharge 5 deliveries, wash the mouthpiece with a suitable solvent and dry. Invert the container in a beaker containing a quantity of absorbent solution. Immerse the mouthpiece under the surface of the absorbent solution (at least 25 mm). Discharge 10 or 20 deliveries. Remove the container, wash the exterior and interior of the mouthpiece with the absorbent solution. Transfer the combined solution and washings to a suitable volumetric flask, and dilute with the absorbent solution to volume. Determine the content, and divide the result by 10 or 20. The average content of active ingredient in an actuation, should be not less than 80% and not more than 120% of the labelled amount of ingredient in an actuation.

Particle or Droplet Size Distribution of Inhalation Preparations Unless otherwise specified, carry out the test for Determination of Particle or Droplet Size Distribution of Inhalation Preparations (Appendix X H), not less 15% of the labelled amount is deposited in the second impingement chamber.

Delivery rate The delivery rate of non-metered dose aerosols should comply with the following requirements.

Procedure Select 4 aerosol containers, remove the caps and covers, actuate each valve for a few seconds, clean the outside of the containers. Weigh each container accurately, immerse in a constant temperature water bath $25^\circ\text{C} \pm 1^\circ\text{C}$ for 30 minutes. After removal and blotting up, unless otherwise specified, actuate each valve continually for accurately 5 seconds. Weigh each container accurately after blotting to remove the residual contents. Return the containers to the constant temperature water bath $25^\circ\text{C} \pm 1^\circ\text{C}$, repeat the foregoing procedure for three times. Calculate the average delivery rate (g/s) for each container, the result should comply with the requirements described in the individual monograph.

Total amount of spray The total amount of spray of non-

metered dose aerosols should comply with the following requirements.

Procedure Select 4 aerosol containers, remove the caps and covers. Weigh each container accurately, actuate each valve continually in a 1000 ml or 2000 ml of conical flask in a fume hood until the container is empty, clean and weigh each container again. The total amount of spray for each container is not less than 85% of the labelled amount.

Sterility Aerosols intended to treat burns, wounds or ulcer should comply with the Test for Sterility (Appendix XI H).

Microbial limit Comply with the requirements for Microbial Limit Test (Appendix XI J).

Powers for spray Powers for spray may be classified as powders for spray for inhalation, for non-inhalation and for topical use according to the route of administration. Powders for spray for inhalation are micronized powders of one or more active ingredients together with or without carriers supplied in capsules, blisters, or powder reservoirs. After breathing by the patient the powder is delivered to the lung. They are administered by dry-powder inhalers. Powders for spray for non-inhalation are preparations of active ingredient together with or without carriers supplied in capsules or blisters. They are sprayed onto mucosa of various body cavities by a special dry-powder administration device. Powders for spray for topical use are products that the drug substance or drug substance with suitable added substance are packed in special administration devices, the drug substance is sprayed onto skin or mucosa with the outside force when used.

The manufacturing and storage of powers for spray should comply with the following requirements.

1. In the processing of powders for spray, suitable carriers or lubricants may be added to improve the flowability of the powders. The added substances should be nonirritating to mucosa of the respiratory tract or its cilia. The added substances of powders for spray for non-inhalation and for topical use should be nonirritating to skin or mucosa.
2. All the component units of the dry-powder inhaler should be nontoxic, nonirritating, stable and compatible with the contents.
3. The particle size of the powder must be not more than $10\ \mu\text{m}$, most of them should be less than $5\ \mu\text{m}$.
4. Unless otherwise specified, powders for spray for topical use should comply with the requirements described under the Powders.
5. Powders for spray should be stored in dark, cool place, and protected from moisture.

6. For powders for spray supplied in capsules or blisters the following contents should be stated on the label: ① the quantity of active ingredient contained in each capsule or blister; ② the capsules are intended for use in an inhaler and are not to be swallowed; ③ the expiration date; ④ the storage conditions.

For multi dose powders for spray for inhalation the following contents should be stated on the label: ① the quantity of each container; ② the content of the active ingredient; ③ the total number of inhalation; ④ the content of active ingredient of each inhalation.

Unless otherwise specified, carry out the tests as follows.

Content uniformity Unless otherwise specified, powders for spray supplied in capsules or blisters should comply with the requirements of the Test for Content Uniformity (Appendix X E).

Weight variation Unless otherwise specified, powders for spray supplied in capsules or blisters should comply with the

following requirements.

Procedure Weigh accurately 20 units, unless otherwise specified, and open each unit without loss of shell material, remove the content as far as possible, weigh the shell of each unit. Calculate the weight of content of each unit, and the average weight of content. Not more than 2 of the individual weights deviate from the average weight by more than the weight variation limit shown in the table, and none deviates by more than twice the limit.

Average weight of content	Weight variation limit
Less than 0.30 g	$\pm 10\%$
0.30 g or more	$\pm 7.5\%$

For the powders for spray, if the Test of Content Uniformity is specified, the test of weight variation is generally not required.

Inhaled percentage Powders for spray supplied in capsules or blisters should comply with the following requirements.

Procedure Unless otherwise specified, select 10 units, weigh each unit accurately. Place them one by one in the inhaler, withdraw the contents by suction at a flow rate of $60 \text{ L} \pm 5 \text{ L}$ per minute for 4 times, each time for 1.5 seconds, weigh each unit again. Remove all the residual contents with a brush or a suitable device, weigh each empty container. Calculate the inhaled percentage, and it is not less than 90%.

Total number of doses per container For powders for spray for inhalation supplied in powder reservoirs.

Procedure Unless otherwise specified, select one container, load the inhaler with a dose by turning the grip. Withdraw by suction at a flow rate of $60 \text{ L} \pm 5 \text{ L}$ per minute. Repeat the procedure until the last labelled dose is withdrawn. Determine the content of the last labelled dose. Repeat the test for a further 3 containers. Total number of doses per container should be not less than the labelled number of the preparation.

Content of active ingredient in a dose Powders for inhalation supplied in multiple dose powder reservoirs should comply with the following requirements.

Procedure Unless otherwise specified, select 6 containers, remove the caps and covers, discard the first 5 doses. Perform the test using the sampling apparatus for uniformity of dosage units of powder for spray for inhalation with 20 ml of a suitable absorbent solution in the container. (as Fig. 1) Place a suitable rubber mouthpiece adapter in the position at the end of the induction port to produce an airtight seal

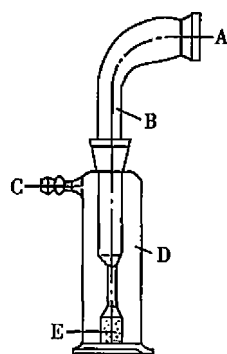


Fig. 1 Apparatus of the test for the uniformity of powder inhalers
A-Mouthpiece; B-Bronchia simulation; C-Outlet; D-160 ml glass container; E-fused glass of 100-160 μm

between the inhaler mouthpiece and the induction port. Prepare the inhaler for use by turning the grip (equivalent to one dose). Delivery the powders into the apparatus at a flow rate of $60 \text{ L} \pm 5 \text{ L}$ per minute for 5 seconds. Repeat the delivery sequence for a further 9 or 19 times. Rinse the interior of the apparatus with the same absorbent solution. Combine the solution and washings and dilute to a suitable volume. Determine the quantity of the active ingredient and divide the result by 10 or 20, to obtain the content of active ingredient in a dose, and it is not less than 65% and not more than 135% of the labelled amount in a dose. If 1 or 2 containers are outside the range of 65% to 135% of the labelled amount in a dose, but not outside range of 50% to 150% of the labelled amount in a dose, test 12 additional containers. The requirements are met if not more than 2 containers of the 18 are outside of the range of 65% to 135% of the labelled amount in a dose, but none outside the range of 50% to 150% of the labelled amount in a dose.

Particle or Droplet Size Distribution of Inhalation Preparations

Unless otherwise specified, carry out the test for Determination of Particle or Droplet Size Distribution of Inhalation Preparations (Appendix X H), not less 10% of the labelled amount is deposited in the second impingement chamber.

Microbial limit Comply with the requirements of Microbial Limit Test (Appendix XI J).

Sprays

Sprays are preparations of solutions or emulsions or suspensions of drugs, packed in special devices, which are released from the container in the form of nebulized substance with pressure of hand pump, high pressure of gas, ultrasonic vibration and others, to the deep respiratory tract, mucosa of various body cavities or the skin to obtain a local or systemic effect, or to the space. Sprays may be classified as sprays for inhalation, for non-inhalation and for topical use according to the route of administration. They are presented as metered dose and non-metered dose sprays. The manufacturing and storage of sprays should comply with the following requirements.

1. In the processing of sprays, suitable auxiliary substances may be added such as solvent, antioxidants, surfactant or other additives. The added substances in the sprays for inhalation should be physiologically acceptable, nonirritating and innocuous to the respiratory tract, skin or mucosa. All auxiliary substances in the sprays for non-inhalation and for topical use should be nonirritating and innocuous to skin or mucosa.
2. All the component units of the atomizing device should be nontoxic, nonirritating, stable and compatible with the contents.
3. The liquid in the solution sprays should be clear. Droplets of the emulsion sprays should be dispersed uniformly in the vehicle. The fine drug powder and the added substance in suspension sprays should be well mixed, and prepared as a stable spray. The particle size of the sprays for inhalation must be not more than $10 \mu\text{m}$, most of them should be less than $5 \mu\text{m}$.
4. The sprays should be stored in dark, cool place, and protected from moisture.
5. For single-dose sprays for inhalation the following contents should be stated: ① quantity of contents; ② the liquid should be put in the inhalation device before use, not be taken orally; ③ the expiration date; and ④ the conditions under which the sprays should be stored. For multi-dose sprays the following contents should be stated

of active ingredient; ③ the total number of deliveries; ④ the content of active ingredient in a dose; ⑤ the conditions under which the sprays should be stored.

Unless otherwise specified, the sprays should comply with the following requirements.

Total number of deliveries per container The metered-dose sprays should comply with the following requirements.

Procedure Select 4 containers, remove the caps and covers. Weigh each container accurately (W_1), shake thoroughly, and delivery the contents for ten times to a container containing a quantity of absorbent solution in a fume hood according to the insert-sheet. Wash the mouthpieces with a suitable solvent, dry, and weigh each container accurately (W_2). Shake, and again delivery the contents for another ten times to the container. Wash the mouthpieces with a suitable solvent, dry and weigh each container accurately (W_3). Open the container, discharge the contents, wash each container with a suitable solvent, dry, and weigh each container accurately (W_4). Calculate the total number of delivery per container by the formula: $10 \times (W_1 - W_4) / (W_2 - W_3)$. Not less than the labelled number of delivery.

Delivery amount in a dose Unless otherwise specified, the metered dose sprays should comply with the following requirements.

Procedure Select 4 containers, discharge several doses according to the insert-sheet, clean the containers, weigh accurately. Continuously discharge 3 doses, clean the containers each time after discharging and weigh each container accurately. Calculate the delivery amount in a dose based on the 3 doses. Continuously discharge 10 doses, clean the containers and weigh each container accurately. Repeat the procedure and calculate the delivery amount in a dose based on the other 3 doses. Continuously discharge 10 doses, clean the containers and weigh each container accurately. Repeat the procedure and calculate the delivery amount in one dose based on the another 4 doses. Calculate the average delivery amount in one dose based on the 10 deliveries. Unless otherwise specified, the result should not less than 80% and not more than 120% of the labelled amount in one delivery. Where the test for content of active ingredient per spray is specified, the test for delivery amount in a dose may not be required.

Content of active ingredient in a unit spray Unless otherwise specified, the metered dose sprays should comply with the following requirements.

Procedure Select 1 container, discharge 5 deliveries according to the insert-sheet, wash the mouthpiece with a suitable solvent and dry thoroughly. Discharge 10 or 20 deliveries (the time interval is 5 second with shaking gently) the delivered substance is collected in a quantity of absorbing solvent (avoiding any loss) Transfer to a suitable volumetric flask, and dilute to volume. Determine the content, and divide the result by 10 or 20. The average content of active ingredient in a unit spray, should be not less than 80% and not more than 120% of the labelled amount of ingredient in a unit spray.

Particle or Droplet Size Distribution of Inhalation Preparations Unless otherwise specified, carry out the test for Determination of Particle or Droplet Size Distribution of Inhalation Preparations (Appendix X H), not less 15% of the labelled amount is deposited in the second impingement chamber.

Weight variation Single-dose sprays should comply with the following requirements.

weight of each unit and the average weight; according to the individual monograph. Not more than 2 of the individual weights deviate from the average weight by more than the weight variation limit shown in the table, and none deviates by more than twice the limit.

Average weight	Weight variation limit
Less than 0.30 g	$\pm 10\%$
0.30 g or more	$\pm 7.5\%$

Fill Multi-dose sprays should comply with requirements of the test for minimum fill (Appendix X F).

Sterility Sprays intended to treat burns, wounds or ulcer should comply with requirements of the Test for Sterility (Appendix XI H).

Microbial limit Unless otherwise specified, sprays should comply with the requirements of Microbial Limit Test (Appendix XI J).

I M Pellicles

Pellicles are preparations in pellicular form processed by the active ingredients with appropriate pellicular material. They are intended for oral use or topical use on external mucous membranes.

The production and storage of pellicles comply with the following requirements.

1. Pellicular materials and other excipients should be innocuous, nonirritating, stable and compatible with the active ingredients. Pellicular materials in general use are polyvinyl alcohol or polyacrylic acid resins, cellulose and other natural materials of high molecular weights.

2. For water-soluble active ingredients, a solution of suitable viscosity may be made by adding pellicular material. For water-insoluble active ingredients, they should be finely powdered and a uniform mixture of the fine powders and the pellicular material may be made.

3. Pellicles should look smooth and without breakage, uniform in colour and in thickness and contain no obvious bubble remainings. Pellicles of multiple dose are prepared with clear and uniform subdivision by pressing and can be separated along the pressed mark.

4. The packaging materials used for pellicles should be innocuous, convenient to use, efficient in prevention from contamination and compatible with the active ingredients and pellicular material.

5. Unless otherwise specified, pellicles are preserved in tightly closed containers, protected from moisture, molds and prevented from deterioration. Unless otherwise specified, pellicles comply with the following requirements.

Weight variation The weight variation complies with the following requirements.

Average weight	Limit of weight variation
0.02 g or less	$\pm 15\%$
More than 0.02 g to 0.2 g	$\pm 10\%$
0.2 g or more	$\pm 7.5\%$

Procedure Unless otherwise specified, take at random 20

weight of each. Calculate the average weight of the samples and compare with the weight of individual sample. Not more than 2 samples deviate outside of the limit of weight variation, and none deviates more than twice of the limit. Where the test for content uniformity is prescribed, the test for weight variation may not be required.

Microbial limit Unless otherwise specified, pellicles comply with Microbial Limit Tests (Appendix XI J).

I N Granules

Granules are dry granular preparations with appropriate particle size made of medicaments and suitable excipients. Granules may be classified into soluble granules (usually known as granules), suspended granules, effervescent granules, enteric-coated granules, sustained-release granules and controlled-release granules. They are intended for oral administration.

Suspended Granules Suspended Granules are dry granules with appropriate particle size made of insoluble solid medicaments and suitable excipients. Water or other suitable liquid is added with shaking before use to distribute and form a suspension for oral administration. Unless otherwise specified, suspended granules comply with Dissolution Test.

Effervescent Granules Effervescent Granules are granules containing sodium bicarbonate and organic acids which release a large amount of carbon dioxide in effervescent appearance when water is added. The active ingredients in effervescent granules are freely soluble in water and in the effervescent solution. Organic acids such as citric acid, tartaric acid, etc. are usually used. Effervescent granules are dissolved or distributed in water before oral use.

Enteric-Coated Granules Enteric-Coated Granules are granules coated with enteric-coating material or made by other suitable method.

Enteric-coated granules prevent the active ingredients from decomposition and failing to effectiveness, from irritation to stomach, or can control the specific-site release of the active ingredients in the intestinal fluid.

Enteric granules comply with Drug Release Test.

Sustained-Release Granules Sustained-Release Granules are granules which release medicaments in a gradual, non-constant rate way in water or a prescriptive release medium. They comply with related requirements for sustained-release preparations (Appendix XX D) and Drug Release Test.

Controlled-Release Granules Controlled-Release granules are granules which release medicaments in a gradual, constant rate way or nearly constant rate way in water or a prescriptive release medium.

They comply with relate requirements for controlled-release preparations and Drug Release Test.

The production and storage of granules should comply with the following requirements.

1. The medicaments and excipients should be mixed well. A suitable temperature is controlled during the manufacture of volatile or heat-labile medicaments, and medicaments unstable to light should be protected from light.

2. Granules should be dry, uniform in particle size and

agglomeration and deliquescence.

3. If necessary, some suitable auxiliary substances, such as flavoring agent, aromatics, colouring agents, dispersing agents and preservatives, etc. may be added during the manufacture.

4. Granules comply with the requirements for tests of dissolution, drug release, content uniformity, microbial limit, etc. If necessary, coated granules should be examined for residue of organic solvents.

5. Unless otherwise specified, granules are preserved in tightly closed containers and stored in a dry place and protected from moisture.

6. The name and content of the active ingredients of single-dose granules should be provided and stated on the label. The name and weight of the active ingredients of multi-dose granules should be provided and stated on the label, and the precise method for subdivision provided.

Unless otherwise specified, granules comply with the following requirements.

Particle size Unless otherwise specified, carry out the test of particle size and its distribution [Appendix IX E, method 2 (2)]. The total weight of granules, which can not pass through No. 1 sieve (2000 μm) and can pass through No. 5 sieve (180 μm), should not be more than 15% of the test sample.

Loss on drying Unless otherwise specified, carry out the method for loss on drying (Appendix VIII L). Dry to a constant weight at 105°C, or at 80°C under vacuum for granules containing sugar, weight loss should not be more than 2.0 percent.

Dispersion Unless otherwise specified, soluble and effervescent granules comply with following requirements.

Procedure for soluble granules To 10 g granules add 200 ml of hot water and stir for 5 minutes, the granules should be completely dissolved or show slight turbidity without foreign matter.

Procedure for effervescent granules Take 6 packs of single-dose packages and transfer each to a 250 ml beaker containing 200 ml of 15-20°C water. Bubbles of carbon dioxide in effervescent appearance should generate at once. Granules of the 6 packs should be dispersed completely or dissolved in the water in 5 minutes.

Dispersion test may not be required for suspended granules or granules that comply with Dissolution Test or Drug Release Test.

Weight variation Weight variation limit of single-dose granules should comply with the following requirements.

Average weight or labelled weight	Weight variation limit
0.1 g or less	$\pm 10\%$
More than 0.1 g to 1.5 g	$\pm 8\%$
More than 1.5 g to 6.0 g	$\pm 7\%$
More than 6.0 g	$\pm 5\%$

Procedure Take 10 packs (bottles) of test sample, discard the wrapper, and accurately weigh the content of each separately. Calculate the weight of each pack and the average weight. Compare the weight of each with the average weight (compare the weight of each with the labelled weight for granules that assay is not required). Not more than 2 individual values deviate outside of the limit, and none deviate more than twice of the limit. The test of weight variation may not be required for granules that comply with the Test for Content Uniformity.

Minimum Fill (Appendix X F).

I O Oral Solutions, Oral Suspensions, Oral Emulsions

Oral Solutions Oral Solutions are clear liquid preparations made of soluble medicaments dissolved in a suitable solvent, intended for oral administration.

Oral Suspensions Oral Suspensions are suspended liquid preparations made of insoluble solid medicaments dispersed in a liquid medium, intended for oral administration. Oral suspensions include also dried suspensions or concentrated suspensions.

Oral Emulsions Oral Emulsions are emulsified preparations of stable oil-in-water emulsions, made of two immiscible liquids.

Oral solutions, oral suspensions or oral emulsions measured in small quantity with a suitable measuring device or in drops are called oral droppings.

The production and storage of oral solutions, oral suspensions and oral emulsions comply with the following requirements.

1. Purified water is commonly used as the solvent for oral solutions or dispersion medium for oral suspensions.
2. Suitable auxiliary substances such as preservatives, dispersion agents, suspending agents, thickening agents, solubilizing agents, wetting agents, buffering agents, emulsifiers, stabilizing agents, flavouring agents and pigments, etc. may be added. The varieties and amount of the selected auxiliary substances comply with related requirements of the National Standards and should not interfere with the stability and testing of the preparations.
3. They should not be contaminated by mould, nor should they become rancid or discoloured, nor should they generate foreign material, gases or other deterioration phenomena.
4. Oral emulsions should be uniformly opal coloured. When they are centrifuged for 15 minutes by 4000 revolutions per minute (about $1800 \times g$), no phase is separated.
5. The particles of oral suspensions should be dispersible uniformly and redispersed easily on shaking when a sediment is produced on standing, and the ratio of sedimental volume should be determined.
6. The package of oral droppings should usually include a dropper with aspirating bulb or other measuring device.
7. Single-dose oral suspensions or oral emulsions comply with the requirements for the Test for Content Uniformity.
8. Unless otherwise stated, they should be preserved in tightly closed containers and protected from light.
9. "Shaking before use" should be designated on the label of oral suspensions. The number of drops per milliliter or per gram should be designated on the label of oral droppings. Unless otherwise specified, oral solutions, oral suspensions and oral emulsions comply with the following requirements.

Weight variation Unless otherwise specified, single-dose dry suspensions comply with the following requirements.

Procedure Weigh individually the content of 20 test samples and calculate the average content weight. Not more than 2 of the individual weight deviate from the average weight by more than $\pm 10\%$ and none more than $\pm 20\%$.

for weight variation may not be required.

Filling Unless otherwise specified, single-dose oral solutions, oral suspensions and oral emulsions comply with the following requirements.

Procedure Take 10 test samples and remove the content as completely as possible and weigh the content weight individually. No content weight should be less than the labelled weight.

Multi-dose oral solutions, oral suspensions, oral emulsions and oral droppings comply with the test of Minimum Fill (Appendix X F).

Loss on drying Unless otherwise specified, carry out the method for loss on drying (Appendix VIII L). The weight loss should not be more than 2.0 percent.

Ratio of sedimental volume The ratio of sedimental volume of oral suspension should be not less than 0.90.

Procedure Unless otherwise specified, shake vigorously 50 ml of the test sample in a stoppered cylinder for 1 minute, and record highness H_0 in the beginning. Allow to stand for 3 hours, record the final highness H . Calculate the ratio of sedimental volume according to the following equation:

$$\text{Ratio of sedimental volume} = H/H_0$$

For oral dried suspensions a certain proportion of water is added according to the monograph concerned, they should be dispersed uniformly on shaking. The ratio of sedimental volume is determined and comply with the above requirements.

Microbial limit They comply with Microbial Limit Tests (Appendix XI J).

I P Powders

Powders are preparations in the form of dry powder made of pulverized and uniform mixtures of medicaments and suitable excipients. They may be classified into oral powders and powders for topical use.

Oral Powders Oral Powders are powders for oral administration and administered directly with water or after dissolving or dispersing in water or other liquid.

Powders for Topical Use Powders for Topical Use may be applied to the skin, mouth, throat, cavities, etc. The powders which are used particularly for therapeutic, prophylactic or lubricating purposes may be called as dusting-powders or dusting preparations.

The production and storage of powders should comply with the following requirements.

1. The ingredients for preparing powders should be finely powdered. Unless otherwise stated, oral powders should be fine powder, powders for topical use should be very fine powder.
2. Powders should be dry, loose, mixed well and uniform in appearance and colour. If they contain poisonous, potent drug, or drug in small dosage, they should be prepared or compoundedly mixed well and sifted.
3. Powders are prepared with or without auxiliary substances. Flavouring, colouring agents or aromatics may be added if necessary.
4. Powders are packaged as single-dose or multi-dose preparations, and for latter a dose dividing tool should be

5. Unless otherwise stated, powders should be preserved in well-closed containers. Powders containing volatile or hygroscopic drugs should be preserved in tightly closed containers.

Unless otherwise specified, powders comply with the following requirements.

Particle size Unless otherwise stated, powders for topical use comply with the following requirements of fineness.

Procedure Weigh accurately about 10 g of the powder and place on a No. 7 sieve, cover the lid on top of the sieve, fit tightly an appropriate receiver. Carry out the test for fineness and its distribution [Appendix IX E, method 2, single screening]. Weigh accurately the fractions passed through the sieve, and not less than 95 percent of the powder should be weighed.

Uniformity of appearance

Procedure Spread evenly a sufficient quantity of powders in an area of about 5 cm² on a piece of smooth paper, press the surface even, observe the powder under a bright light. It should be uniform in colouration with no discolourations and colour stains.

Loss on drying Unless otherwise specified, carry out the test for loss on drying (Appendix VIII L).

Loss on drying to constant weight at 105°C should be not more than 2.0%.

Weight variation The weight variation of powders packaged in single-dose should comply with the requirement of the following table.

Average weight or labelled weight	Weight variation limit
0.1 g or less	±15%
More than 0.1 g to 0.5 g	±10%
More than 0.5 g to 1.5 g	±8%
More than 1.5 g to 6.0 g	±7%
More than 6.0 g	±5%

Procedure Weigh accurately the content of each 10 packs (bottles) of powders and calculate the average content weight. Compare the content weight with the average weight (compare the weight of each with the labelled weight for powders that assay is not required). Not more than 2 packs deviate outside of the weight variation limit, and none of individual weight deviates by more than twice the limit.

Where the Test for Content Uniformity is specified, the test for weight variation may not be required.

Filling Multi-dose packaged powders comply with the test of Minimum Fill (Appendix X F).

Sterility Powders used for burns or skin injuries comply with Test for Sterility (Appendix XI H).

Microbial limit Unless otherwise specified, comply with the requirements of Microbial Limit Tests (Appendix XI J).

I Q Ear Preparations

Ear preparations are preparations intended for direct application to the auditory meatus to display topical therapeutic effect.

Ear preparations may be classified into liquid ear preparations (ear drops, ear washes, ear sprays), semi-solid ear

solid ear preparations (ear powders, ear pilules, ear tampons), etc. They can also be packed in a solid form with a solvent, from which solutions or suspensions are prepared before use.

Ear Drops Ear Drops are clear solutions, suspensions or emulsions made of medicaments, suitable excipients and suitable solvents or dispersion media such as water or glycerol, etc., intended for instillation in external auditory meatus. They can also be in the form of powders, granules, masses or tablets with a separate solvent, from which clear solutions or suspensions are prepared before administration.

Ear Washes Ear Washes are liquid ear preparations in the form of clear aqueous solutions made of medicaments and suitable excipients, intended for cleaning the external auditory meatus. They are usually aqueous solutions of physiological pH value; when used for injuries and surgical procedures, they should be sterilized.

Ear Sprays Ear Sprays are liquid ear preparations in the form of clear solutions, suspensions or emulsions made of medicaments and suitable excipients and are intended for administration to the auditory meatus through nebulization by atomizing devices.

Ear Ointments Ear Ointments are semi-solid ear preparations in the pasty form of solution or suspension made of uniform mixtures of medicaments and suitable excipients.

Ear Creams Ear Creams are semi-solid ear preparations in the form of cream made of uniform mixtures of medicaments and suitable excipients.

Ear Gels Ear Gels are semi-solid ear preparations in the form of gel made of medicaments and suitable excipients.

Ear Tampons Ear Tampons are solid ear preparations made of medicaments and suitable excipients, intended to be inserted into the external auditory meatus.

Ear Powders Ear Powders are solid ear preparations in the form of powder made of medicaments and suitable excipients, intended to be put or insufflated into the external auditory meatus.

Ear Pilules Ear Pilules are solid ear preparations in the form of sphere or almost sphere shape made of medicaments and suitable excipients, intended to be applied in the external or medium auditory meatus.

The production and storage of ear preparations should comply with the following requirements.

1. Ear preparations may contain a variety of excipients used for adjusting tension, viscosity, or pH value of the preparations, increasing the solubility of active ingredients, stabilizing the preparation and providing adequate antimicrobial properties. These excipients should not adversely affect the intended medicinal action of the preparation, and should not be nocuous nor topically irritant. Solvents (for example, water, glycerol or fatty oil, etc.) should not exert harmful pressure on the eardrum. Unless otherwise stated, multi-dose packaged aqueous ear preparations should contain bacteriostatics of suitable concentration; bacteriostatics may not be added if the preparation itself has sufficient bacteriostatic effect.

2. Unless otherwise stated, for ear preparations packaged in multi-dose, an integral dropper or suitable device should be provided, usually consisting of a screw cap incorporating with a dropper and rubber or plastic teat. The container should be innocuous and properly cleaned, and compatible with the medicaments and excipients. The wall of containers should be uniform and of definite thickness. The containers should not contain more than 10 ml or 5 g of the preparation.

3. Ear solutions should be clear and without sediments of foreign materials. Ear suspensions may show a sediment which is readily dispersed on shaking. Ear emulsions may show evidence of separation but are easily reformed on shaking.

4. Unless otherwise stated, ear preparations comply with the general requirements for preparations of the dosage forms concerned. For example, eye ointments should comply with the requirements of ointments.

5. Ear preparations comply with the requirements of the Test for Content Uniformity, etc.

6. Unless otherwise stated, ear preparations should be preserved in well closed containers.

7. Ear preparations must not be used for exceeding 4 weeks after opening.

Unless otherwise specified, ear preparations comply with the following requirements.

Ratio of sedimental volume The ratio of sedimental volume of suspended ear drops should be not less than 0.90.

Procedure Unless otherwise stated, shake vigorously 50 ml of the test sample in a stoppered cylinder for 1 minute, and record highness H_0 in the beginning. Allow to stand for 3 hours, record the final highness H . Calculate the ratio of sedimental volume according to the following equation:

$$\text{Ratio of sedimental volume} = H/H_0$$

Weight variation Unless otherwise specified, solid ear preparations comply with the following requirements.

Procedure Weigh individually 20 test samples (or their contents) and determine the average weight. Not more than 2 of the individual weight deviate from the average weight by more than $\pm 10\%$ and none more than $\pm 20\%$.

Where the Test for Content Uniformity is specified, the test for weight variation may not be required.

Filling Semi-solid and liquid ear preparations comply with the test of Minimum Fill (Appendix X F).

Sterility Ear drops and ear washes for surgical procedures, injured ear and perforated ear-drum comply with Test for Sterility (Appendix XI H).

Microbial limit Unless otherwise stated, they comply with the requirements of Microbial Limit Tests (Appendix XI J).

I R Nasal Preparations

Nasal preparations are preparations intended for direct administration to the nasal cavities to obtain a systemic or local therapeutic effect.

Nasal preparations may be classified into liquid nasal preparations (nasal drops, nasal washes, nasal sprays), semi-solid nasal preparations (nasal ointments, nasal creams, nasal gels) and solid nasal preparations (nasal powders, nasal powders for spray, nasal sticks), etc. They can also be packed in a solid form with a solvent, from which solutions or suspensions are prepared before use.

Nasal Drops Nasal Drops are liquid nasal preparations in the form of clear solutions, suspensions or emulsions made of medicaments and suitable excipients, intended for administration to the nasal cavities. The medicaments may be packed in the form of powder, granules, masses or tablets with a separate solvent, from which clear solutions or

Nasal Washes Nasal Washes are liquid nasal preparations made of medicaments in isotonic aqueous solutions of physiological pH value, intended for washing nasal cavities. Nasal washes used for nasal injuries or surgical procedures should be sterilized.

Nasal Sprays Nasal Sprays are liquid nasal preparations in the form of clear solutions, suspensions or emulsions made of medicaments and suitable excipients, intended for administration to the nasal cavities through nebulization by atomizing devices.

Nasal Ointments Nasal Ointments are semi-solid nasal preparations in the pasty form of solution or suspension made of medicaments with suitable bases.

Nasal Creams Nasal Creams are semi-solid nasal preparations in the form of cream made of uniform mixtures of medicaments with suitable bases.

Nasal Gels Nasal Gels are semi-solid nasal preparations in the form of gel made of medicaments with suitable bases.

Nasal Powders Nasal Powders are solid nasal preparations in the form of powder made of medicaments and suitable excipients, intended for insufflation into nasal cavities with a suitable tool.

Nasal Powders for Spray Nasal Powders for Spray are solid nasal preparations in the form of powder made of medicaments and suitable excipients, intended for the powders to be sprayed into nasal cavities by a suitable valve system.

Nasal Sticks Nasal Sticks are solid nasal preparations in the form of stick or almost stick shape made of medicaments and suitable excipients, intended for inserting into nasal cavities. The production and storage of nasal preparations comply with the following requirements.

1. Nasal preparations may contain auxiliary substances to adjust the viscosity and pH value, to increase the solubility of the medicaments, to stabilize the preparation, or to maintain the shape of the preparation. Unless otherwise stated, aqueous nasal preparations of multi-dose should contain bacteriostatics of suitable concentration; bacteriostatics may not be required when the preparation itself has sufficient bacteriostatic effect.

2. Nasal preparations packaged in multi-dose should be provided with an integral dropper or with a screw cap incorporating with a dropper and rubber or plastic teat. The containers should be innocuous and cleanly washed, and compatible with the medicaments and excipients. The wall of the containers should be of a definite and uniform thickness. Unless otherwise stated, the containers hold not more than 10 ml or 5 g of the preparation.

3. Nasal solutions should be clear without sediments or foreign material. Nasal preparations in the form of suspension may show a sediment which is readily dispersed on shaking. Nasal preparations in the form of emulsion may show evidence of separation but are easily reformed on shaking.

4. The particle size of the medicaments and excipients of nasal powders for spray should be mostly in the range of 30-150 μm .

5. Nasal preparations should be nonirritating and do not adversely affect the function of the nasal mucosa and its cilia. Aqueous nasal preparations should be isotonic.

6. Unless otherwise stated, nasal preparations comply with the general requirements for preparations of the dosage forms concerned. For example, nasal ointments should comply

7. Nasal preparations comply with the requirements of the Test for Content Uniformity.

8. Unless otherwise stated, nasal preparations should be preserved in well-closed containers.

9. Nasal preparations packaged in multi-dose must not be used for exceeding 4 weeks after opening.

Unless otherwise specified, nasal preparations comply with the following requirements

Ratio of sedimental volume Unless otherwise specified, the ratio of sedimental volume of suspended nasal drops should be not less than 0.90.

Procedure Unless otherwise stated, shake vigorously 50 ml of the test sample in a stoppered cylinder for 1 minute, and record highness H_0 in the beginning. Allow to stand for 3 hours, record the final highness H . Calculate the ratio of sedimental volume according to the following equation:

$$\text{Ratio of sedimental volume} = H/H_0$$

Weight variation Unless otherwise specified, solid nasal pre-parations comply with the following requirements.

Procedure Weigh individually 20 test samples (or their contents) and determine the average weight. Not more than 2 of the individual weight deviate from the average weight by more than $\pm 10\%$ and none more than $\pm 20\%$.

Where the Test for Content Uniformity is specified, the test for weight variation may not be required.

Filling Semi-solid and liquid nasal preparations comply with the test of Minimum Fill (Appendix X F).

Sterility Nasal preparations for surgical procedures or injuries comply with Test for Sterility (Appendix XI H).

Microbial limit Unless otherwise specified, they comply with the requirements of Microbial Limit Tests (Appendix XI J).

I S Lotions, Irrigants, Enemas

Lotions Lotions are liquid preparations in the form of solutions, suspensions or emulsions containing medicaments, intended for bathing or smearing the unbroken skin.

Irrigants Irrigants are sterile solution intended for irrigating open injuries or cavities.

Enemas Enemas are liquid preparations of aqueous or oily solutions or suspensions, intended to be perfused into rectum for therapy, diagnosis or nutrition. The production and storage of lotions, irrigants and enemas comply with the following requirements.

1. They should be innocuous and without local irritation. Irrigants should be sterile.

2. During storage, lotions in the form of emulsion may show evidence of separation but are easily reformed on shaking. Lotions in the form of suspension may show a sediment which is readily dispersed on shaking to give a suspension which remains sufficiently stable to enable the correct dose to be delivered. Lotions which deteriorate easily should be prepared before use.

3. Irrigants may be made of medicaments, electrolytes or isotonic modifiers dissolving in water for injection; lotions may also be water for injection, of which "for irrigation"

Irrigants are usually isotonic to blood. Irrigants should be clear when examined visually under suitable conditions. The containers of irrigants comply with the requirements of those of injections.

4. Irrigants should not be used as injection. "For use only once" should be designated on the label of irrigants and the remainder should be discarded. Enemas of large volume should be warmed to body temperature before use.

5. Unless otherwise stated, lotions are preserved in well-closed containers, irrigants in very tightly closed containers, enemas in tightly closed containers. Lotions, irrigants and enemas comply with the following requirements.

Filling Unless otherwise specified, lotions, irrigants and enemas comply with the test of Minimum Fill (Appendix X F).

Sterility Irrigants comply with Test for Sterility (Appendix XI H).

Microbial limit Lotions and enemas comply with the requirements of Microbial Limit Tests (Appendix XI J).

Bacterial endotoxin or Pyrogens

Unless otherwise specified, irrigants comply with the requirements of the Test for Bacterial Endotoxin (Appendix XI E) or Test for Pyrogens (Appendix XI D). The bacterial endotoxin per milliliter should be less than 0.5 EU endotoxin.

Irrigants which can not be examined by the test for bacterial endotoxin should comply with the requirements for the test of pyrogens. Unless otherwise specified, the dose is 10 ml per kilogram body weight of rabbit.

I T Liniments, Paints, Pigments

Liniments Liniments are liquid preparations in the form of solutions, suspensions or emulsions, intend for external use to rub on unbroken skin.

Paints Paints are liquid preparations in the form of aqueous or oily solutions, suspensions or emulsions, intended to be smeared on the skin or mucous membrane of mouth or throat with the aid of gauze or cotton impregnated with the liquid.

Pigments Pigments are liquid preparations made of medicaments dissolved or dispersed in a solvent containing film-forming material, intended for external use on affected area to form a film.

The production and storage of liniments, paints and pigments comply with the following requirements.

1. They should be innocuous and without local irritation.

2. During storage, liniments or paints in the form of emulsion may show evidence of separation but are easily reformed on shaking. Liniments or paints in the form of suspension may show a sediment which is readily dispersed on shaking to give a suspension which remains sufficiently stable to enable the correct dose to be delivered. Liniments or paints which deteriorate easily should be prepared before use.

3. Generally used solvents for liniments include water, ethanol, liquid paraffin, glycerol or vegetable oil, etc. Paints are basically glycerol solutions of disinfectants or anti-inflammatory agents, and ethanol or vegetable oil may also be used as the solvents.

by epiderm. It is necessary to put the liniments on flannel or other soft tissues first, and then apply it gently to the affected area. The flannel or other soft tissues used must be clean. Pigments are intended for smearing on the affected area. After evaporation of the organic solvents, a film is generated to protect the affected area and the medicaments released slowly to exert therapeutic effect. Pigments are usually used for injured dermatosis without exudate, etc. Film-forming material generally used for pigments include polyglycol, polyethylene pyrrolidone, ethylcellulose and polyglycol aldehyde methylacetal, etc.; plasticizers used include glycerol, propylene glycol, dibutyl phthalate, etc.; solvents used include ethanol, etc.

5. They should not be rancid, discolouring, etc. If necessary, preservatives and antioxidants may be added.

6. Unless otherwise specified, they should be preserved in well-closed containers and protected from light.

7. Unless otherwise stated, paints and pigments must not be used for exceeding 4 weeks after opening.

8. "Not for oral use" should be designated on the label.

Unless otherwise stated, liniments, paints and pigments comply with the following requirements.

Filling Unless otherwise stated, liniments, paints and pigments comply with the requirements of Minimum Filling (Appendix X F).

Microbial limit They comply with the requirements of Microbial Limit Tests (Appendix XI J).

I U Gels

Gels are thick liquid or semi-solid preparations in the form of uniform suspension or cream containing medicaments with suitable gelling excipients. Unless otherwise stated, gels are restricted to topical use such as skin or body cavities (nasal cavity, vagina and rectum, etc.). Emulsified gels are also known as emulsion gels. Gels consisted of natural high molecular bases such as tragacanth are also known as mucilages. A gel of small particles of inorganic chemical medicaments (e.g. aluminum hydroxide), which consists of a network of discrete colloidal particles of drug substances, is classified as a two-phase dispersion system, and is also referred to as a magma. Magma may have thixotropic property; a semi-solid is formed on standing which becomes liquid on stirring or shaking.

Gel bases are single-phase dispersion systems and classified into hydrophilic and hydrophobic. Hydrophilic gel bases usually consist of water, glycerin or propylene glycol gelled with cellulose derivative, carbomer and alginates, tragacanth, gelatin, starch, etc. Hydrophobic gel bases consist of liquid paraffin with polyethylene or fatty oil gelled with colloidal silica or aluminum soap or zinc soap, etc.

The production and storage of gels comply with the following requirements.

1. Colloid particles in suspended gels should disperse uniformly. No sedimentation or caking occurs.

2. Gels should be uniform, fine and smooth, and kept in gel structure without drying up or being liquified at room temperature.

3. Wetting agents, preservatives, antioxidants, emulsifiers, thickening agents and percutaneous accelerators may be

4. Gel bases should not interact physically or chemically with the medicaments.

5. Unless otherwise stated, gels should be preserved in tightly close containers, protected from light, at a temperature below 25°C, and not allowed to freeze.

6. The label of gels states that they should be shaken well before use.

Unless otherwise specified, gels comply with the following requirements.

Particle size Unless otherwise specified, take suitable amount of suspended gels and spread a quantity of the content to three slides separately to form a thin layer with an area approximately corresponding to that of the cover-glass. Carry out the test for determination of particle size and its distribution (Appendix IX E, method 1), no particle greater than 180 μm in dimension is allowed.

Filling They comply with the test of Minimum Filling (Appendix X F).

Sterility Gels intended for use for severe injuries comply with Test for Sterility (Appendix XI H).

Microbial limit They comply with the requirements of Microbial Limit Tests (Appendix XI J).

I V Patches

Patches are a class of laminar pharmaceutical preparations applied to skin to produce systemic or topical effect. Patches normally consist of an outer covering, a drug reservoir, which may have a rate controlling membrane or not, a contact adhesive and a protective liner being removed before applying the patch to the skin. Patches are intended to be applied to the surface of the unbroken skin, include the surface of the ill skin and the broken skin. Transdermal patches are intended to be applied to the surface of the unbroken skin in order to deliver the active substance(s) to the systemic circulation after passing through the skin barrier.

There are several diffusion patterns for the Transdermal patches. The active substance(s) may delivered to the skin and the systemic circulation directly through a reservoir. Perhaps the active substance(s) may delivered to the skin and the systemic circulation through the rate controlling membrane and the adhesive liner. The activity duration of the active ingredient(s) is determined by its (their) quantity in the patch and the release rate from the patch.

The outer covering of transdermal patches is impermeable to the active substance(s) and normally impermeable to water. The reservoir of transdermal patches can be the matrix style or the controlling membrane style.

The protective liner works on preventing the adhesion and protecting the preparation, generally consists of preventing adhesion paper, a sheet of plastic or metal material. When removed, the protective liner does not detach the preparation reservoir or the adhesive liner from the patch.

When applied to the dried, clean and unbroken skin, the patches adheres firmly to the skin by gentle pressure of the hand or the fingers and can be peeled off without causing appreciable injury to the skin or detachment of the preparation from the outer covering. The patch must not be irritant or sensitizing to the skin, even after repeated applications.

The manufacturing and storage of patches should comply

1. The materials and excipients of patches should comply with the relevant requirements of national standards, innocuous, non-irritating, stable and compatible with active ingredient(s). The commonly used materials include aluminum foil-ethylene composite membrane, adhesion-preventive paper, ethylene-vinyl acetate copolymer, acrylic acid or polyisobutylene pressure-sensitive adhesive, silicone rubber and polyethylene glycol, etc.
2. Substances such as surfactant, emulsifier, humectant, preservative or antioxidant may be added to patches if necessary. Transdermal absorption promoter may be added to transdermal patches.
3. The appearance of the patches should be intact and clean, the applying area should be uniform, and the cut border should be smooth, without sharp edges.
4. Active ingredient(s) may be dissolved in solvent and filled into the reservoir. No air bubble is allowed to contain in the reservoir which is sealed without leakage. The active ingredient(s) suspended in the preparation should be homogenous, stable and spreaded evenly.
5. Pressure-sensitive adhesive should be spreaded evenly. Organic solvent residual should be monitored (Appendix VIII

P) when Organic solvent is used in the processing.

6. It should be stated on the label that the patches should not be applied to individuals with a history of allergy to solvent such as ethanol etc.
7. The content uniformity, the drug release, the adhesive force of the patches should comply with the requirements.
8. Unless otherwise specified, patches should be preserved in well closed containers.
9. The quantity of active substance(s) per patch, the total activity duration and the effective area of the releasing surface should be stated on the label of patches. Unless otherwise specified, the following corresponding tests should be conducted for the patches.

Content Uniformity Transdermal patches should comply with the Test for Content Uniformity (Appendix X E).

Drug Release Test Transdermal patches should comply with the Drug Release Test (Appendix X D, method 3).

Microbial limit Unless otherwise specified, comply with the requirements of Microbial Limit Tests (Appendix XI J).

Appendix III General Identification Tests

Acetates

(1) Heat a quantity of the substance being examined with sulfuric acid and ethanol; the characteristic odour of ethyl acetate is liberated.

(2) To a neutral solution of the substance being examined add 1 drop of ferric chloride TS; a deep red colour is produced which disappears on addition of dilute mineral acid.

Aluminium Salts

(1) Add sodium hydroxide TS to a solution of the substance being examined; a gelatinous white precipitate appears which is soluble in an excess of sodium hydroxide TS.

(2) Add ammonia TS to a solution of the substance being examined until a gelatinous white precipitate is formed. Add a few drops of sodium alizarinsulfonate IS; the precipitate becomes cherry red in colour.

Ammonium Salts

(1) Heat a quantity of the substance being examined with an excess of sodium hydroxide TS; the characteristic odour of ammonia is perceived, the vapour turns moistened red litmus paper to blue and blackens a strip of filter paper moistened with mercurous nitrate TS.

(2) To a solution of the substance being examined add 1 drop of alkaline mercuric potassium iodide TS; a reddish brown precipitate is produced.

Antimony Salts

(1) Acidify a solution of the substance being examined with acetic acid, heat on a water bath and to the hot solution add a few drops of sodium thiosulfate TS; an orange red precipitate is produced gradually.

(2) Acidify a solution of the substance being examined with hydrochloric acid, pass hydrogen sulfide gas into the solution; an orange precipitate, soluble in ammonium sulfide TS or sodium sulfide TS, is produced.

Barium Salts

(1) Moisten the substance being examined with hydrochloric acid on a platinum wire, it imparts a yellowish green colour to a nonluminous flame, or a blue colour when viewed through a green glass plate.

(2) Add dilute sulfuric acid to a solution of the substance being examined; a white precipitate is produced which is insoluble in hydrochloric acid or nitric acid.

Benzoates

(1) Add ferric chloride TS to a neutral solution of the substance being examined; a dull yellow precipitate is formed which turns to white on addition of dilute hydrochloric acid.

(2) Introduce a quantity of the substance being examined into a dry test tube, add sulfuric acid and heat gently; no charring occurs, a white sublimate of benzoic acid is deposited on the inner wall of the test tube.

Bismuth Salts

(1) Add potassium iodide TS to a solution of the substance being examined; a reddish brown colour or dark brown precipitate is produced, the precipitate is soluble in an excess of the reagent, forming a yellowish brown solution. Dilute the solution with water; an orange precipitate is produced.

(2) Acidify a solution of the substance being examined with dilute sulfuric acid, add a quantity of 10% thiourea solution, an intense yellow colour is produced.

Borates

(1) A solution of the substance being examined, acidified with hydrochloric acid, turns turmeric paper to brownish red, the colour deepens on drying and becomes greenish black when moistened with ammonia TS.

(2) Mix a quantity of the substance being examined with sulfuric acid and add methanol, when the mixture is ignited, it burns with a green-bordered flame.

Bromides

(1) Add silver nitrate TS to a solution of the substance being examined; a curdy, pale yellow precipitate is formed which is slightly soluble in ammonia TS and practically insoluble in nitric acid.

(2) Add chlorine TS dropwise to a solution of the substance being examined; bromine is liberated, add chloroform and shake, a yellow or reddish brown colour is developed in the chloroform layer.

Calcium Salts

(1) Moisten the substance being examined with hydrochloric acid on a platinum wire, it imparts a brick red colour to a nonluminous flame.

(2) Add 2 drops of methyl red IS to a solution of the substance being examined (1→20), neutralize with ammonia TS and then acidify with hydrochloric acid. Add ammonium oxalate TS; a white precipitate is produced which is soluble in hydrochloric acid but insoluble in acetic acid.

Carbonates and Bicarbonates

(1) Add dilute acid to a solution of the substance being examined, it effervesces with the evolution of carbon dioxide, producing a white precipitate when passed into calcium hydroxide TS.

(2) Add magnesium sulfate TS to a solution of the substance being examined; a white precipitate is produced immediately (carbonates) or on boiling (bicarbonates).

(3) A solution of the substance being examined is colourless or only slightly coloured on the addition of phenolphthalein IS (bicarbonates); or an intense red colour is produced (carbonates).

Chlorides

(1) Acidify a solution of the substance being examined with nitric acid and add silver nitrate TS; a curdy, white precipitate is formed which is soluble in ammonia TS and reprecipitated on addition of nitric acid. Organic bases should be removed by the addition of ammonia TS and filtration prior to the test.

(2) Mix a small quantity of the substance being examined with an equal part of manganese dioxide, moisten with sulfuric acid and heat gently; chlorine is evolved which turns a strip of moistened starch-potassium iodide paper to blue.

Citrates

(1) To 2 ml of a solution of the substance being examined equivalent to about 10 mg of citric acid, add a few drops of dilute sulfuric acid and heat to boiling, then add a few drops

of potassium permanganate TS and shake; the violet colour disappears. Divide the solution into two portions, to one portion add a drop of mercuric sulfate TS, to the other portion add a few drops of bromine TS; a white precipitate is produced in both solutions.

(2) To about 5 mg of the substance being examined add about 5 ml of pyridine-acetic anhydride (3 : 1), shake, a yellow to red or violet-red colour is produced.

Copper Salts

(1) Add a few drops of ammonia TS to a solution of the substance being examined; a light blue precipitate is produced which is soluble in an excess of the reagent, forming a dark blue solution.

(2) Add potassium ferrocyanide TS to a solution of the substance being examined; a reddish brown colour or precipitate is produced.

Ferric Salts

(1) Add potassium ferrocyanide TS to a solution of the substance being examined; a dark blue precipitate is formed which is insoluble in dilute hydrochloric acid, it decomposes to form a brown precipitate on addition of sodium hydroxide TS.

(2) Add ammonium thiocyanate TS to a solution of the substance being examined; a red colour is produced.

Ferrous Salts

(1) Add potassium ferricyanide TS to a solution of the substance being examined; a dark blue precipitate is formed which is insoluble in dilute hydrochloric acid, it decomposes to form a brown precipitate on addition of sodium hydroxide TS.

(2) To a solution of the substance being examined add a few drops of a 1% solution of *o*-phenanthroline in ethanol; a deep red colour is produced.

Iodides

(1) Add silver nitrate TS to a solution of the substance being examined; a curdy, yellow precipitate is produced which is insoluble in nitric acid or ammonia TS.

(2) Add chlorine TS dropwise to a solution of the substance being examined; iodine is liberated, add chloroform and shake, a violet colour is produced in the chloroform layer; if starch IS is added instead of chloroform, a blue colour is produced.

Lactates

To 5 ml of a solution of the substance being examined equivalent to about 5 mg of lactic acid in a test tube, add 1 ml of bromine TS and 0.5 ml of dilute sulfuric acid. Heat on a water bath with stirring until the colour is discharged, add 4 g of ammonium sulfate and mix well, add dropwise along the inner wall of the tube 0.2 ml of a 10% solution of sodium nitroprusside in dilute sulfuric acid and 1 ml of concentrated ammonia TS, allow to stand for 30 minutes without mixing; a dark green ring is developed at the interface of the two layers.

Lithium Salts

(1) Alkalize the solution of the substance being examined with sodium hydroxide TS, add sodium carbonate TS, a white precipitate is produced on boiling which is soluble in ammonium chloride TS.

(2) Moisten the substance being examined with hydrochloric acid on a platinum wire, it imparts a crimson colour to a nonluminous flame.

(3) To a quantity of the substance being examined add dilute sulfuric acid or soluble sulfates solution, no precipitate is produced (distinction from strontium).

Magnesium Salts

(1) Add ammonia TS to a solution of the substance being

on addition of ammonium chloride TS. Add 1 drop of disodium hydrogen phosphate TS and shake; a white precipitate insoluble in ammonia TS is produced.

(2) Add sodium hydroxide TS to a solution of the substance being examined; a white precipitate is produced, filter, the precipitate is insoluble in an excess of sodium hydroxide TS but is coloured reddish brown on addition of iodine TS.

Malonylureas

(1) Dissolve about 0.1 g of the substance being examined in 1 ml of sodium carbonate TS and 10 ml of water, shake for 2 minutes and filter. To the filtrate add a few drops of silver nitrate TS; a white precipitate is produced which redissolves on shaking, but it is insoluble in an excess of the reagent.

(2) Dissolve about 50 mg of the substance being examined in 5 ml of pyridine solution (1 → 10), add 1 ml of copper pyridine TS; a violet colour or precipitate is produced.

Mercuric Salts

(1) Add sodium hydroxide TS to a solution of the substance being examined; a yellow precipitate is produced.

(2) Add potassium iodide TS to a neutral solution of the substance being examined; a scarlet precipitate is produced which is soluble in an excess of the reagent. To the solution add sodium hydroxide TS and an ammonium salt; a reddish brown precipitate is produced.

(3) When applied to bright copper foil, solutions of mercury salts, free from an excess of Aitric acid, yield a deposit that upon rubbing, becomes bright and silvery in appearance.

Mercurous Salts

(1) To a quantity of the substance being examined add ammonia TS or sodium hydroxide TS; a black colour is developed.

(2) To a quantity of the substance being examined add potassium iodide TS and shake; a yellowish green precipitate is produced, changing to greyish green rapidly and then to greyish black gradually.

Nitrates

(1) Mix cautiously a solution of the substance being examined with an equal volume of sulfuric acid and allow to cool, add ferrous sulfate TS along the inner wall of the test tube; a brown ring is developed at the interface of the two layers.

(2) To a solution of the substance being examined add cautiously sulfuric acid and metallic copper; a reddish brown fume is evolved on heating.

(3) Add dropwise potassium permanganate TS to a solution of the substance being examined; the violet colour does not disappear (distinction from nitrites).

Organic Fluorinated Compounds

Weigh about 7 mg of the substance being examined, carry out the method for oxygen flask combustion (Appendix VII C), using 20 ml of water and 6.5 ml of 0.01 mol/L sodium hydroxide solution as the absorbing liquid. To 2 ml of the resulting solution add 0.5 ml of alizarin fluorine blue TS and 0.2 ml of a solution containing 12% of sodium acetate in dilute acetic acid, dilute with water to 4 ml and add 0.5 ml of cerous nitrate TS; a bluish violet colour is produced. Perform a blank determination in the same manner.

Phosphates

(1) Add silver nitrate TS to a neutral solution of the substance being examined; a light yellow precipitate is formed which is freely soluble in ammonia TS or dilute nitric acid.

(2) Add magnesium ammonium chloride TS to a solution of the substance being examined; a white crystalline precipitate is produced.

(3) To a solution of the substance being examined add

precipitate soluble in ammonia TS is produced on heating.

Potassium Salts

(1) Moisten the substance being examined with hydrochloric acid on a platinum wire, it imparts a violet colour to a nonluminous flame. If sodium is also present, the yellow colour can be screened out by viewing through a blue glass plate.

(2) Ignite the substance being examined to remove any ammonium salt contaminated, cool, dissolve it in water, add acetic acid and a 0.1% solution of sodium tetraphenylborate; a white precipitate is produced.

Primary Aromatic Amines

To about 50 mg of the substance being examined add 1 ml of dilute hydrochloric acid and boil gently to effect dissolution if necessary, cool, add a few drops of 0.1 mol/L sodium nitrite solution and alkaline β -naphthol TS; a precipitate coloured from orange yellow to scarlet is formed depending on the identity of the substance being examined.

Salicylates

(1) To a dilute solution of the substance being examined add 1 drop of ferric chloride TS; a violet colour is produced.

(2) Add dilute hydrochloric acid to a solution of the substance being examined; a white precipitate of salicylic acid is produced which is soluble in ammonium acetate TS.

Silver Salts

(1) Add dilute hydrochloric acid to a solution of the substance being examined; a curdy, white precipitate is produced which is soluble in ammonia TS and reprecipitated on addition of nitric acid.

(2) Add potassium chromate TS to a neutral solution of the substance being examined; a brick red precipitate is produced which is soluble in nitric acid.

Sodium Salts

(1) Moisten the substance being examined with hydrochloric acid on a platinum wire; it imparts an intense yellow colour to a nonluminous flame.

(2) Add zinc uranylacetate TS to a neutral solution of the substance being examined; a yellow precipitate is produced.

Stannous Salts

One drop of an aqueous solution of the substance being examined turns ammonium molybdophosphate test paper to blue.

Sulfates

(1) Add barium chloride TS to a solution of the substance being examined; a white precipitate is formed which is insoluble in hydrochloric acid or nitric acid.

(2) Add lead acetate TS to a solution of the substance being examined; a white precipitate is formed which is soluble in ammonium acetate TS or sodium hydroxide TS.

(3) Add hydrochloric acid to a solution of the substance being examined; no white precipitate is produced (distinction from thiosulphates).

Sulfites and Bisulfites

(1) Add hydrochloric acid to the substance being examined; the pungent odour of sulfur dioxide is perceived, the vapour blackens a strip of filter paper moistened with mercurous nitrate TS.

(2) Add iodine TS dropwise to a solution of the substance being examined; the colour of iodine is discharged.

Tartrates

(1) To a neutral solution of the substance being examined in a clean test tube, add a few drops of ammoniacal silver nitrate TS and heat in a water bath; silver is deposited on the inner wall of the test tube as a mirror.

(2) Acidify a solution of the substance being examined with acetic acid, add 1 drop of ferrous sulfate TS and 1 drop of hydrogen peroxide TS, make the solution alkaline with sodium hydroxide TS when the colour is discharged; a violet colour is produced.

Tropane Alkaloids

To about 10 mg of the substance being examined add 5 drops of fuming nitric acid, evaporate to dryness on a water bath, a yellow residue is obtained. Cool, moisten the residue with 2-3 drops of ethanol, add a small pellet of potassium hydroxide; an intense violet colour is produced.

Zinc Salts

(1) Add potassium ferrocyanide TS to a solution of the substance being examined; a white precipitate is formed which is insoluble in dilute hydrochloric acid.

(2) Acidify a solution of the substance being examined with dilute sulfuric acid, add 1 drop of 0.1% copper sulfate solution and a few drops of mercuric ammonium thiocyanate TS; a violet precipitate is produced.

Appendix IV Spectrophotometry

Spectrophotometry is a method used in qualitative and quantitative analysis in which the light absorption or the intensity of light emission of the substance being examined is measured at a definite wavelength or within a definite range of wavelength.

The spectral ranges involved in pharmaceutical analysis mainly consist of 3 regions: (1) the ultraviolet region (200-400 nm), (2) the visible region (400-760 nm) and (3) the infrared region (2.5-25 μm or 4000-400 cm^{-1}). The instruments used are the ultraviolet-visible spectrophotometer, visible spectrophotometer (or colourimeter), infrared spectrophotometer or atomic absorption spectrophotometer. All instruments should be calibrated regularly to insure the precision and the accuracy.

When monochromatic radiation passes through an absorbing medium, the absorbance of the radiation is proportional to the concentration of the absorbing substance and the thickness of the absorbing medium, this relation is expressed by the following equation:

$$A = \lg 1/T = ECL$$

Where A is the absorbance, T is the transmittance, E is the absorption coefficient, C is the concentration of the substance expressed in g per 100 ml, calculated on the dried or dehydrated basis and L is the absorption path length expressed in cm. The term $E_1^{1\%}$ is used in this pharmacopoeia to denote the absorbance of a 1% solution in a 1 cm cell.

The wavelength of the selective absorption and the corresponding absorption coefficient are physical constants of the substance being examined. When the absorption coefficient of a substance is known, its content can be calculated from the above equation. In the visible region, the content of a colourless substance can be determined colourimetrically after the addition of a colour developing agent or any other treatment.

IV A Ultraviolet-Visible Spectrophotometry

Calibration and performance test of the instrument

1. Wavelength The change of environment may affect the mechanical parts of the spectrophotometer and cause a drift of the wavelength scale, therefore it must be calibrated regularly and immediately before the measurement. Mercury lamp is the best choice of light source for this purpose, the following spectral lines of the mercury lamp can be used: 237.83 nm, 253.65 nm, 275.28 nm, 296.73 nm, 313.16 nm, 334.15 nm, 365.02 nm, 404.66 nm, 435.83 nm, 546.07 nm and 576.96 nm. The wavelength scale may also be calibrated by means of the 486.02 nm and 656.10 nm lines of deuterium discharge lamp. Holmium glass filter exhibits sharp absorption peaks at 279.4 nm, 287.5 nm, 333.7 nm, 360.9 nm, 418.5 nm, 460.0 nm, 484.5 nm, 536.2 nm

wavelength. However, the exact values for the position of these peaks may change slightly depending on the commercial source of the filter or along with the time goes by.

2. The absorbance scale. Check the absorbance with a solution of potassium dichromate in sulfuric acid. Dissolve about 60 mg of potassium dichromate primary standard, previously dried to constant weight at 120°C and accurately weighed, in 0.005 mol/L sulfuric acid solution to make 1000 ml. Check the absorbance at wavelength indicated in the following table and calculate the absorption coefficient which should accord with the specified range in the table when compared with the specified absorption coefficient.

Wavelength/nm	235(min)	257(max)	313(min)	350(max)
Specific absorbance $E_1^{1\%}$	124.5	144.0	48.6	106.6
Maximum tolerance	123.0- 126.0	142.8- 146.2	47.0- 50.3	105.5- 108.5

3. Limit of stray light. Stray light may be detected at the given wavelength with suitable solutions indicated in the following table. The transmittance of these solutions measured in a 1 cm quartz cell against water should accord with the limit specified in the table.

Reagent	Concentration/% (g/ml)	Wavelength/ nm	Transmittance/ %
Sodium Iodide	1.00	220	<0.8
Sodium Nitrite	5.00	340	<0.8

Requirements for the solvents

The organic solvents containing heteroatoms usually have strong absorption at the lower wavelength. Thus, their ranges of use should be less than the cut off wavelength. For example, the cut off wavelength of methanol and ethanol is 205 nm. Otherwise, impurity of solvents would enhance the interference of absorption. The solvent used in spectrophotometric determinations should be checked for any interfering absorption peak around the selected wavelength for the measurement of the absorbance being examined. The absorbance of a solvent should not exceed 0.40 in the range of 220 nm to 240 nm, 0.20 in the range of 241 nm to 250 nm, 0.10 in the range of 251 nm to 300 nm and 0.05 at wavelengths above 300 nm, when measured in a 1 cm quartz cell against air.

Procedure

Unless otherwise specified, the same batch of solvent used to prepare the solution of the substance being examined should be employed as the blank in matched 1 cm quartz cells. The wavelength of maximum absorption should be checked by measuring the absorbance of the substance being examined in the vicinity of the specified wavelength, within a range of ± 2 nm, to check the wavelength of the absorption maximum is correct or not. Unless otherwise specified, the absorption maximum must be within ± 2 nm as specified in the monograph, otherwise, the identity, purity of the substance and the correctness of the wavelength of the

spectrophotometer should be considered. The assay should be carried out at the wavelength of maximum absorption. The concentration of the solution should be adjusted to give an absorbance reading of 0.3 to 0.7 where the experimental error is the smallest. The width of the spectral slit must be smaller than the tenth of half-width of the absorption band, otherwise low absorbance will be resulted. The slit width is appropriate if further reduction does not result in an increase of the absorbance reading. The absorbance of an unmatched cell with the solvent concerned as a blank must be subtracted from the absorbance of the substance being examined or be automatically deducted by the spectrophotometer.

When the pH value affects the results determined, the pH of the test preparation should be adjusted equal to that of the reference preparation.

Ultraviolet spectrophotometry used for identification and quality tests is proceeded according to the method described in the items specified under the corresponding monograph.

Ultraviolet spectrophotometry is used for assay usually as the following methods.

(1) *Reference substance comparison method* Prepare separately solutions of the substance being examined and CRS according to the method described under item of the individual monograph. The content of the CRS in the solution should be within $100\% \pm 10\%$ of the labelled amount of the solution prepared with substance being examined and with solvent of the same batch. Determine the absorbances of solutions of test preparation and of reference preparation at specified wavelength, calculate the concentration of the test preparation in the solution according to the following equation:

$$C_x = (A_x/A_R)C_R$$

Where C_x is the concentration of the test preparation; A_x is the absorbance of the test preparation; C_R is the concentration of the reference preparation and A_R is the absorbance of the reference preparation.

(2) *Absorption coefficient method* Prepare the solutions of the substance being examined according to the method described under the individual monograph, determine the absorbance at specified wavelength. Calculate the concentration of the test preparation with the absorption coefficient specified in the monograph concerned. Usually, absorption coefficient should be more than 100. Pay attention to the calibration and check of the instrument being used.

(3) *Chemometric methods* Carry out the assay as described under the specified monograph. Absorbances are measured at wavelengths of the ascending or descending position of the absorption curve, the minor variation of the wavelength may affect the result significantly. It is essential to determine the reference and test preparations under the same condition. Commonly, chemometric method is not suitable for the assay.

(4) *Colourimetry* Colourimetry is used with the addition of suitable developer before determination when the substance being examined has no strong absorption in the ultraviolet-visible region, or though absorption in that region, to avoid the interference or increase the sensitivity. Colourimetric determination should be carried out with a reference substance concomitantly. Unless otherwise specified, an equal volume of solvent, added with the same reagent and treated in the same manner is used as blank. Calculate the concentration of test preparation as "(1) Reference substance comparison method" described under the above method (1).

If the linear relation between absorbance and concentration is

preparations containing gradient amounts of the reference substance should be measured, and a calibration curve should be produced by plotting the absorbance against concentration. The concentration of the test preparation can be determined by interpolating its absorbance on the calibration curve.

IV C Infrared Spectrophotometry

Equipment and Calibration

Fourier-transform infrared spectrophotometers or dispersive infrared spectrophotometers are often used for pharmaceutical analysis. The wave-number scale of an infrared spectrophotometer may be calibrated by use of a polystyrene film of 0.04 mm thickness. The absorption peaks at 3027 cm^{-1} , 2851 cm^{-1} , 1601 cm^{-1} , 1028 cm^{-1} and 907 cm^{-1} are used for the calibration. Tolerance should be not more than $\pm 5\text{ cm}^{-1}$ in the vicinity of 3000 cm^{-1} and not more than $\pm 1\text{ cm}^{-1}$ in the vicinity of 1000 cm^{-1} for the Fourier-transform infrared spectrophotometer.

The resolution factor of the instrument between $3110\text{--}2850\text{ cm}^{-1}$ requires that seven peaks should be clearly isolated, the depth of the trough from the maximum absorption at about 1583 cm^{-1} to the minimum at about 1589 cm^{-1} should be not less than 12% transmittance and that from the maximum at about 2851 cm^{-1} to the minimum at about 2870 cm^{-1} should be not less than 18% transmittance.

Unless otherwise specified, the nominal resolution factor of the instrument should not be less than 2 cm^{-1} .

Preparation and Determination

1. *Identification for drug substances* Unless otherwise specified, for the identification test the substance being examined must be prepared according to the method described in each volume of "Atlas of Infrared Spectra of Drugs", edited by Chinese Pharmacopoeia Commission. Detailed procedures see also the Introduction of the Atlas.

2. *Identification for preparations* The test preparation should be prepared as specified in the individual monograph. If excipients have no interference after treatment, compare directly with the reference spectrum of its drug substance. If excipients have interference to some extent, according to the reference spectrum of its drug substances, choose 3 to 5 specific peaks of absorption, where excipients have no interference for the component being examined, in the fingerprint region, and take these positions as the basis for identification. The tolerance of the wave-number determined should less than 0.5% of specified wave-number.

3. *Polymorphism inspection, limit test of the isomers and assay* The method of sample preparation and determination is performed according to the procedure described in the individual monograph.

Announcements

1. In the monograph where infrared absorption spectrum is concordant with the reference spectrum refers to the spectrum specified in the above "Atlas of Infrared Spectra of Drugs", consisted of Vol. I (1995 edition), Vol. II (2000 edition) and Vol. III (2005 edition). If the spectra for the same compound are described in different volume, the latter one should be taken as the reference.

2. The spectrum of a solid substance may be different from the reference spectrum due to polymorphism. In this case, the substance being examined should be pre-treated according

Atlas or individual monograph. If the crystalline type and suitable pre-treatment method are not specified, the reference substance can be used. The substance being examined and the reference substance are recrystallized synchronously under the same condition and then be determined and compared. If the crystalline type is specified, the reference substance with corresponding crystalline type should be used.

3. Several factors such as difference in instrument performance of various models, inadequate or successive grinding in preparation of the disc, moisture affect or halide carrier, may give rise to unsatisfactory spectrum in shape. It should be kept in mind during the comparison with the reference spectrum.

IV D Atomic Absorption Spectrophotometry

Atomic absorption spectrophotometry is used in the determination of metal elements and some non-metal elements in the atomic state.

The light of characteristic wavelength emitted from a cathodic discharge lamp is absorbed when it passes through the atomic vapor generated from sample containing the element being examined atomized to the ground state. The assay of the element being examined is tested by determining the decreased degree of light intensity of radiation. Atomic absorption obeys the general rule for absorption spectrophotometry. The assay is carried out by comparing the absorbance of the test preparation with that of the reference preparation.

Apparatus

An atomic absorption spectrophotometer consists of a light source, an atomic generator, a monochromator and a detector system. Some are equipped with a background compensation system and automatic sampling system, etc.

1. Light source A hollow-cathode discharge lamp is usually used. The cathode is made of the element being examined.

2. Atomic generator There are four main types: flame atomizer, graphite furnace atomizer, hydride-generated atomizer and cold vapor atomizer.

(1) *Flame atomizer* It mainly consists of a nebulizer and a burner. Its function is to nebulize the test solution into aerosol which is mixed with combustion gas. And the mixture is introduced into the flame generated by the burner. So that the substance being examined is to be dried, evaporated to form the ground state atoms of the element being examined. The burning flame is generated by different mixtures of gases, acetylene-air is mostly used. By modifying the proportion of combustion gas, the temperature of the flame can be controlled, and a better stability and a better sensitivity can be obtained.

(2) *Furnace atomizer* It consists of electric furnace and a power supply. Its function is to dry and incinerate the substance being examined. During the stage of high temperature atomization, the ground state atoms of the element being examined are to be formed. Graphite is commonly used as the heater. Protection gas is introduced into the furnace to avoid oxidation and used to transfer the sample vapor.

(3) *Hydride-generated atomizer* It consists of hydride generator and atomic absorption cell. It is used for the

stannum and antimony etc. Its function is to reduce the element to be examined in acidic medium to the low-boiling and easily pyrolyzed hydride. And then the hydride is swept by a stream of carrier gas into the atomic absorption cell which consists of quartz tube and heater etc., in which the hydride is pyrolyzed by heating to form the ground-state atom.

(4) *Cold vapor atomizer* It consists of a mercury vapor atomizer and an absorption cell. It is suitable for the determination of mercury. Its function is to reduce the mercuric ion into mercury vapor which is swept into the quartz absorption cell by carrier gas.

3. Monochromator Its function is to separate the specified wavelength radiation from the electromagnetic radiations radiated from the light source. The optical path of the apparatus should assure the good spectra resolution and has the ability to work well at the condition of narrow spectral band ($<0.2 \text{ nm}$). The commonly used wavelength region is $190.0-900.0 \text{ nm}$.

4. Detector system It consists of a detector, a signal processor and a recording system. It should have relatively higher sensitivity and better stability, and can follow the rapid change of the signal absorption.

5. Background compensation system System employed for the correction of atmospheric effects on the measuring system. Four principles can be utilized for background compensation: continuous spectrum sources (a deuterium lamp is often used in the UV region), the Zeeman effect, the self-inversion phenomena and the nonresonance spectrum.

In the analysis using atomic absorption spectrophotometry, the interference to the determination caused by background and other reasons should be noticed. Changes of some experimental conditions, such as the wavelength, the slit width, the atomizing condition, etc., may affect the sensitivity, the stability and the interference. If it is flame, the suitable wavelength, slit width and flame temperature, the addition of complexing agents and releasing agents, and the use of Standard addition method may eliminate interference. If it is furnace, the selection of suitable background compensation system and the addition of suitable matrix modifying agents, etc. may remove the interference. Background compensation method should be selected as specified in the individual monograph.

Procedure

Method 1 (Direct calibration method) Prepare not less than 3 reference solutions of the element being examined of different concentrations, covering the range recommended by the instrument manufacturer and add separately the corresponding reagents as that for the test solution and prepare the blank reference solution with the corresponding reagents. Measure the absorbances of the blank reference solution and each reference solution of different concentrations separately, record the readings and prepare a calibration curve with the average value of 3 readings of each concentration on the ordinate and the corresponding concentration on the abscissa.

Prepare a test solution of the substance being examined as specified in the monograph, adjust the concentration to fall within the concentration range of the reference solution. Measure the absorbance 3 times, record the readings and calculate the average value. Interpolate the mean value of the readings on the calibration curve to determine the concentration of the element.

Method 2 (Standard addition method) Place equal volumes of the test preparation prepared as specified in the individual

each of the flasks, except the first one, add an accurately measured amount of the reference preparation containing increasing amounts of the element being determined. Dilute separately with de-ionized water to the volume and proceed as directed in the direct calibration method. Measure the absorbances and record the readings. Plot the mean values of each group of 3 readings against the corresponding concentration of the element contributed by the reference preparation, extrapolate the straight line to intersect with the axis of zero absorbance. The interception represents the concentration of the element contributed by the test preparation (as Fig. 2). Calculate the concentration of the element in the test preparation from the result so obtained. This method can be used only when the standard curve obtained in method 1 is linear and passes the origin.

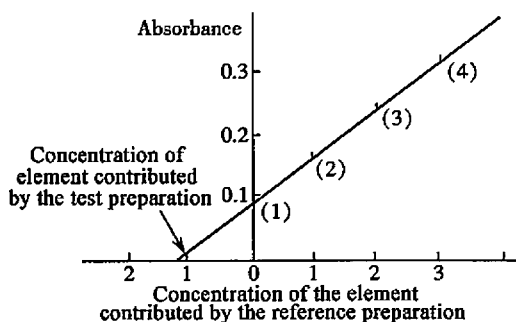


Fig. 2

When used in the test for impurities, prepare two test preparations of the same concentration as specified in the monograph. To one of the test preparation add an amount of the reference substance equivalent to the limit of the element specified in the monograph. Proceed as directed above and measure this solution to give an appropriate reading a ; then measure the test preparation without the addition of the reference substance under the same condition and record the reading b ; b is not greater than $(a-b)$.

IV E Fluorimetry

When substances are exposed to ultraviolet or visible radiation, some of them may emit fluorescence at a wavelength longer than that of the exciting radiation. The excitation and emission spectra of a substance can be used for qualitative analysis. The intensity of the fluorescence emitted by a substance, when the intensity and wavelength of the exciting radiation, the solvent and the temperature are constant, is directly proportional to the concentration of the substance within a definite range, therefore, this relation can be used for quantitative determinations. The sensitivity of fluorescence spectrophotometry is usually higher than that of UV and visible spectrophotometry. However, if a solution is too concentrated, a self-quenching effect and an absorption of the exciting radiation near the surface may result in a declination of the intensity of emitted radiation, and the intensity of fluorescence emitted is not directly proportional to the concentration. Therefore, fluorescence spectrophotometry should be carried out only in dilute solutions.

Procedure The instrument used is fluorometer or fluorometry spectrophotometer. Select the excitation and emission bands and prepare the reference and the test solutions as specified in the monograph.

selected reference substance to determine the linear relation of fluorescence intensity and concentration. When the linear relation is good, adjust the sensitivity of the instrument with appropriate dilutions of the reference solution before each test; record the fluorescence intensities of the test preparation and reference preparation and their corresponding blanks. The following equation can be used for calculation of the content in the test preparation:

$$C_x = \frac{R_x - R_{xb}}{R_r - R_{rb}} \times C_r$$

Where C_x is the concentration of the test preparation; C_r is the concentration of the reference preparation; R_x is the fluorescence intensity of the test preparation; R_r is the fluorescence intensity of the reference preparation; R_{xb} and R_{rb} are the fluorescence intensity of the corresponding blanks.

The range within which the fluorescence intensity is directly proportional to the concentration of the substance is usually very narrow, therefore, the ratio $(R_x - R_{xb}) / (R_r - R_{rb})$ should not be less than 0.5 or more than 2, otherwise the concentration of the solutions should be adjusted and the measurements made again. If the fluorescence intensity is not strictly proportional to the concentration, the previously drawn calibration curve under the same conditions should be used.

For a substance which decomposes on exposure to light or its relaxation time is too long, in order to avoid the fluorescence intensity affected by multi-irradiation of the exciting radiation, the sensitivity of the instrument maybe checked with a stable reference solution of another fluorescent substance with excitation and emission bands similar to those of the substance being examined in place of reference substance of the substance being examined. For instance, quinine in dilute sulfuric acid is usually used for blue fluorescence, sodium fluorescence for green fluorescence and rhodamine B for red fluorescence.

Announcements The interferences of fluorometry are great due to high sensitivity.

- (1) The purity of solvent may markedly affect the intensity of fluorescence, blank test should be carried out and the solvent distilled in a glass distillator before use if necessary.
- (2) The presence of suspended particles may cause the light to be scattered, therefore, it is necessary to eliminate such particles by centrifugation or filtration with a sintered glass filter.
- (3) All glasswares and cells must be cleaned thoroughly.
- (4) It is also important to regulate the temperature because it would notably affect the fluorescence intensity.
- (5) Oxygen dissolved in the solution has a strong quenching effect, it can be removed by passing a current of inert gas through the solution when necessary.
- (6) The effect on the fluorescence intensity by the pH value of the solution and the purity of the reagents, etc. should be noticed during the determination.

IV F Flame Photometry

When a test solution containing the element of alkali metals and alkaline-earth metals being examined is introduced into a flame as the form of aerosol by an equipment of nebulization, the element being examined is atomized by the heat energy of the flame and excited its characteristic spectrum. The content of the element being examined is determined by measuring the light intensity of the element using

reference solution and the test solution.

Apparatus Flame photometer consists of a combustion system including nebulizer-burner, combustion lamp, combustion gas and supply of assisted combustion gas, a monochromator and a detector.

The combustion gas is often a mixture of air-coal gas or air-liquefied petroleum gas (LPG) using air as assisted-combustion gas and coal gas or LPG as combustion gas.

Any variation of the experimental condition, such as type

and state of flame, the pressure supplied by air-compressor may affect and interfere with the sensitivity and steadiness of the instrument, so they should be selected as specified in the monograph.

Procedure When used for assay and limit test of impurities, flame photometry is carried out respectively as method 1 and 2 described under Atomic Absorption Spectrophotometry (Appendix IV D).

Appendix V Chromatography

Depending on the mechanism of the separation process, chromatographic can be classified into adsorption chromatography, partition chromatography, ion-exchange chromatography, size-exclusion chromatography etc.

Adsorption chromatography is based on the different affinity of individual components to the adsorbent (stationary phase), so that they can be eluted successively with a solvent or gas (mobile phase). The adsorbents commonly used are aluminum oxide, silica gel, polyamide powder etc.

Partition chromatography is based on the distribution of individual components between two phases. The stationary phase is coated on or chemically bonded to a solid support of large surface area. The mobile phase is a liquid or a gas. The supports commonly used are silica gel, kieselguhr, diatomaceous earth, cellulose powder, polymers with suitable functional groups etc.

In ion-exchange chromatography, the stationary phase is either a cation exchange resin or an anion exchange resin. The mobile phase is usually an aqueous buffer solution, sometimes a definite quantity of organic solvent is added to modify the exchange property.

Size exclusion chromatography is also known as gel permeation chromatography or gel filtration chromatography. It is based on the different permeability of components of different molecular size into a support of definite pore size. Molecular sieves, cross-linked polystyrene gels, glucosan gels, silica gel and porous glass beads are commonly used as the stationary phase. Water or organic solvent is used as the mobile phase, depending on the chemical characteristics of the support and the substance being examined.

Chromatography may be classified into paper chromatography, thin layer chromatography, column chromatography, gas chromatography, high performance liquid chromatography and so on based on the method of separation.

Solvents used in chromatography must be of high purity and must not react with the substance being examined. Except gas chromatography, the operation is carried out at room temperature, unless otherwise specified. In column chromatography, paper chromatography and thin layer chromatography, the coloured zones can be detected visually, colourless substances can be detected under ultraviolet radiation of 254 nm or 365 nm. In paper chromatography or thin layer chromatography, colourless substances can also be detected by spraying with a colour-developing agent. Silica gel plates containing a fluorescent substance are sometimes used in thin-layer chromatography, so that colourless substance can be detected by the fluorescence quenching method. In column chromatography, gas chromatography and high performance liquid chromatography, the components can be detected by a suitable detector connected to the outlet of the column. In column chromatography, the components sometimes can be determined quantitatively by a suitable method after fractionation.

V A Paper Chromatography

Paper chromatography is a partition chromatographic technique, in which paper is used as a support and the water or other substance contained in the paper is used as a stationary phase.

The substance being examined is developed by the mobile phase, after which the shift ratio value (R_f) could be used to denote the location of each component. (R_f is the ratio of the distance between the center of the origin and that of the spots to the distance between the center of the origin and the frontal of the mobile phase). In practice, R_f values may vary considerably due to experimental conditions. Therefore, the identification of a compound is usually carried out by comparing the behaviour of the compound to be identified with that of a reference substance under the same conditions. For drug identification, the position and colour (or fluorescence) of the main spots of the substance being examined on the chromatogram should be identical with those of the reference substances. For purity inspection, the number or colour intensity (or fluorescence intensity) of the impurities contained should be examined according to the requirements specified under each monograph, after a certain amount of substance being examined has been developed. For assay, the main chromatographic spot could be cut out from the paper, eluted with a solvent and subjected to a suitable measurement.

1. Apparatus and Materials

(1) *Developing chamber* It is usually a glass chamber, cylindrical or rectangular, which could be tightly closed with a glass lid. When it is used for descending method, a separator could be inserted through the lid with a hole on it for the addition of the mobile phase. A solvent trough supported by a rack is placed inside near the top of the chamber, a glass rod is used for holding the chromatographic paper, on both sides of the trough, there are two glass rods used to guide the paper so that no part of it is in contact with the wall of the trough. When it is used for ascending method, the hole on the lid is blocked by a stopper with a glass hook where the paper is suspended. The hook is capable of being lowered without opening the chamber. Remove the trough and rack.

(2) *Sample applicator* Microsyringe or capillary tubes with a rack are often used, which could ensure a correct and compact position of the applied spot.

(3) *Chromatographic filter paper* Filter paper should be clean and uniform in texture and thickness, and has a tensile strength. It should contain no impurities which may affect developing process or react with visualizing reagent employed, and affect the separation or identification. It may be pretreated before use if necessary. For descending method, cut a piece of filter paper along the grain direction

into strips of sufficient length and a convenient width, and draw a fine pencil line horizontally across the paper at such a distance from one end to make the line a few centimeters below the guide rod. When this end is secured in the solvent trough and the remainder of the paper is hanging freely outside the trough. The lower end of the paper may be cut into saw-toothed form to facilitate the mobile phase to drop down homogeneously, if necessary. For ascending method, the length of the paper is about 25 cm, the width of the paper is varied as required. Sometimes the paper can be rolled into cylindrical form to save space, the spotting line is about 2.5 cm from the lower edge of the paper.

2. Procedure

(1) *Descending method* Dissolve the substance being examined in a suitable solvent or solvent mixture to prepare a solution of specified concentration. Apply the solution in portions to the pencil line, allow it to dry in air or in a stream of warm air before the next application. The spots are commonly 2-4 mm in diameter, and spaced about 1.5-2.0 cm apart from each other in circular shape. Place the spotted end of paper in the solvent trough and hang the paper freely over the guide rod. Put a Petri dish containing the specified solvent or a strip of chromatographic filter paper moistened with the specified solvent into the chromatographic chamber to pre-equilibrate the chamber with the vapour of the specified solvent. Introduce a sufficient quantity of the mobile phase into the solvent trough and allow it to move along the chromatographic paper for the prescribed distance. Remove the chromatographic paper from the chromatographic chamber, mark the position of the solvent frontal and visualize the chromatogram prescribed in the monograph when the solvent is volatilized.

(2) *Ascending method* The solution of substance being examined is applied on the pencil line as directed in the descending method. The chamber is saturated with the vapour of a specified solvent or the developer placed in it. Lower the hook so that the paper is immersed in the developer to a depth of 0.5 cm, allow the mobile phase to ascend for about 15 cm, unless specified otherwise. Remove the paper from the chamber, mark the position of the solvent frontal and visualize the chromatogram as prescribed in the monograph when the solvent is volatilized.

One dimensional chromatography is that the development proceeds along one direction. Sometimes two-dimensional chromatography may be performed by turning the filter paper at right angle and then continue the development with the original developer or a different solvent system. Other chromatographic techniques, such as multiple development, continuous development and wedge shaped strip development etc., may also be used.

V B Thin-layer Chromatography

Thin-layer chromatography is a separation technique in which the test solutions are deposited on the thin-layer plate. The chromatogram obtained after development and visualization can be compared with that of appropriate reference substance under the same conditions. The results can be used for drug identification and impurity testing.

1. Apparatus and Materials

(1) Thin-layer plates

Home-made plates Unless otherwise specified, the glass plates should be smooth, flat and dry, no bead on it after

Silica gel G, Silica gel GF₂₅₄, Silica gel H, Silica gel H₂₅₄, Diatomaceous earth, Diatomaceous earth G, Aluminum oxide, Aluminum oxide G, Microcrystalline cellulose, Microcrystalline cellulose G, etc. are commonly used stationary phases. Their particle size is usually 5-40 μm in diameter.

For coating the plate, the adsorbent or support can be applied to the glass plate with or without a binder. When the binder is needed, mix the adsorbent or support with 10%-15% of gypsum ($\text{CaSO}_4 \cdot 2\text{H}_2\text{O}$, dried at 140°C for 4 hours) and sufficient water, or with a 0.2%-0.5% solution of carboxymethyl-cellulose sodium as binder. Triturate the mixture to a homogeneous paste and spread the slurry on the glass plates. *Spreader* is used to spread the adsorbent or support on glass plate to form a uniform layer of definite thickness.

Pre-coated plates It includes normal thin-layer plates and high-performance thin-layer plates, such as silica gel thin-layer plates, silica gel GF₂₅₄ thin-layer plates polyamide thin-layer plates, aluminum film thin-layer plates etc.

(2) *Sample applicator* Same as described under Paper Chromatography

(3) *Developing chamber* Glass chamber of suitable size with tight lid and a flat bottom or twin trough may be used.

(4) *Visualization reagents* As specified in the monograph. The spots can be visualized by spraying, exposure to vapour of I_2 or immersion.

(5) *Visualization device* The spray visualization requires that the visualizing reagent should be ejected by the compressed gas as fine and even fogdrops. Special glass apparatus or suitable glass tank can be used for the immersion visualization. The twin trough chamber or desiccator with suitable size can be used for iodine vapour method.

(6) *Detection device* It consists of a dark chamber with filter, a light source with visible light, short (254 nm) and long (360 nm) UV wavelengths light, and photographic equipment. The light source should have enough illumination.

2. Procedure

(1) Preparation of thin layer plate

Home-made plates Unless otherwise specified, one part of stationary phase and three parts of water are triturated in one direction to a homogeneous paste, remove gas bubbles on the surface, put the paste in the spreader, spread on glass plates. The thickness of the layer is generally 0.2-0.3 mm. Allow the plate to dry on a horizontal plane, activate at 110°C for 30 minutes and store in a desiccator with silica gel.

Commercial pre-coated plates The plates should be usually activated in an oven at 110°C for 30 minute before use. Polyamide thin-layer need not be activated. Aluminum film thin-layer plates can be cut to meet the need, but it should be noted that silica gel thin-layer of thin-layer bottom can not be damaged after cutting. If be polluted during storage by impurities in air, thin-layer plates can be ascending washed by suitable solvent in developing chamber before use. The plates may be activated by heating in an oven at 110°C and stored in a desiccator.

(2) *Sample application* Unless otherwise specified, apply the sample to the plate using an sample applicator, circular spots are spaced 2.0 cm from the end of the plate. The distance between the adjacent spots is usually 1.0-2.0 cm, which can be adjusted according to the diffusion of the spot in order not to interfere with the detection. It is essential not to

phase and the particle size of the support, the flow rate of the mobile phase and the ratio of each component in the mixed mobile phase, the time span in the gradient elution program, the temperature of the column, the injection volume and the sensitivity of the detectors could be changed appropriately to meet the requirement of the system suitability test. But for some certain monographs, in which only the specific brand of packing material is able to satisfy the requirement of the separation, clear indications should be given under them.

2. The system suitability test

The suitability test of the chromatographic system generally includes four indexes, number of theoretical plates, resolution, repeatability and tailing factors, in which the resolution and the repeatability are more practical indexes.

To carry out the suitability test of the chromatographic system according to the requirement under the individual monograph is to test the chromatographic system by using specific reference substance. The separation conditions of the chromatography should be adjusted in case if the requirement cannot be met.

(1) *Theoretical plates of the column* (n) Inject the test solution or the internal standard specified under the monograph into the system according to the prescribed chromatographic conditions. Record the chromatogram and measure the retention time (t_R (in minutes or length unit), the same as below, which should be in the same unit) and the peak width at half peak height ($W_{h/2}$) of the principle component peak of the test solution or that of the internal standard. Calculate the theoretical plates of the chromatographic column by the equation: $n = 5.54(t_R/W_{h/2})^2$.

(2) *Resolution* (R) No matter in qualitative analysis or quantitative analysis, the peak(s) of substance being examined and other peaks, such as internal standard peak(s) or specific impurity peak(s) must have good resolution. The equation for calculating the resolution is:

$$R = \frac{2(t_{R2} - t_{R1})}{W_1 + W_2}$$

Where t_{R2} is the retention time of the latter of the two adjacent peaks, t_{R1} is the retention time of the former of the two adjacent peaks.

W_1 and W_2 are the peak width of the two adjacent peaks (as Fig. 3).

Unless specified otherwise, the resolution value should not be less than 1.5 in quantitative analysis.

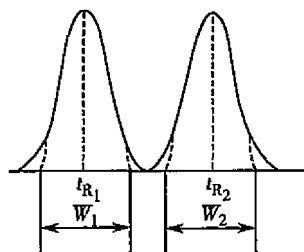


Fig. 3

(3) *Repeatability* Inject the reference solution described under the monograph for 5 times successively. Unless specified otherwise, the relative standard deviation of the measured value of the peak areas should be no more than 2.0 per cent.

According to the measurement of the correction factor specified under each monograph, prepare a series of reference solutions equivalent to 80%, 100% and 120% of the content of the substance being examined, each containing

solution at least 2 times, calculate the average correction factors, the relative standard deviation of which should be no more than 2.0%.

(4) *Tailing factor* (T) In order to guarantee the performance of the separation and the precision of the measurement, the tailing factor should be inspected to see whether it meets the prescription under each monograph. The equation for calculating the tailing factor is as follows:

$$T = \frac{W_{0.05h}}{2d_1}$$

Where $W_{0.05h}$ is the peak width at 5% of the peak height, d_1 is the distance between the perpendicular line passing through the peak maximum and that of the leading edge of the peak (as Fig. 4).

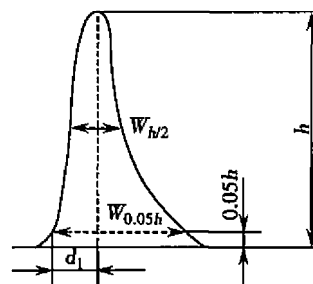


Fig. 4

Unless otherwise specified, the T value should be within 0.95-1.05 in the quantitative analysis by using peak height. In the quantitative analysis by using peak area, the over deviation of the T value will also effect the detection and the quantification precision of the small peak(s).

3. Procedure

(1) Corrected internal standard method for the determination of individual impurities or the main components

Prepare solutions containing an accurately weighed quantity of the reference substance and the internal standard respectively as specified in the monograph. Accurately measure each solution and prepare the reference solution for determining the correction factors. Inject a certain amount of solution into the equipment and record the chromatogram. Measure the peak area or height of the reference substance and the internal standard and calculate the correction factor according to the following equation:

$$\text{Correction factor}(f) = \frac{A_s/C_s}{A_R/C_R}$$

Where A_s is the peak area or the peak height of the internal standard

A_R is the peak area or the peak height of the reference substance

C_s is the concentration of the internal standard

C_R is the concentration of the reference solution

Prepare solutions containing the substance being examined and the internal standard as described in the monograph. Inject the solution into the equipment and record the chromatogram. Measure the peak area or the peak height of the substance being examined and that of the internal standard. Calculate the content as follows:

$$\text{Content}(C_x) = f \times \frac{A_x}{A_s/C_s}$$

Where A_x is the peak area or peak height of the substance being examined (or its impurity)

C_x is the concentration of the solution of the substance being examined (or its impurity)

internal standard

C_s is the concentration of the internal standard solution

f is the correction factor.

If an equal amount of the internal standard of the same concentration is used both in preparing the reference solution for measuring the correction factor and in preparing the test solution, that is $C_s = C'_s$. In this case accurate weighing is not necessary for preparing the internal standard solution.

(2) External standard method for the determination of the individual impurity or the main component

Prepare solutions containing an accurately weighed quantity of the reference substance and the substance being examined respectively and inject a certain amount of each solution into the equipment. Record the chromatogram and measure the peak area (or peak height). Calculate the content as follows:

$$\text{Content}(C_x) = C_R \frac{A_x}{A_R}$$

Where each symbol has the same meaning as that mentioned above.

As the micro syringe is not able to control the amount of solution being injected precisely, the sampling loop or automatic sampler may be used in measuring the content of the impurity and main components in the substance being examined.

(3) Corrected peak areas of impurities compared with that produced by the main peak of a diluted solution of substance being examined

This method could be used to measure the content of the impurity. Prepare solutions containing an accurately weighed quantity of the reference substances of impurities and the main component as specified in the monograph. Inject a volume and record the chromatogram. Calculate the correction factor of the impurity according to the method described in the (1). The correction factor could be directly recorded in the individual monograph and used for correction of the measured peak areas of impurities. These impurities, which need correction computation, are generally located by the relative retention time to the main component as the reference and all these data are recorded in the individual monograph.

When measuring the content of the impurities, dilute the solution of the substance being examined to a concentration as specified in the individual monograph so that its peak area is around that produced by the impurities in the original concentration. Inject and adjust the attenuation of the detector (limited by the noise level that can be accepted) or vary the injection volume (limited by the load ability of the column) until the peak height of the main component is about 10%-25% of the full scale or the peak area which could be accurately measured (generally, for the impurity, the content of which is lower than 0.5%, the RSD of the peak area should be less than 10%; while for the impurity, the content of which is between 0.5%-2%, the RSD of peak area should be less than 5%; for the impurity whose content is higher than 2%, the RSD of the peak area should be less than 2%). Inject separately an appropriately amount of test solution and reference solution. The recorded time span of the test solution, unless specified otherwise, should be 2 times that of the main component. Measure the peak areas of each impurity on the chromatogram of the test solution. Multiply them by the respective correction factors and then compare them with the peak area of the main component of the reference solution and calculate the content of the impurities accordingly.

(4) Peak areas of impurities compared with that produced

examined

This method could be used when the impurity reference substance is not available. Prepare the reference solution according to method (3) and adjust the attenuation of the detector. Inject separately an appropriate volume of the test solution and reference solution. The record time span of the former should be 2 times the retention time of the main component, unless specified otherwise. Measure the peak areas of the impurities on the chromatogram of the test solution and compare them with those of the main component of the reference solution and calculate the content of the impurities.

If there are some impurities in the substance being examined which are not completely separated from the solvent peak, record the chromatogram I of the substance being examined according to the specification and then record the chromatogram II of the pure solvent of equal volume. The peak area of the solvent solution on the chromatogram II is subtracted from the total peak area of the impurities in the chromatogram I (including the solvent peak). The result is equal to the correction peak area of the total impurities. Calculate the content of the impurities accordingly.

(5) Peak area normalization method

As the deviation of this method is so large that it can be only used to roughly inspect the contents of impurities in the substance being examined. It is not suitable for the determination of minute impurities, unless specified otherwise. In this method, the peak area of the impurities and the total peak area on the chromatogram except the solvent peak are measured. Calculate the peak area of each impurity and the percentage of their sum in the total peak area.

V E Gas Chromatography

Gas chromatography (GC) is a separation technique in which the mobile phase, an inert gas known as carrier gas, is passing through the chromatographic column packed with packing materials for separation and determination. The substance or its derivatives are injected into the vaporizer with a micro-syringe and vaporized, separated on the stationary phase, each component passes through the detector in succession and a chromatogram is thus recorded by integrator, recorder or data acquisition system.

1. General requirements for the instrument

The apparatus consists of a carrier gas source, an injector port, a chromatographic column contained in an oven, a detector and a data acquisition system. The injection port, column, and detector are temperature-controlled.

(1) **Carrier gas source** The mobile phase of gas chromatography is gas, known as carrier gas. Carrier gases used are usually nitrogen, helium and hydrogen. The gas is supplied by a high-pressure steel cylinder or high-purity gas generator and passes through suitable pressure-reducing valves and a flow meter to the injector port and column. The gas selection depends on the properties of the substances being examined and the species of the detector. The commonly used carrier gas is nitrogen, unless specified otherwise.

(2) **Injection port** Direct injections of solutions and headspace injection are the usual modes of injection. Direct injection may be carried out by using a syringe or an injection valve, or into a vaporization chamber which may be equipped with a stream splitter. The temperature of the

when using direct injection. The volume of solution injected is not more than several μl . The smaller the column diameter the less volume of injected solution is. Capillary column is used with injectors which is able to split samples into two fractions to avoid overloading.

Headspace injectors are suitable for separation and determination of volatile component in solid or liquid substance being examined. The test solutions produced with solid or liquid substance being examined and stored in tightly closed containers are heated in the chamber for a period of time, allowing the volatile components in the test solution to reach a equilibrium between the nongaseous phase and the gaseous phase. A predetermined amount of the head-space of the vial is flushed into the column by automatic syringe.

(3) **The chromatographic column** The chromatographic columns are classified into the packed columns and capillary columns. The packed columns, which are made of stainless steel or glass, are 2-4 mm in internal diameter and 2-4 m in length. The columns are packed with the sorbent, porous polymer bead or the supports coated with liquid phase, particle size of which is 0.25-0.18 mm, 0.18-0.15 mm or 0.15-0.125 mm. The support usually used is acid washed and silanized diatomaceous earth or porous polymer beads; the liquid phase commonly used is methylpolysiloxane, polysilphenylene of different consist, polyethyleneglycol etc. The capillary columns are made of glass or quartz. The inner wall of the column is coated or cross-linked with stationary liquid, the internal diameter is usually 0.25 mm, 0.32 mm or 0.53 mm, the length is 5-60 m, and the film thickness of the stationary liquid is 0.1-5.0 μm . The stationary liquid commonly used are methyl polysiloxane, phenylmethyl polysiloxane with different ratio of composition and carbowax, etc. New packed and capillary column must be conditioned before use to remove oxygen and residual solvents. The chromatographic column must be conditioned before use until the baseline is stable if the column is not in use long time.

(4) **The column oven** The temperature-controlled precision of the oven should be $\pm 1^\circ\text{C}$ and fluctuation of temperature should be less than 0.1°C per hour, as the temperature fluctuation of oven will influence the reproducibility of chromatographic analysis result. Temperature-controlled system may be classified into constant temperature and temperature programming.

(5) **Detector** The detectors suitable for the gas chromatography include flame-ionization detector (FID), thermal conductivity detector (TCD), nitrogen-phosphorus detector (NPD), flame-photometer detector (FPD), electron-capture detector (ECD), mass spectrometric detector (MSD) etc.. FID responses well to hydrocarbon and is suitable for the determination of most drug compounds; NPD is sensitive to organic nitrogen and phosphorus compounds; FPD is sensitive to organic sulfur and phosphorus compounds; ECD is suitable for determination of halogen compounds; MSD can offer chemical construction information of the compounds which is useful for structure verification. Unless specified otherwise, the detector should be FID which employs hydrogen as combustion gas and air as combustion-supporting gas. When FID is used, its temperature is higher than that of the column and not less than 150°C to prevent condensation of the vapour, which usually is $250-350^\circ\text{C}$.

(6) **Data process system** It is classified into recorder, integrator and computer station etc.

If necessary, parameters which specified under the individual monograph, except the kind of the detector, the type of the stationary phase and the material of the column, other parameters such as the internal diameter and length of the

stationary phase, the flow rate of carrier gas, the temperature of the column, the injection volume, the sensitivity of the detector etc, may be varied to meet the requirement of the system suitability test. Usually the chromatogram is completed within 30 minutes.

2. System suitability test

The requirements are the same as described under High Performance Liquid Chromatography, unless otherwise specified.

3. Procedure

(1) Corrected internal standard method for the determination of individual impurities or the main component.

(2) External standard method for the determination of individual impurities or the main component.

(3) Peak area normalized method.

The specific content of (1)-(3) is the same as described under High Performance Liquid Chromatography.

(4) Standard addition method for the determination of individual impurities or the main component. Dissolved an accurately weighed quantity of impurities or reference substance of the substance to be examined to produce reference solution with a suitable concentration. Measure accurately the solution and add to the test solution, then calculate the content of individual impurities or the main component by internal standard method or external standard method. Deduct the content of added standard solution and gain the content of individual impurities or the main component in the test solution.

The content may also be calculated by the following equation. The correction factor is the same as that of adding the reference solution.

$$\frac{A_{is}}{A_x} = \frac{C_x + \Delta C_x}{C_x}$$

The concentration C_x of component being examined may be calculated by the following equation.

$$C_x = \frac{\Delta C_x}{(A_{is}/A_x) - 1}$$

Where C_x is the concentration of component X being examined;

A_x is the peak area of component X being examined;

ΔC_x is the concentration of added reference substance of component being examined.

A_{is} is the peak area of component X after adding reference substance of component being examined.

In quantitative assay of gas chromatography, a major source of error is the irreproducibility in the amount of sample injected, which is affected by retaining time of syringe and room temperature, notably when manual injections are made with a syringe. The effects of variability can be minimized by an internal standard. Automatic injectors greatly improve the reproducibility of sample injections and reduce the need for internal standards. When headspace injectors are equipped, the effect of matrix may be eliminated by standard addition method because the test solution and reference solution are in different matrix. When the quantitative result of standard addition method is different from others, the result of standard addition method should be adopted.

V F Electrophoresis

supporting medium (such as paper, cellulose acetate, agarose gel and polyacrylamide gel, etc.), in which the electrically charged test samples (protein and nucleic acid, etc.) migrate towards the electrode of opposite charge under the action of an electric field. Each component migrates at its own speed and is separated in narrow zone. The electrophoretogram and percentage content of every component can be examined with appropriate assaying methods. Unless otherwise specified, carry out the following methods.

Method 1 Paper electrophoresis

1. Apparatus

The apparatus consists of two parts, electrophoretic chamber and a direct current power source.

The horizontal electrophoresis chamber shown in figure (as Fig. 5), consists of two troughs A and a hermetic lid B made of glass (or appropriate material). Both troughs are separated respectively into two compartments by plexiglass plate C (or appropriate material). In the outer compartments, there are platinum electrodes D with a diameter of 0.5-0.8 cm connected to the outside power supply by insulated cables through the trough walls; and in the inner compartments, there are movable plexiglass stands supporting the filter papers.

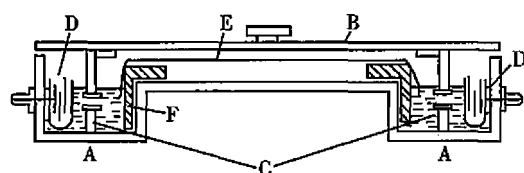


Fig. 5 The horizontal electrophoresis chamber

The power source supplying a direct current is composed with a voltage stabilizer. Ordinary voltage electrophoresis refers to that proceeded at 100-500 V, and high voltage electrophoresis refers to that proceeded at 500-10000 V.

2. Procedure

(1) *Electrophoretic buffer* Citrate buffer solution (pH 3.0): Dissolve 39.04 g of citric acid ($C_6H_8O_7 \cdot H_2O$) and 4.12 g of sodium citrate ($C_6H_5Na_3O_7 \cdot 2H_2O$) in 4000 ml of water.

(2) *Filter paper* Immerse a chromatographic filter paper in formic acid solution (1 mol/L) overnight, and then wash with water until the pH value of elute is not lower than 4. Dry the filter paper at 60 °C and preserve for use. The filter paper can be cut into strips of 27 cm in length and 18 cm in width, or appropriate for the size of electrophoresis chamber. Draw a line about 5-8 cm from one end of the paper and, along the line, mark points every 2.5-3 cm apart for application of the solution being examined.

(3) *Loading the samples* It may be divided into two categories, wet applying and dry applying. In wet applying, immerse the trimmed paper entirely into the citrate buffer (pH 3.0), take out and remove the surplus buffer solution with filter paper. Place the paper in the stand and place the application line near the cathode and the both ends of the paper immersed into the buffer solution. Apply 10 μ l of the test solution, accurately measured, to 3 marked points using microinjector. Leave two marked points for blank control. Dry applying is suitable for dilute samples. In this method, apply the test solution on the paper, after drying, apply again and repeat these steps until all the sample solution has been completed. Wet the filter paper with sprayer and allow the application spots wet at the end.

(4) *Electrophoresis* Fill the troughs of the chamber with

Connect the cables to the power source on a constant voltage mode. Adjust the voltage gradient to about 18-20 volts per cm of the paper and allow electrophoresis to proceed for about one hour and forty-five minutes. Remove the paper, dry immediately in a current of air, examine under ultraviolet light (254 nm) and mark the violet spot with pencil.

(5) *Assay* Cut the spots containing the test sample in the filter paper, as well as a piece of blank filter paper with a similar area, into slim strips and place into test tubes respectively. Add accurately measured 5 ml of hydrochloric acid solution (0.01 mol/L) to each tube, shake thoroughly and allow to stand for 1 h. Filter through a No. 3 sintered glass filter and collect the filtrate, or collect the supernatant by natural sedimentation or centrifugation. Measure the absorbance of the collected solutions at the wavelength as specified in the monograph and calculate the content.

Method 2 Cellulose acetate film electrophoresis

1. *Apparatus* The electrophoretic chamber and power source supplying direct current are the same as that of paper electrophoresis.

2. Reagents

(1) *Barbital buffer solution* (pH 8.6) Dissolve 2.76 g of barbitone and 15.45 g of barbital sodium in water to produce 1000 ml.

(2) *Amino black staining solution* Dissolve 0.5 g of amino black 10B in a mixture of 50 ml of methanol, 10 ml of glacial acetic acid and 40 ml of water.

(3) *Washing solution* Mix together 45 ml of ethanol, 5 ml of glacial acetic acid and 50 ml of water.

(4) *Hyalinization solution* Mix together 25 ml of glacial acetic acid and 75 ml of dehydrated ethanol.

3. Procedure

(1) *Cellulose acetate film* Cut the cellulose acetate foil into strips with a dimension of 2 cm \times 8 cm, immerse in the barbital buffer solution (pH 8.6), with the glossy side upwards. After steeping, take out the strip and press between filter paper to remove surplus buffer solution. Place the strip on the electrophoretic support with the glossy side downwards, immerse into the barbital buffer solution (pH 8.6) through filter paper bridge.

(2) *Application of sample and electrophoresis* Apply to the foil as a band at 2 cm from the cathode edge 2-3 μ l of test solution with a protein content of about 5%. Allow the electrophoresis to proceed at a voltage gradient of 10-12 V/cm until the electrophoretic bands are 4-5 cm apart.

(3) *Staining* After electrophoresis, remove the strip and immerse in amino black staining solution for 2-3 minutes, wash with washing solution until the background is free from colour.

(4) *Hyalinization* Immerse the washed and dry foil in the hyalinization solution for 10-15 minutes, remove and place evenly on a clean glass plate. After drying, it will become a transparent film and ready to be measured in a spectrophotometer and be kept as specimen for long-term preservation.

(5) *Assay* The electrophoretogram of the cellulose acetate foil that is untreated for hyalinization can be examined by the method specified in the monograph. Generally, the elution method or scanning method is used to determine the relative percentage content of every protein component in the sample. Elution method: Press the washed foil dry with filter paper, clip out every electrophoretic band derived from the test solution and immerse separately in 1.6% solution of sodium

complete. Measure the absorbance at appropriate wavelength. At the same time, cut out a corresponding band of foil without proteins, treated in the same manner as blank. Calculate the total absorbance and the percentage content of each protein component in the sample.

Scanning method: Scan the dry cellulose acetate foil with chromatographic scanner by means of reflection (for non-transparent film) or transmission (for transparent film). The scanning chromatogram for every protein component is recorded automatically with the length of foil as abscissa and the absorbance as ordinate. Calculate the percentage content for each protein component in the sample, which also could be performed by integrater.

Method 3 Agarose-gel electrophoresis

1. Apparatus The electrophoretic chamber and power source supplying direct current are the same as that of paper electrophoresis.

2. Reagents

(1) *Acetic acid-lithium salt buffer solution* (pH 3.0) Mix 50 ml of glacial acetic acid and 800 ml of water, adjust to pH 3.0 with lithium hydroxide and dilute to 1000 ml with water.

(2) *Toluidine blue solution* Dissolve 0.1 g of toluidine blue in 100 ml of water.

3. Procedure

(1) *Gel preparation* Add about 0.2 g of agarose to 10 ml of water, heat in a water-bath to swell completely, add 10 ml of hot acetic acid-lithium salt buffer solution (pH 3.0) and shake thoroughly, spread on a glass plate with an appropriate dimension (2.5 cm × 7.5 cm or 4 cm × 9 cm) to yield a layer of about 3 mm thick while it is still warm. Allow it to congeal and to form a uniform thickness gel without bubbles.

(2) *Preparation of the reference substance solution and test solution* Prepare the solutions as described in the monograph.

(3) *Loading the sample and electrophoresis* Fill the electrophoresis troughs with acetic acid-lithium salt buffer solution (pH 3.0), place the gel plate on the electrophoretic support and immerse into the electrophoretic buffer solution through filter paper. Apply separately 1 µl of sample solutions to the gel at the cathode edge. Connect the electrodes to the power supply immediately and allow the electrophoresis to proceed at voltage gradient of about 30 V/cm, and a current of 1-2 mA/cm for about 20 minutes. Switch off the current.

(4) *Staining and destaining* Remove the gel plate and stain the gel with toluidine blue solution. Destain the excess by washing with water until the background being colourless.

Method 4 Polyacrylamide-gel electrophoresis

1. Apparatus It consists of power source supplying constant current and disc or plate electrophoretic troughs. The electrophoretic chamber is assembled with upper trough and lower trough, in which platinum electrodes are fixed and connected by the insulated cables to the power supply at constant current mode.

2. Reagents

(1) *Solution A* Dissolve 36.6 g of tris-hydroxymethyl methylamine, 0.23 ml of N, N, N', N'-tetramethylethylene diamine and 48 ml of hydrochloric acid solution (1 mol/l) in water to produce 1000 ml. Store in an amber

(2) *Solution B* Dissolve 30.0 g of acrylamide and 0.74 g of N, N'-methylene bisacrylamide in water to produce 100 ml, filter and store in an amber coloured bottle, place in refrigerator.

(3) *Electrode buffer solution* (pH 8.3) Dissolve 6 g of tris (hydroxymethyl) methylamine, 28.8 g of glycine in water to produce 1000 ml, store in refrigerator. Dilute to 10 volumes before use.

(4) *Bromophenol blue indicator solution* Dissolve 0.1 g of bromophenol blue in 3.0 ml of sodium hydroxide solution (0.05 mol/l) and 5 ml of 95% ethanol solution by gentle heating, add 20% ethanol solution to produce 250 ml.

(5) *Staining solution* To 2.5 ml of 0.25% (g/ml) coomassie brilliant blue G₂₅₀ solution add 12.5% (g/ml) trichloroacetic acid solution to produce 10 ml.

(6) *Dilute staining solution* Dilute 2 ml of staining solution with 12.5% (g/ml) trichloroacetic acid solution to produce 10 ml.

(7) *Destaining solution* 7% acetic acid solution.

3. Procedure

(1) *Gel preparation* Dissolve 2.9 g of urea in 2 ml of solution A and 5.4 ml of solution B, add 4 ml of water, evacuate to remove air bubbles. Add 2 ml of 0.56% ammonium persulphate to form gel solution. Introduce the gel solution along the wall of the tubes using a syringe fitted with long needle or a thin pipette into glass tubes (10 cm × 0.5 cm) with rubber stopper at the bottom, until the gel column raises up to 6-7 cm. Air bubbles must not be trapped at the bottom of the tube. Cover the gel mixture in the tubes with a layer of water and allow to set for about 30 minutes. Gel polymerization is complete when a sharp interface form between the gel and water layer. Remove the water layer.

(2) *Preparation of the reference substance solution and test sample solution* Prepare the solutions as prescribed in the monograph.

(3) *Electrophoresis* Fit the tubes with prepared gel into the disc electrophoresis trough. Apply separately 50-100 µl of sample solution or reference substance solution to the tubes. To each tube add 1-2 drops of glycerol or 40% solution of sucrose and 1 drop of 0.04% bromophenol blue indicator solution to prevent from diffusion. Alternatively, several drops of 0.04% bromophenol blue indicator solution could be added directly to the buffer solution in upper trough. Fill the top of glass tubes with electrolyte buffer solution. Connect the electrodes to the power supply and allow electrophoresis to proceed at a constant current of 1 mA per tube for several minutes, then increase the current to 2-3 mA per tube. Switch off the current when the bands of bromophenol blue migrate to 1 cm from the bottom of glass tube.

(4) *Staining and destaining* After electrophoresis, extrude the gel by injecting water between the gel and the wall of the tube from the bottom by means of a syringe fitted with a fine needle. Immerse the gel strips for 10-30 minutes in staining solution or overnight in dilute staining solution. Wash with water and decolourize in destaining solution until the background of the gel in the zone without protein is transparent.

(5) *Results valuation* Examine the gel strips under lamp. Determination is made by comparing the position and colour of the bands between the reference substance and the test sample.

Relative mobility: The electrophoretic bands of the test sample and the reference substance can be compared by means of relative mobility, which can be calculated as

$$\text{Relative mobility}(R'_m) = \frac{\text{distance from origin to test sample zone or reference substance zone}}{\text{distance from origin to bromophenol blue zone}}$$

Scanning: Scan the clear gel strips in a thin layer scanner with double wavelength or gel electrophoretic scanner, calculate the percentage content of individual component based on its peak area.

Method 5 SDS-polyacrylamide gel electrophoresis

Determining the molecular weight of proteins by the way of SDS-polyacrylamide gel electrophoresis (SDS-PAGE) is based on the experience that great majority of proteins can bind with sodium dodecyl sulfate (SDS), a kind of cation surfactant, to form complex. The negative charges carrying by the protein complexes are much higher than that of the natural proteins, resulting in eliminating the discrepancy in charge effect derived from different proteins. Therefore, the relative mobility (R'_m) of protein depends completely on its molecular weight, and the molecular weight of test sample can be interpolated from the standard curve of the log of the known molecular weight of the standard proteins against their relative mobilities.

1. Apparatus Unless otherwise specified, it is the same as that of polyacrylamide gel electrophoresis.

2. Reagents

(1) **30% Acrylamide solution** Dissolve 60 g of acrylamide and 1.6 g of N, N' -methylene bisacrylamide in 200 ml of water, filter, store in a brown bottle and keep in low temperature.

(2) **Separating gel buffer solution** Dissolve 36.3 g of tris-hydroxymethyl methylamine in 70 ml of water, adjust pH to 8.8 with hydrochloride acid and dilute with water to 100 ml.

(3) **Stocking gel buffer solution** Dissolve 6.0 g of tris-hydroxymethyl methylamine in 70 ml of water, adjust pH to 6.8 with hydrochloride acid and dilute with water to 100 ml.

(4) **Electrode buffer solution** Dissolve 6.0 g of tris-hydroxymethyl methylamine, 28.8 g of glycine and 1.0 g of SDS in water to produce 1000 ml.

3. Procedure

(1) **Gel preparation** Prepare separating gel solution using a mixture of 30% acrylamide solution-separating gel buffer solution-20% SDS solution-10% ammonium persulphate solution (freshly prepared) - N, N, N', N' -tetramethylethylenediamine-water (5.0 : 1.5 : 0.08 : 0.1 : 0.01 : 5.3), and pour into electrophoretic troughs to the required heights. Seal the top of separating gel with water, polymerized, pour out the water. Pour stocking gel solution using a mixture of 30% acrylamide solution-stockung gel buffer solution-20% SDS solution-10% ammonium persulphate solution- N, N, N', N' -tetramethylethylenediamine-water (0.8 : 1.3 : 0.025 : 0.05 : 0.005 : 2.4) on the separating gel, insert the comb of the sample (seal the top of stocking gel with water for disk troughs). Polymerized, remove the comb or pour out water.

(2) **Reference and test solution preparation** Carry out the method of individual monograph.

(3) **Electrophoresis** Vertical plate electrophoretic troughs; at constant voltage mode for 80 V of starting voltage. When the test solution move into separating gel, adjust the voltage to 150-200 V. When the bands of bromophenol blue migrate to 1 cm from the bottom of glass plate, stop electrophoresis.

4. Staining

(1) Staining with coomassie brilliant blue

① **Reagents** Fixing solution: Dissolve 5 g of trichloroacetic acid in 200 ml of water, add 200 ml of methanol, add water to produce 500 ml.

Staining solution: Dissolve 0.5 g of coomassie brilliant blue R_{250} in 200 ml of water, add 200 ml of methanol and 50 ml of glacial acetic acid, add water to produce 500 ml.

Destaining solution: To 400 ml of methanol and 100 ml of glacial acetic acid add water to produce 1000 ml, mix well.

Storing solution: To 75 ml of glacial acetic acid add water to produce 1000 ml, mix well.

② **Fixing and staining** Immerse the gel slice or strips for 30 minutes in fixing solution, for 1-2 hours in staining solution, decolourize in destaining solution until the background of the gel in the zone without protein is transparent, and then preserve it in the storing solution.

(2) Silver staining

① **Reagents** Silver nitrate solution: To 0.8 g of silver nitrate in 4 ml of water. Add this solution dropwise to a mixture of 0.1 mol/L sodium hydroxide-25% ammonium solution (20 : 15), mix well, add water to produce 100 ml.

Fixing solution: To 50 ml of methanol and 54 μ l of 37% formaldehyde solution, add water to produce 100 ml.

Developing solution: To 2.5 ml of 1% citric acid solution and 270 μ l of 37% formaldehyde solution, add water to produce 500 ml.

Stopping solution: To 100 ml glacial acetic acid add water to produce 1000 ml.

② **Fixing and staining** Immerse the gel slice for 2 hours at least in fixing solution; wash the gel with water for 1 hour at least; for 15 minutes in 1% glutaraldehyde solution; wash twice the gel slice with water, each time for 15 minutes, for 15 minutes in silver nitrate solution, wash three times the gel slice with water, each time for 15 minutes; Immerse the gel slice in developing solution, when all bands is examined, put the gel slice in stopping solution.

5. Calculation

Measure the migration distance of the dye zone and the protein zone, and the length of gel strip before staining and after decolourization. Calculate the relative mobility by the following formula:

$$\text{Relative mobility}(R'_m) = \frac{\text{migration distance of the protein zone}}{\text{the length of gel strip after destaining}} \times \frac{\text{the length of gel strip before staining}}{\text{migration distance of the dye zone}}$$

(1) Relative mobility of main component in the test solution is identical to that of reference standard.

(2) **Molecular weight** Plot graphically in semi-log coordinate paper by taking the R'_m as abscissa and the log of the molecular weight of the standard proteins as ordinate. Interpolate the molecular weight of the test sample from the standard curve.

(3) **Purity** Scan the clear gel in a thin layer scanner with double wavelength or gel electrophoretic scanner and calculate the percentage content of individual component based on its peak area.

V G Capillary Electrophoresis

Capillary electrophoresis is a separation technique using

generally suitable for determination of molecular weight of protein and peptide. Carry out the method stated in the monograph, using a column and reference substances suitable for the molecular weight of samples. Reference substance and samples should both be processed by dithiothreitol (DTT) and sodium lauryl sulfate (SDS) in order to break disulfide bond and make the molecule configuration and conformation concord. Usually the processed protein and peptides which have been turned to a straight line are separated. Plot a graph of the retention time of the reference substance as a function of the logarithm molecular weight and calculate the equation of linear regression, $\lg M_w = a + bt_R$. Calculate molecular weight or subunit molecular weight from the regression equation

(2) *Determination of molecular weight and molecular weight distribution of polymers* Molecular weight of biopolymers, such as amylose, nucleic acid and collagen, is usually unhomogeneous. Molecular weight and molecular weight distribution of the biopolymer is a key index. To determine the molecular weight and molecular weight distribution of biopolymers, it is important to adopt reference substances with similar structures and properties to the samples.

Carry out the method stated in the monograph, unless otherwise specified, use molecular weight reference substance and suitable GPC software, plot a graph of the retention time of the reference substance as a function of the logarithm of weight-average molecular weight and calculate the equation of linear regression $\lg M_w = a + bt_R$. Process the result with suitable GPC software and calculate the molecular weight and molecular weight distribution of samples.

$$\begin{aligned} M_n &= \sum RI_i / \sum (RI_i / M_i) \\ M_w &= \sum (RI_i / M_i) / \sum RI_i \\ D &= M_w / M_n \end{aligned}$$

Where M_n is number-average molecular weight

M_w is weight-average molecular weight

D is distribution coefficient

RI_i is peak height of samples at retention time i

M_i is molecular weight of samples at retention time i

(3) *Determination of macromolecule impurities* Macromolecule impurities are the impurities with higher molecular weight than drug molecule, which produced during

procedure of manufacture or storage and cannot be removed completely (sensitizing polymers). Separation is carried out according to the chromatographic condition stated in the monograph.

Quantitative method

① *Peak areas of impurities compared with those produced by the main peak of the sample* See the section of High Performance Liquid Chromatogram. The method is typically used for determination of macromolecule impurities with low content in the samples.

② *Peak area normalization method* See the section of High Performance Liquid Chromatogram.

③ *Retention time limit method* Unless otherwise specified, it is specified that component with shorter retention time than that of the main peak is not allowed to be detected. This method is typically used to control macromolecule impurities in the mixture.

④ *External standard method by the substance to be examined* This method is typically used for determination of macromolecule impurities in β -lactam antibiotics by Sephadex G-10 gel chromatography system. Except for some oligomers, macromolecule impurities in β -lactam antibiotics are not retained in this system and only appear to be one peak. Calculate content of the macromolecule impurities by external standard method, using the substance to be examined as reference substance.

Announcements Processing method for Sephadex G-10

Packing chromatographic column Soak about 15 g of Sephadex G-10 with water for 48 hours before packing and make it swelling thoroughly, stir to expel air bubbles. Slowly add the mixture as slurry into the chromatographic tube. Wash down the Sephadex G-10 adhering to the inner wall of the tube with water, smooth the surface of the column. Newly packed column should be eluted with water for 4-6 hours to expel air bubbles.

Loading the sample Both automatic inject valve and manual loading can be adopted to load the substance being examined into the column. Add the test solution slowly along the inner wall of the tube, care should be taken that the packing material is not disturbed. Wash down the samples adhering to the inner wall of the tube with 3-5 ml mobile phase after sample solution permeate through the column surface.

Appendix VI

VI A Determination of Relative Density

Relative density is defined as the ratio of the mass density of a substance to that of water under the same conditions of temperature and pressure. Unless otherwise specified, the measuring temperature is 20°C.

Relative density of the pure substance is a constant under particular condition. But, when the substance is not purified the determined value of relative density changes with the purity. So relative density is indicative of the identity and purity of the substance being examined.

The relative density of a liquid can be determined with a pycnometer (as Fig. 6 or as Fig. 7). In some cases, the Westphal balance (as Fig. 8) is used, for example, in the determination of the relative density of a volatile liquid.

The temperature of the determination environment of the pycnometer and balance should be a little bit below 20°C or that specified under individual monograph.

1. Pycnometric method

(1) Fill a clean, dry and accurately weighed pycnometer (as Fig. 6) with the substance being examined (keep the temperature below 20°C or that specified under individual monograph), fix the thermometer (no air bubble is left in the pycnometer). Place the pycnometer in a water bath maintained at 20°C or the specified temperature, allow to stand in the water bath for several minutes, so as to raise the temperature of the content to 20°C or to the temperature specified in the monograph. Wipe away the liquid overflowed from the side tube with a piece of filter paper and put the cap immediately. Remove the pycnometer from the water bath and clean off any material on the outside with a piece of filter paper, weigh the pycnometer accurately and calculate the weight of its content.

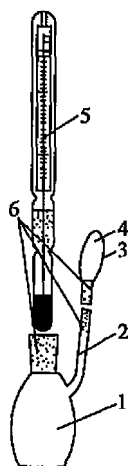


Fig. 6



Fig. 7

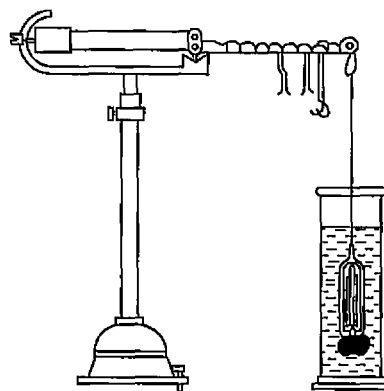


Fig. 8

Discard the content of the pycnometer and wash the pycnometer with water, fill it with freshly boiled and cooled water. Determine the weight of the water in the pycnometer in a similar manner. The relative density of the substance being examined can be calculated from the following formula:

$$\text{Relative density} = \frac{\text{weight of the substance being examined}}{\text{weight of water}}$$

(2) Fill a clean, dry and accurately weighed pycnometer (as Fig. 7) with the substance being examined (keep the temperature below 20°C or that specified under individual monograph). Insert the capillary stopper and wipe away the overflowed liquid with a piece of filter paper. Place the pycnometer in a water bath maintained at 20°C or the specified temperature, allow to stand in the water bath for several minutes.

Some of the liquid spills out through the capillary constantly with the rise of the temperature of the content. Wipe away the overflowed liquid with a piece of filter paper at any time until the fluid does not overflow anymore. Remove the pycnometer from the water bath rapidly. Proceed as described under method (1), starting from the words "clean off any material on the outside with a piece of filter paper..."

2. Hydrostatic method

Fill the glass cylinder of the Westphal balance (as Fig. 8) with freshly boiled and cooled water to about 80% of the volume. Place the cylinder and stir the content of it in a water bath maintained at 20°C or the specified temperature. Dip the plunger hung on the end of the beam into the water in the cylinder, the liquid in the cylinder should be 1.0000. Adjust the equilibrating screw until the beam is horizontal. Discard the water and wipe away any water left in the cylinder, fill the cylinder with the substance being examined to about 80% of the volume and adjust the temperature as mentioned above. Dip the plunger into the substance being examined and equilibrate again by placing suitable riders at appropriate marks along the beam. The reading gives directly the relative density of the substance being examined.

VI E Determination of Optical Rotation

The plane of polarized light can be rotated clockwise or counterclockwise when plane polarized light passes through some liquids or solutions of compounds which are optically active. Optical rotation is expressed in degrees by which the plane of polarization is rotated under specified condition. Specific optical rotation is defined as the optical rotation measured under given wavelength and temperature, when polarized light passes through a layer of a solution 1 dm thick containing 1 g of optically active substance per ml. The measurement of specific optical rotation (or optical rotation) may be used as an identification test, a purity test or a method of assay.

Unless otherwise specified, the values of optical rotation cited in this method are measured at 20°C with sodium D line (589.3 nm), in a tube of 1 dm. Conversion factor should be applied if the tube used is not of the appropriate length. Optical rotation is measured with a calibrated polarimeter accurately read to 0.01°. Rinse the polarimeter tube several times with the liquid or solution prepared as described in the individual monograph. Fill the polarimeter tube slowly with the liquid or solution, taking care to avoid creating or leaving air bubbles. Put the tube into the polarimeter and read the degrees of optical rotation. Substances are described as dextrorotatory or levorotatory according to whether the plane of polarization is rotated clockwise or counterclockwise, respectively, as viewed toward the light source. Dextrorotation is designated (+) and levorotation is designated (-). Carry out 3 measurements, take the average and calculate the specific optical rotation from one of the following equations:

$$\text{For liquids} \quad [\alpha]_D^t = \frac{\alpha}{l d}$$

$$\text{For solid substances} \quad [\alpha]_D^t = \frac{100 \alpha}{l c}$$

Where $[\alpha]$ is specific optical rotation;
D is sodium D line;
 t is measuring temperature;
 l is the length of the polarimeter tube, dm;
 α is the observed rotation in angular degrees;
 d is the relative density of the liquid;
 c is the weight of solute (g) in 100 ml of the solution, calculated on the dried basis or anhydrous basis.

Standard quartz polarimetric tube may be used to calibrate the polarimeter, the deviation of reading should comply with the requirements.

Announcements (1) Blank tests should be performed to check the zero point before and after each measurement. If the deviation of reading does not comply with the requirements after measurement, repeat the measurement.

(2) The temperature of the solution being tested should be kept constant at 20°C ± 0.5°C (or at the temperature specified in the individual monograph).

(3) Liquids or solutions of solid substance should be completely dissolved, and the test solution should be clear.

(4) The specific rotation of a liquid or a substance in solution is affected by several factors including light source, wavelength, solvent, concentration and temperature. When describing the specific optical rotation, the measuring condition should be provided.

VI F Determination of Refractive Index

Refraction takes place when a beam of light is transmitted from a transparent medium into another transparent medium, since the velocity of light changes in a medium of different density. The refractive index of a substance is the ratio of the velocity of light in air to its velocity in the substance. The refractive index may also be defined as the ratio of the sine of the angle of incidence to the sine of the angle of refraction:

$$n = \frac{\sin i}{\sin r}$$

Where n is the refractive index;
 i is the angle of incidence;
 r is the angle of refraction.

The refractive index varies with the temperature of the substance being examined and the wavelength of incident light. It decreases with the increase of temperature. The shorter the wavelength of incident light, the larger the refractive index. Refractive indices are usually stated in terms of sodium line D at a temperature of t and symbolized by n_D^t . The measurement of refractive index is employed to establish the identity of oils and test for purity of the substance being examined.

Unless otherwise specified, the values of refractive index cited in this method are measured at 20°C with sodium line D (589.3 nm) against air (White light may be used if an Abbe refractometer is available).

The refractometer should be able to give readings accurate to 0.0001 in the range of 1.3-1.7. If an Abbe refractometer or other equivalent instrument is used, the measurement should be conducted at 20°C ± 0.5°C (or in accordance with the temperature stated under individual monograph). Three readings should be taken and the mean value is used as the refractive index of the substance being examined. The readings of the refractometer should be calibrated before use with a prism or against water. The refractive index of water is 1.3330 at 20°C, 1.3325 at 25°C and 1.3305 at 40°C.

VI G Determination of Viscosity

Viscosity is the property of a liquid related to resistance to flowing. It is defined in terms of kinetic viscosity, kinematic viscosity or intrinsic viscosity. The viscosity of a substance being examined can be used for purity check. There are two major kinds of fluids; Newtonian and non-Newtonian. The shearing force needed for Newtonian fluids does not change as the flow rate is changing. Pure liquids and solutions of low molecular weight substances belong to this category. For non-Newtonian fluids, the shearing force needed varies with flow rate. This category of liquid consists of high polymer solutions, suspensions, emulsifying dispersive liquids and surfactant solutions.

Viscosity can be determined with viscosimeters. Many types of viscosimeter can be used for this purpose. In this method, the capillary type and the rotating type are adopted. Linear velocity cannot be adjusted when capillary viscosimeter is used, it is therefore unsuitable for the determination of the viscosity of non-Newtonian fluids. But it is convenient for the viscosity determination of diluted polymer solutions or liquids

viscosity determination of non-Newtonian fluids.

The kinetic viscosity of a liquid (η) is the shearing force required per square centimeter to cause the liquid flow at a rate of 1 centimeter per second. The unit of kinetic viscosity is expressed in pascal second ($\text{Pa} \cdot \text{s}$). The ratio of the kinetic viscosity to the density of the liquid at the same temperature multiplied by 10^{-6} equals to kinematic viscosity of the liquid (ν), which is expressed in mm^2/s .

In this method, the kinematic viscosity of the liquid determined under specified condition by measuring the flow time (in seconds) through Ostwald-type viscosimeter and multiplying by the constant (mm^2/s^2) of the same viscosimeter determined using a calibration liquid.

The viscosity of solvent, η_p , increases usually with the dissolution of polymers of high molecular weight. The ratio of the viscosity of a solution (η), to that of the solvent (η_p), is termed as "relative viscosity (η_r)" which is usually expressed by the ratio of flow time (T/T_0) measured with Ubbelohde-type viscosimeter. When the concentration of high polymer is low, the ratio of logarithmic value of relative viscosity to the concentration of polymer solution is the intrinsic viscosity (η) of that polymer. The mean molecular weight of the polymer concerned may be estimated from its intrinsic viscosity.

Apparatus (1) *Constant temperature water bath* A glass or plexiglass vessel, 30 cm or more in internal diameter, 40 cm or more in height, equipped with a mechanical stirrer and an electric heating device.

Unless otherwise specified, kinetic viscosity or kinematic viscosity is measured at $20^\circ\text{C} \pm 0.1^\circ\text{C}$.

(2) *Thermometer* Graduated in divisions of 0.1°C .

(3) *Stopwatch* Graduated in divisions of 0.2 second.

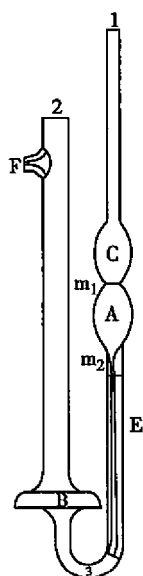


Fig. 11 Ostwald-type

viscosimeter
1—main tube;
2—wide tube;
3—bending tube;
A—measuring bulb;
B—reservoir;
C—buffering bulb;
E—capillary tube;
F—side tube;
 m_1, m_2 —circular mark

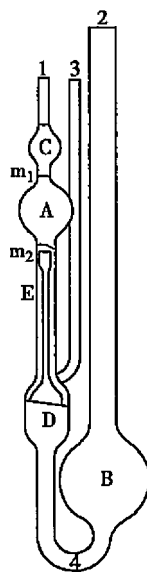


Fig. 12 Ubbelohde-type

viscosimeter
1—main tube;
2—wide tube;
3—side tube;
4—bending tube;
A—measuring bulb;
B—reservoir;
C—buffering bulb;
D—suspended-level reservoir;
E—capillary tube;
 m_1, m_2 —circular mark

(4) *Ostwald-type Viscosimeter* (as Fig. 11) Internal diameter of the capillary tube is $0.8 \text{ mm} \pm 0.05 \text{ mm}$, $1.0 \text{ mm} \pm 0.05 \text{ mm}$, $1.2 \text{ mm} \pm 0.05 \text{ mm}$, $1.5 \text{ mm} \pm 0.1 \text{ mm}$ or $2.0 \text{ mm} \pm 0.1 \text{ mm}$.

(5) *Rotating viscosimeter*

(6) *Ubbelohde-type viscosimeter* (as Fig. 12) Unless otherwise specified, the capillary tube E is $0.5 \text{ mm} \pm 0.05 \text{ mm}$ in internal diameter, $140 \text{ mm} \pm 5 \text{ mm}$ long and the capacity of bulb A is $3.5 \text{ ml} \pm 0.5 \text{ ml}$ (with an appropriate dropping time of 120-180 seconds).

Method 1 Determination of kinematic or kinetic viscosity with Ostwald-type viscosimeter

Select a suitable viscosimeter with required internal diameter of the capillary tube as described under individual monograph.

Connect a rubber tubing to the side tube F of the Ostwald-type viscosimeter, block the mouth of tube 2 with a finger and turn the viscosimeter upside down so that tube 1 is plunged into the liquid or the solution being examined. Suck from the other end of the rubber tubing until the liquid or solution is filled to the mark m_2 . Remove the viscosimeter and immediately revert it, wipe away the liquid adhering to the exterior of tube 1 and disconnect the rubber tubing from side tube F and connect it to tube 1. Place the viscosimeter upright in the water bath so that the water surface is above the middle of bulb C. Allow to stand in the water bath for 15 minutes, suck from the other end of the rubber tubing until the liquid or solution fills the bulb A and rises above the mark m_1 . Release the suction and allow the liquid to drop spontaneously. Record the time required for the liquid surface to drop from m_1 to m_2 . Repeat this measurement 3 times or more and perform another series of measurements with a second sample of the liquid or solution, the dropping time recorded in each case should not deviate from the mean value by more than $\pm 5\%$. Calculate the kinematic (or kinetic) viscosity of the liquid (or solution) being examined using the average of the results of the two samplings as follows:

$$\nu (\text{mm}^2/\text{s}) = K t$$

$$\eta (\text{Pa} \cdot \text{s}) = 10^{-6} K t \rho$$

Where K is constant of the viscosimeter determined using standard liquid of known viscosity, mm^2/s^2 ;

t is the mean dropping time, s;

ρ is the density of the solution being examined, measured at the same temperature, kg/m^3 .

Method 2 Determination of kinetic viscosity with rotating viscosimeter

Rotating viscosimeters for the determination of kinetic viscosity of a liquid are based on the measurement of shearing forces during rotation in a liquid medium. Calculate the kinetic viscosity of the substance being examined as follows:

$$\eta (\text{Pa} \cdot \text{s}) = K \cdot (T/\omega)$$

Where K is constant of the rotating viscosimeter determined using standard liquid of known viscosity;

T is torque;

ω is the angular velocity.

Commonly used types of rotating viscosimeters are as follows:

(1) *Coaxial cylinder rotating viscosimeter*. Fill the gap of internal and external cylinders, which revolve individually, with the substance being examined. When one cylinder is revolving at specified angular velocity or torque, measure the angular velocity or the torque transmitted to the other cylinder, thus the viscosity of the substance being examined can be calculated.

cylinder into the substance being examined and make it revolve at specified angular velocity. Measure the torque exerted on the surface of the cylinder, thus the viscosity of the substance being examined can be calculated.

(3) Cone-plate viscosimeter. Fill the gap of a cone and a flat plate, which can revolve coaxially, with the substance being examined. Measure the torque or the angular velocity exerted on the cone or the plate, thus the viscosity of the substance being examined can be calculated.

(4) Rotating spindle viscosimeter. Select a proper spindle specified under individual monographs, immerse the spindle into the substance being examined, make the spindle revolve at specified angular velocity, and measure the torque exerted on the spindle, thus the viscosity of the substance being examined can be calculated.

Select a proper one among the commonly used rotating viscosimeters according to the character and the range of viscosity of the substance being examined.

Measure the kinetic viscosity according to the instructions for the operation of the specified rotating viscosimeter described under individual monographs.

Method 3 Determination of intrinsic viscosity with Ubbelohde-type viscosimeter

Dissolve the substance being examined in a solvent to produce a solution of appropriate concentration as described under individual monograph, filter through a No. 3 sintered glass filter and discard the initial filtrate (about 1 ml). Fill not less than 7 ml of the successive filtrate along the inner wall of tube 2 into bulb B of a clean and dry Ubbelohde-type viscosimeter. Place the viscosimeter upright in the constant temperature water bath ($25^{\circ}\text{C} \pm 0.05^{\circ}\text{C}$, unless otherwise specified) so that bulb C is entirely immersed under the surface of water. Allow it to stand in the water bath for 15 minutes. Connect a rubber tubing to tube 1 and 3 and clamp the rubber tubing connected to tube 3. Suck from the end of the rubber tubing connected to tube 1 until the solution rises to the middle of bulb C. Release the suction and remove the clamps of tube 3 and tube 1 in succession and allow the solution to drop spontaneously. Record the time required for the surface of the solution to drop from m_1 to m_2 . Repeat the operation once more. The difference between the two measurements should not be more than 0.1 second and take the average value as the dropping time of the solution being examined (T). Perform the same determination with the solvent previously filtered through a No. 3 sintered glass filter. Repeat the operation once more. The values of the two measurements should be the same and it is taken as the dropping time of the solvent (T_0). Calculate the intrinsic viscosity as follows:

$$\text{Intrinsic viscosity } [\eta] = \frac{\ln \eta_r}{C}$$

Where η_r is T/T_0 ;

C is concentration of the solution being examined, g/ml.

VI H Determination of pH Value

The pH value of an aqueous solution is determined by a pH meter using a glass electrode as the indicator electrode, and a saturated calomel electrode as the reference electrode. Metrological verification of the pH meter should be carried out at regular intervals to meet the related national requirements. Before each measurement, the pH meter should be calibrated with the standard buffer solutions prepared as follows, or those of a declared pH value accurate

department of certified reference material (CRM).

1. Standard buffer solutions used for the calibration of pH meters are prepared as follows.

(1) *Standard tetraoxalate BS* Dissolve 12.71 g of potassium tetraoxalate, previously dried at $54^{\circ}\text{C} \pm 3^{\circ}\text{C}$ for 4-5 hours and accurately weighed, in water to produce 1000 ml.

(2) *Standard biphthalate BS* Dissolve 10.21 g of potassium biphthalate, previously dried at $115^{\circ}\text{C} \pm 5^{\circ}\text{C}$ for 2-3 hours and accurately weighed, in water to produce 1000 ml.

(3) *Standard phosphate BS* Dissolve 3.55 g of anhydrous disodium hydrogen phosphate and 3.40 g of potassium dihydrogen phosphate, previously dried at $115^{\circ}\text{C} \pm 5^{\circ}\text{C}$ for 2-3 hours and accurately weighed, in water to produce 1000 ml.

(4) *Standard sodium tetraborate BS* Dissolve 3.81 g of sodium tetraborate, accurately weighed (avoid efflorescence), in water to produce 1000 ml. Preserve the solution in well closed polyethylene containers, protected from carbon dioxide in the air.

(5) *Standard calcium hydroxide BS* Use the supernatant of a saturated solution of calcium hydroxide, saturated with carbon dioxide-free water at 25°C . Store protected from carbon dioxide in the air. Discard and repeat the preparation if the solution becomes turbid.

Standard buffer solutions mentioned above must be prepared from the certified reagents for pH determination. The exact pH values of the standard buffer solutions at different temperatures mentioned above are given in the following table.

Temp. $^{\circ}\text{C}$	Standard buffer solutions ^①				
	1	2	3	4	5
0	1.67	4.01	6.98	9.64	13.43
5	1.67	4.00	6.95	9.40	13.21
10	1.67	4.00	6.92	9.33	13.00
15	1.67	4.00	6.90	9.28	12.81
20	1.68	4.00	6.88	9.23	12.63
25	1.68	4.01	6.86	9.18	12.45
30	1.68	4.02	6.85	9.14	12.29
35	1.69	4.02	6.84	9.10	12.13
40	1.69	4.04	6.84	9.07	11.98
45	1.70	4.05	6.83	9.04	11.84
50	1.71	4.06	6.83	9.01	11.71
55	1.72	4.08	6.83	8.99	11.57
60	1.72	4.09	6.84	8.96	11.45

① The standard buffer solutions are numbered here in the same sequence as shown in the preceding paragraph.

2. Announcements Operate the pH meter according to the manufacturer's instructions and pay attention to the following precautions when pH value is determined.

(1) Select two standard buffer solutions with difference in pH value of 3 units before determining test solution, and the pH value of the test solution is between that of two standard buffer solutions.

(2) Calibrate the apparatus using the primary standard buffer solution whose pH value is closer to test solution, adjusting the meter (fixed position) to read the appropriate pH value given in table mentioned above.

(3) Then calibrate the apparatus using the second standard buffer solution. The deviation should not be more than \pm

observed pH value meet the value in the table mentioned above if it is not. Repeat the adjusting procedure for fixed position and slope until the difference between the observed value on the apparatus and the value of standard buffer solution is not more than 0.02 pH units. Otherwise the apparatus should be examined or the electrode should be exchanged till comply with the requirement.

(4) The electrode should be rinsed with water and dried (or rinsed with the solution being examined) before each measurement.

(5) A highly alkaline glass electrode should be used if the pH value of the solution being examined is high. The error caused by alkalinity should be corrected if the electrode used is apt to produce such an error.

(6) The determination of the pH value of a liquid with weak

buffering capacity (e.g. water) should be conducted after the pH meter is calibrated with standard potassium biphthalate BS and repeated after the pH meter is calibrated with standard sodium tetraborate BS. The readings should not be recorded until the shift in 1 minute is within 0.05 unit. The pH value of the liquid being examined is the mean value of the two readings provided that they do not differ by more than 0.1 unit.

(7) Freshly boiled and cooled distilled water with a pH value of 5.5-7.0 should be used for preparing standard buffer solutions and dissolving the substance to be examined in pH determinations.

(8) Usually, the standard buffer solutions can be kept for 2-3 months, but should not be used if any turbidity, mould or precipitate is discovered.

Appendix VII

VII A Potentiometric Titration and Dead-stop Titration

The potentiometric method and dead-stop method may be used for the confirmation of end point or the colour change of indicators at the end point. Using a suitable electrode system, these methods can be applied to oxidation-reduction, neutralization aqueous solution or non-aqueous solution, argentometric and nitrite titrations as well as the method 1 of volumetric determination of water. Two different electrodes are used in potentiometric titration, one is an indicator electrode, whose potential is sensitive to the ionic concentration of the substance being examined, the other is a reference electrode, whose potential is constant. At the end point of the titration, the ionic concentration of the substance being examined changes sharply, causing an abrupt increase or decrease of the potential (a potential jump) of the indicator electrode.

In the dead-stop titration, a low voltage of about 50 mV is applied across two same platinum electrodes. Since the electrodes are polarized, there is no current or only a very weak current flows. When the end point is reached, a slight excess of the titrant depolarizes the electrodes and a current flows, causing a permanent deflection of the galvanometer needle. On the other hand, if non-polarized electrodes are polarized, the deflected galvanometer needle turns back to zero permanently.

Apparatus In potentiometric titration, a pH meter or potentiometer, or any model of a potentiometric titration apparatus may be used. In dead-stop titration, any model of a dead-stop titration apparatus or an assembly illustrated in the following figure may be used (as Fig. 13).

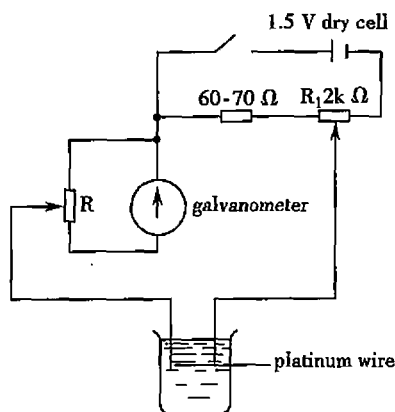


Fig. 13

the value of R is approximately equivalent to the critical damping resistance of the galvanometer

Unless otherwise specified, the sensitivity of galvanometer is

10^{-9} A per graduation for nitrite titration. The electrode system employed are shown in the following table.

Procedure	Electrode system	Note
Redox titration in aq. solution	Platinum-calomel	Platinum electrode cleaned with nitric acid containing a small quantity of ferric chloride, or with chromic acid cleaning solution
Neutralization titration in aq. solution	Glass-calomel	
Neutralization titration in non-aqueous solution	Glass-calomel	Use a saturated solution of KCl in dehydrated methanol as the salt bridge. Wash the glass electrode after each titration and immerse in water while not in use
Argento-metric titration	Silver-glass	Silver electrode cleaned with dilute nitric acid
	Silver-KNO ₃ salt bridge-calomel	
Hydrogen displacement in $-C\equiv CH$	Glass-KNO ₃ salt bridge-calomel	
Mercury potentiometric titration	Platinum-mercury-mercurous sulfate	Platinum electrode rinsed with water after being immersed in 10% (w/v) sodium thiosulfate. Platinum-mercury-mercurous sulfate electrode rinsed with water after being immersed in dilute nitric acid
Dead-stop titration	Platinum-platinum	Cleaned with nitric acid containing a small quantity of ferric chloride, or with chromic acid cleaning solution

Titration

(1) **Potentiometric Titration** Place a beaker containing the solution of the substance being examined on a magnetic stirrer, dip the electrodes into the solution and start the stirrer. Add the titrant from a burette in portions, record the potential after each addition. When the end point is nearly reached, add the titrant dropwise and record the potential. Add a few drops more after the potential jump and record the potential reading.

Potentiometric end point detection Plot an $E-V$ curve with the potential (E) as ordinate and the volume of titrant (V) as abscissa, the midpoint of the rapid ascent or descent portion is the end point. Alternatively, plot a $(\Delta E/\Delta V)-V$ curve (ΔE is the potential difference between successive measurements and ΔV is the volume of titrant added between successive measurements), the volume corresponding to the maximum of $\Delta E/\Delta V$ is the end point. Also the end point can be determined by second derivative method. Plot a $\Delta^2 E/V^2-V$ curve, calculate the difference between successive

$\Delta V^2 = 0$ is the end point.

If the colour changes of an indicator at the end point is to be checked, add the indicator solution before the titration and observe the colour changes in the vicinity of the end point.

(2) Dead-stop Titration For the indication of the end point of diazotization reaction by a nitrite titration, apply a voltage of about 50 mV across the electrodes by adjustment R_1 . Place an accurately weighed quantity of the substance being examined in a beaker on a magnetic stirrer, add 40 ml water and 15 ml of hydrochloric acid solution (1 → 2), unless otherwise specified, stir to effect dissolution. Add 2 g of potassium bromide, dip the electrodes into the solution, plunge the burette into the solution so that about 2/3 of the tip is under the liquid surface, titrate with sodium nitrite (0.1 or 0.05 mol/L) VS quickly with stirring. Withdraw the burette tip when the end point is nearly reached, rinse it with water and add the washings to the solution, continue the titration slowly until the galvanometer needle is permanently deflected.

For the indication of the end point of the method 1 of volumetric determination of water, adjust the resistance R_1 until the galvanometer shows an initial current of 5-10 μ A, titrate with Fischer reagent until the current rises to 50-150 μ A abruptly and the deflection of galvanometer needle persists for a few minutes.

VII B Non-aqueous Titration

Non-aqueous titration is carried out in a non-aqueous solvent and used mainly for the determination of organic bases; organic salts of hydrohalic acid, phosphoric acid and sulfuric acid or organic acids and the alkali metal salts of organic acids, as well as some weak organic acids.

Non-aqueous Solvents

(1) Acidic solvents The relative alkalinity of weak organic bases can be remarkably enhanced in acidic solvents. The most commonly used acidic solvent is glacial acetic acid.

(2) Basic solvents The relative acidity of weak organic acids can be remarkably enhanced in basic solvents. The most commonly used basic solvent is dimethylformamide.

(3) Amphiprotic solvents They have the properties of acids and bases. The most commonly used amphiprotic solvent is methanol.

(4) Aprotic solvents They are neither acidic nor basic, such as benzene, chloroform etc.

Method 1

Unless otherwise specified, dissolve an accurately weighed quantity, equivalent to about 8 ml of perchloric acid (0.1 mol/L) VS, of the substance being examined in 10-30 ml of glacial acetic acid, add 1-2 drops of the indicator solution as specified in the monograph and titrate with perchloric acid (0.1 mol/L) VS. The colour change of the indicator should be checked by potentiometric method and a blank determination performed to make any necessary correction.

If the temperature at which the titration is performed differs by more than 10°C from the temperature at which the perchloric acid VS was standardized, the titrant must be standardized again. If the difference does not exceed 10°C, the concentration of the titrant can be corrected as follows:

$$N_1 = \frac{N_0}{1 + 0.0011(t_1 - t_0)}$$

Where 0.0011 is the volume expansion coefficient of glacial acetic acid

t_0 is the temperature at which perchloric acid VS was standardized;

t_1 is the temperature at which the titration is performed;

N_0 is the concentration of perchloric acid VS at t_0 ;

N_1 is the concentration of perchloric acid VS at t_1 .

When the substance being examined is a salt of hydrohalic acids, the titration should be carried out after the addition of 3-5 ml of mercuric acetate TS. Phosphates and sulfates can be titrated directly, but in the case of sulfates, the reaction stops when bisulfate is formed. In the titration of nitrates, the end point should be determined by potentiometric method, because the indicator can be discoloured by nitric acid.

In non-aqueous potentiometric titration, the indicator electrode is a glass electrode and the reference electrode is a saturated calomel electrode using a saturated solution of potassium chloride in dehydrated methanol as the salt bridge.

Method 2

Unless otherwise specified, dissolve an accurately weighed quantity, equivalent to 8 ml of the titrant (0.1 mol/L), of the substance being examined in a solvent specified in the monograph, add 1-2 drops of the specified indicator solution and titrate with the specified basic titrant (0.1 mol/L). The colour change of the indicator should be checked by potentiometric method and a blank determination performed to make any necessary correction.

In the course of the titration, protect the solvent and titrant from atmospheric carbon dioxide and moisture, avoid the evaporation of the titrant.

The electrodes used in potentiometric titration is the same as that described in method 1.

VII C Oxygen Flask Combustion

In the oxygen flask method, organic substances containing halogen or sulfur are burned in a combustion flask filled with oxygen, the combustion products are absorbed with an absorbing liquid which is then analysed to determine the content of halides, sulfur etc.

Apparatus A 500, 1000 ml or 2000 ml hard glass conical flask with a tightly fitted ground glass stopper is used as the combustion flask. One end of a platinum wire 1 mm in diameter is fused into the stopper, the other end of the wire is twisted into a helix or attached to platinum gauze. The length of the wire is about 2/3 of that of the bottle (as Fig. 14 A).

Procedure Weigh accurately a specified quantity of the substance being examined (solid material should be finely powdered). Unless otherwise specified, the substance being examined is wrapped in a piece of ashless filter paper as illustrated in Fig. 14 B and C. If the substance being examined is a liquid, stick a piece of ashless filter paper (16 mm × 6 mm) onto the center of a piece of cellophane adhesive paper and another piece (6 mm × 35 mm) to the protruding part (as Fig. 14 D and as Fig. 14 E). Weigh accurately, fold the paper as illustrated in Fig. 14 F, leaving the upper end open. Add the liquid being examined dropwise to the filter paper, close the end immediately and weigh again accurately. The difference of two weighings indicate the weight of the substance being examined.

Secure the package containing the substance being examined, in the platinum gauze or helix, leaving the narrow strip out. Place the specified absorbing liquid in the flask, moisten the

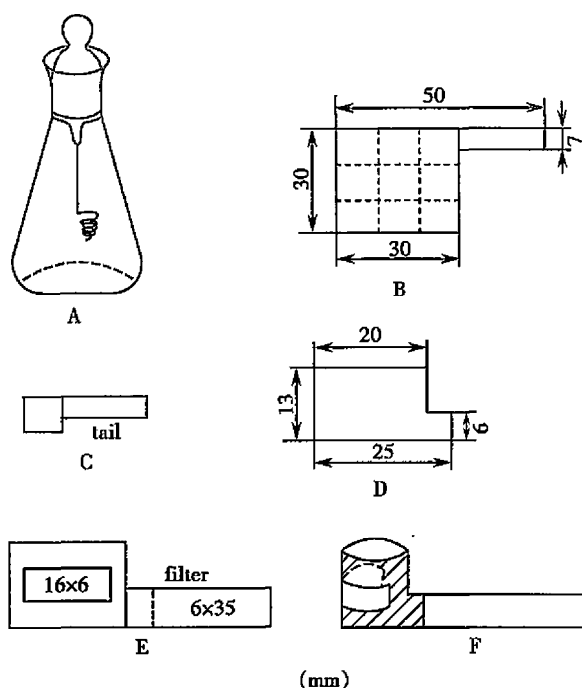


Fig. 14

neck of the flask with water, fill the flask with oxygen for 1 minute. The stream of oxygen should be introduced near the surface of the liquid, so as to expel the air from the flask completely and cover the flask with a watch glass. Light the free end of the narrow strip of filter paper and immediately insert the stopper. Hold the stopper firmly in place and add a little water around the rim of the flask. When the combustion is complete, shake the flask until the fume produced is completely absorbed. Allow to stand for 15 minutes, wash the stopper and the platinum wire with a little water and add the washings to the absorbing liquid. Carry out the assay as specified in the monograph and perform a blank determination in the same manner.

Annotations Protective measures should be taken against explosion.

VII D Determination of Nitrogen

Method 1 (Macro Method) Place an accurately weighed quantity of the substance being examined equivalent to about 25-30 mg of nitrogen in a 500 ml Kjeldahl flask. Solid or semi-solid substances may be wrapped in a sheet of nitrogen-free filter paper and then transferred to the Kjeldahl flask. Add successively 10 g of potassium sulfate or anhydrous sodium sulfate, 0.5 g of powdered cupric sulfate and then add slowly 20 ml of sulfuric acid along the inner wall of the Kjeldahl flask inclined at an angle of 45°. Heat the mixture gently, keep the temperature below boiling point until frothing subsides. Raise the temperature and boil the mixture briskly until a clear, green solution is obtained. Continue the heating for 30 minutes, unless otherwise specified. Cool, add cautiously 250 ml of water along the inner wall of the flask, mix well and allow to cool. Add 75 ml of 40% sodium hydroxide solution along the inner wall of the flask to form a layer beneath the acid solution. Add a few pieces of zinc granules, connect one end of a nitrogen bulb to the flask and the other end to a condenser. The 500

ml conical flask add 50 ml of 2% boric acid solution and 10 drops of a mixed methyl red-bromocresol green IS. Dip the end of the condenser into the boric acid solution, mix the contents of the Kjeldahl flask by gentle rotation and distill. When 250 ml of distillate is collected, draw the end of the condenser above the surface of the distillate. Continue the distillation for about 1 minute and rinse the tip of the condenser with water. Titrate the distillate with sulfuric acid (0.05 mol/L) VS until the colour changes from bluish green to greyish-violet. Perform a blank determination and make any necessary correction. Each ml of sulfuric acid (0.05 mol/L) VS is equivalent to 1.401 mg of N.

Method 2 (Semi-micro Method) The distillation plant (as Fig. 15). The apparatus consists of a 1000 ml round bottom flask A, a safety tube B, a distillator C with a nitrogen bulb, a funnel D, a condenser E and a 100 ml conical flask F. G and H are two clamps.

Add a few drops of methyl red IS and a quantity of water in flask A and acidify with dilute sulfuric acid, add a few pieces of zinc granules. Add about 50 ml of water through funnel D, close clamp G, turn on the condensation water and heat the water in flask A to boiling. Stop heating when water vapour condenses and drips out of the condenser. The water in distillator C backflushes to tube B on the closure of clamp H. Open clamp G and drain the water in tube B. Close the stopcock of tube B and clamp G, dip the end of the condenser into about 50 ml of water which backflushes to C and B in turn, again drain the water in tube B. Repeat this process 2-3 times so that the apparatus inside is washed clean.

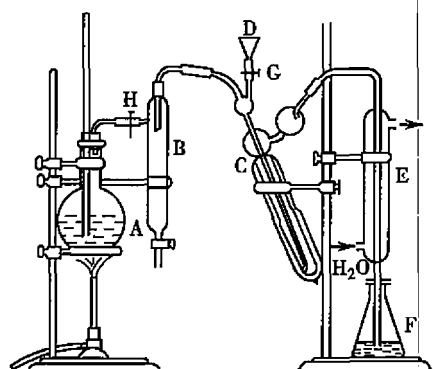


Fig. 15

Place an accurately weighed quantity of the substance being examined equivalent to 1.0-2.0 mg of nitrogen in a 30-50 ml Kjeldahl flask, add 0.3 g of potassium sulfate or anhydrous sodium sulfate and 5 drops of 30% cupric sulfate solution, then add dropwise 2.0 ml of sulfuric acid along the wall of the flask. Place a funnel on top of the Kjeldahl flask inclined at an angle of about 45°, heat the mixture gently, keep the temperature below boiling point until frothing subsides. Raise the temperature and boil the mixture briskly until a clear, green liquid is obtained. Continue the heating for 10 minutes more, unless otherwise specified, allow to cool and add 2 ml of water.

To the conical flask F add 10 ml of 2% boric acid solution and 5 drops of a mixed methyl red-bromocresol green IS. Dip the end of the condenser into the boric acid solution. Transfer the content of the Kjeldahl flask into the distillator C through funnel D, rinse the Kjeldahl flask and funnel several times with small amounts of water. Add 10 ml of 40% sodium hydroxide solution and again wash the funnel several times with small amounts of water. Close clamp G and heat the mixture in flask A and distill with stirring until the

colour of the boric acid solution changes from red to bluish green. Continue the distillation for 10 minutes more. lift the end of the condenser above the surface of the distillate, flash the condenser with steam for about 1 minute and stop the distillation and wash the tip of the condenser with water. Titrate the distillate with sulfuric acid (0.005 mol/L) VS until the colour changes from bluish green to greyish violet. Perform a blank determination and make any necessary correction (the volume of distillate collected in the blank determination should be approximately the same as that collected in the determination made with the substance being examined, i.e. about 70-75 ml). Each ml of sulfuric acid 0.005 mol/L VS is equivalent to 0.1401 mg of N. The amount of sulfuric acid should be increased when the substance being examined is more than 0.1 g so as to make the digestion complete, and the amount of sodium hydroxide solution should also be increased proportionally.

VII E Determination of Ethanol

The gas chromatographic method (Appendix V E) is used for the determination of the content expressed in percentage (ml/ml) of ethanol (C_2H_5OH) in various preparations at 20°C, unless otherwise specified.

Chromatographic system suitability Measure accurately 4 ml, 5 ml, 6 ml of dehydrated ethanol, add separately 5 ml of *n*-propanol (as internal standard) and dilute with water to 100 ml, mix well (diluted further, if necessary). Carry out the method for gas chromatography (Appendix V E), using porous polymer beads of ethylvinylbenzene cross-linked with divinylbenzene 0.25-0.18 mm in diameter as the support; maintain the column temperature at a range of 120-150°C. The performance of the instrument complies with following requirements.

- (1) The number of theoretical plates of the column is more than 700 calculated with reference to *n*-propanol.
- (2) The resolution of the peaks of ethanol and *n*-propanol is more than 2.
- (3) Carry out 5 replicate injections for each of the three solutions mentioned above, the relative standard variation of 15 correction factors is not more than 2.0%.

Procedure Measure accurately a quantity of the solution being examined (equivalent to 5 ml of ethanol) and 5 ml of *n*-propanol, dilute with water to 100 ml and mix well as the test preparation.

Measure accurately 5 ml each of dehydrated ethanol and *n*-propanol, maintained at 20°C dilute with water to 100 ml and mix well as the standard preparation.

The standard preparation and the test preparation may be further diluted if necessary.

Carry out successively 3 injections of the standard preparation, followed by 3 injections of the test preparation at the above conditions. Calculate the mean value of the correction factor obtained from the 3 injections of the standard preparation, and the mean value of ethanol content obtained from the 3 injections of the test preparation.

Annotations (1) Be sure that no peak due to impurity corresponding to the internal standard appears in the chromatogram obtained from the test preparation in the absence of internal standard.

(2) The relative deviation of individual values of the correction factor and the ethanol content should not be more than 1.5% of their mean value respectively, otherwise the

(3) System suitability must comply with the requirements described above, when any supports are used.

VII F Determination of Hydroxypropoxy

Apparatus The apparatus is shown in Fig. 16. D is the 25 ml boiling flask provided with a side arm, the outlet is fitted with an aluminium foil-jacketed fractionating column E of 95 mm long; C is an adapter bleeder tube with a capillary tip of 0.25-1.25 mm in inner diameter, inserting into the distilling flask; B is the steam generating tube (25 mm × 150 mm) with capillary tip of 0.25-1.25 mm in inner diameter, attached to the bleeder tube C; F is a condenser with a jacket of 100 mm long attached to E. G is a graduated, stoppered conical flask of 125 ml in capacity to collect the distillate. D and B are immersed in an electric heated oil bath A, adjusting to keep the temperature at 155°C.

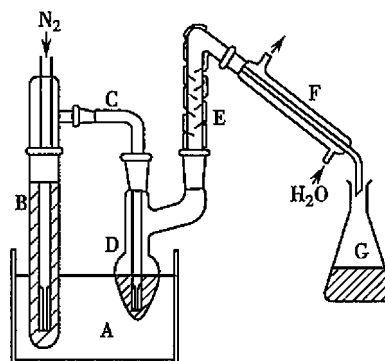


Fig. 16

Procedure Place a quantity of the substance being examined, specified under individual monograph and accurately weighed, in the distilling flask D, add 10 ml of 30% (g/g) solution of chromium trioxide. Fill the steam generator B with water almost to the bottom of the joint, assemble the apparatus. Immerse B and D in the oil bath (glycerin may be used) until the liquid surface in the bath reach the level of the chromium trioxide solution in D. Start the cooling water in condenser, pass nitrogen gas through the flask at a rate of 1 bubble per second if necessary. Raise the temperature of the oil bath to 155°C within 30 minutes and maintain at the temperature throughout the determination to collect about 50 ml of the distillate. Detach the condenser from the fractionating column and rinse with water. Combine the washings with the distillate, add 2 drops of phenolphthalein IS, titrate with sodium hydroxide (0.02 mol/L) VS to a pH of 7.0 ± 0.1 (determined by the pH meter). Record the volume consumed, V_1 (ml), add 0.5 g of sodium bicarbonate and 10 ml of dilute sulfuric acid, allow the solution to stand until the evolution of carbon dioxide ceases. Add 1.0 g of potassium iodide, stopper the flask, shake thoroughly and allow it to stand in the dark for 5 minutes. Titrate with sodium thiosulfate (0.02 mol/L) VS to the end point, using 1 ml of starch IS, and record the consumed volume of sodium thiosulfate solution, V_2 (ml). Perform a blank test and record the consumed volumes of sodium hydroxide (0.02 mol/L) VS and sodium thiosulfate (0.02 mol/L) VS as V_3 and V_4 respectively. Calculate from the following expression:

$$\text{Percentage of } OCH_2CHOHCH = \frac{(V_1 - V_3) \times 100}{V_2 - V_4} \times 100\%$$

Where K is the blank correction coefficient M_1V_a/M_2V_b ;
 W is weight of the substance being examined, g;
 M_1 is the concentration of sodium hydroxide volumetric solution;
 M_2 is the concentration of sodium thiosulfate volumetric solution.

0.0751 is the milli-molar weight of hydroxy propoxy group.

VII G Determination of Methoxyl

Apparatus As Fig. 17. The apparatus consists of a 50 ml round bottom flask (A) with a capillary side arm of 1 mm in diameter to provide an inlet for a stream of carbon dioxide or nitrogen. The flask is fitted with an upright air condenser (E) about 25 cm long and about 9 mm in internal diameter, bent at the top into an outlet which is contracted into a glass capillary of 2 mm in diameter, dipping into a small scrubber (B) containing about 2 ml of water. The outlet of the scrubber is a tube of about 7 mm in diameter with a removable tube of 4 mm in diameter as the termination, dipping below the surface of the liquid in the first (C) of two receivers (C and D) connected in series.

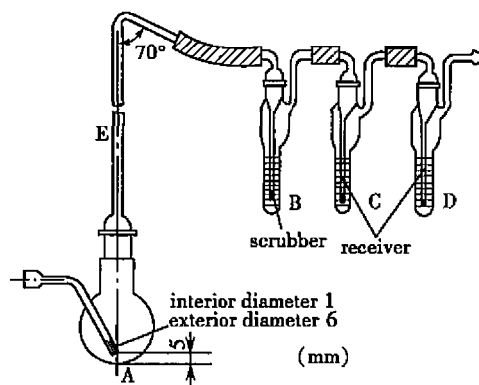


Fig. 17

Procedure Place a quantity of the dry substance being examined equivalent to approximate 10 mg of methoxyl group, accurately weighed, in the boiling flask. Add 2.5 ml of melted phenol and 5 ml of hydroiodic acid and connect the apparatus in their right position. Add to the two receivers 6 ml and 4 ml respectively of a solution of 10% potassium acetate in glacial acetic acid and 0.2 ml of bromine. Pass a slow, uniform stream of carbon dioxide or nitrogen through the side arm into the flask (1-2 bubbles per second are suitable), heat the liquid gently at such a rate that the boiling liquid vapour rises halfway up the condenser (The temperature of oil bath rises to 135-140°C in about 30 minutes). Usually, the reaction is completed in 45 minutes at the temperature (The time of heating is determined by the characteristic and/or structure of substance being examined. If it contains more than two methoxyl groups, the time of heating should be 1-3 hours). Disconnect the apparatus and transfer the contents of two receivers into a 250 ml stoppered conical flask containing 5 ml of 25% sodium acetate solution. Wash the inside of two receivers with water up to about 125 ml in total volume. Add 0.3 ml of formic acid, rotate the flask until the colour of bromine is discharged. Add further 0.6 ml of formic acid, stopper the flask, shake thoroughly to remove the excess bromine and allow to stand for 1-2

hours. Titrate with sodium thiosulfate (0.1 mol/L) VS. Perform a blank test to make any necessary correction. Each ml of sodium thiosulfate (0.1 mol/L) VS is equivalent to 0.5172 mg of methoxyl group.

VII H Tests of Fats and Fatty Oils

If a liquid sample being examined shows turbid owing to the separation of stearin, warm the container on a water bath at 50°C until the sample melts to form a clear liquid. If it does not become clear on warming, centrifuge or filter through a dry filter with hot-water jacket. Mix while hot and not solidified, weigh as many portions as needed for the various determinations, using preferably a weighing bottle having a pipette dropper, or a weighing beaker having a glass spoon. Solid sample is previously melted at a temperature not more than 10°C above its melting range, centrifuge or filter and then weigh.

Determination of relative density Carry out the method for Determination of relative density (Appendix VI A).

Determination of refractive index Carry out the method for Determination of refractive index (Appendix VI F).

Determination of melting range Carry out the method for Determination of melting range (Appendix VI C, method 2).

Determination of congealing point of fatty acids

(1) **Preparation of the fatty acids** Heat 75 g of 20% (g/g) solution of potassium hydroxide in glycerin and 50 g of the substance being examined, in a 800 ml beaker, at 150°C with frequent stirring for about 15 minutes until saponification is complete. Cool to about 100°C, add 500 ml of freshly boiled water, stir and mix well, add slowly 50 ml of sulfuric acid solution (1→4), and heat the solution until the fatty acids separate clearly as a transparent layer. Transfer the fatty acids to another beaker while hot, wash the acids with freshly boiled water repeatedly until the washing shows yellow colour to methyl orange IS. Collect the clear fatty acids in a dry small beaker while hot, add 5 ml of dehydrated ethanol, mix well and heat gently until there is no small bubbles evolved.

(2) **Determination of congealing point** Carry out the method for Determination of congealing point (Appendix VI D), using the dry fatty acid obtained above.

Determination of acid value Acid value is the number of mg of potassium hydroxide required to neutralise the free acid in 1 g of fat, fatty oil or other related substances. In its determination, sodium hydroxide (0.1 mol/L) VS may also be used.

Presumed acid value	Quantity of substance being examined/g
0.5	10
1	5
10	4
50	2
100	1
200	0.5
300	0.4

Unless otherwise specified, weigh accurately a quantity of the substance being examined as indicated in the above table, in a 250 ml conical flask, add 50 ml of a mixture of ethanol-ether (1 : 1) which has been neutralised to 1.0 ml of phenolphthalein IS with sodium hydroxide (0.1 mol/L) VS before use, shake to effect the solution (heat under reflux gently, if necessary, until the substance is completely dissolved). Titrate the resulting solution with sodium hydroxide (0.1 mol/L) VS until a pink colour which persists for 30 seconds is obtained. Take the number of ml of sodium hydroxide (0.1 mol/L) VS required as *A* and weight of substance being examined (g) as *W*, calculate the acid value from the expression:

$$\text{Acid value} = \frac{A \times 5.61}{W}$$

Use semi-micro burette of 10 ml in capacity for the titration when the acid value is less than 10.

Determination of saponification value The saponification value is the number of mg of potassium hydroxide required to neutralise and saponify the free acids and esters contained in 1 g of fat, fatty oil or other related substances. Weigh accurately a quantity of the substance, equivalent to about 250/maximum saponification value of the substance, in a 250 ml conical flask, add 25 ml, accurately measured, of ethanolic potassium hydroxide (0.5 mol/L) VS, heat under reflux for 30 minutes, cool. Rinse the inner wall of condenser and the lower part of stopper with 10 ml of ethanol, add 1 ml of phenolphthalein IS, titrate with hydrochloric acid (0.5 mol/L) VS until the pink colour just disappears. Heat the solution to boiling, continue the titration if pink colour reappears. Note the volume (ml) of hydrochloric acid (0.5 mol/L) VS required in titration for the substance being examined as (*A*). Perform a blank determination and note the volume (ml) of hydrochloric acid (0.5 mol/L) VS required in blank determination as (*B*). Calculate the saponification value from the expression:

$$\text{Saponification value} = \frac{(B-A) \times 28.05}{W}$$

Where *W* is the weight of the substance being examined, g.

Determination of hydroxyl value The hydroxyl value is the number of mg of potassium hydroxide equivalent to the hydroxyl group contained in 1 g of the substance being examined after acetylation.

Presumed hydroxyl value	Quantity of substance being examined/g
10-100	2.0
100-150	1.5
150-200	1.0
200-250	0.75
250-300	0.60

Unless otherwise specified, weigh accurately a quantity of the substance being examined as indicated in the table, in a 250 ml dry glass stoppered conical flask, add 5 ml, accurately measured, of acetylation agent (prepared by dissolving 14.4 g of *p*-toluene-sulfonic acid in 360 ml of ethyl acetate in a 500 ml conical flask, then add slowly 120 ml of acetic anhydride, mix well and allow to stand for 3 days). Moisten the glass stopper with a small quantity of pyridine, stopper the flask tightly and shake gently to effect the solution. Place the flask in a water bath at $50^{\circ}\text{C} \pm 1^{\circ}\text{C}$ for 25 minutes (shake gently at every 10 minutes interval). Cool, add 20 ml of a mixture of pyridine-water (3 : 5). After 5 minutes, add 8-10 drops of cresol red-thymol blue mixed

sodium hydroxide) (1 mol/L) VS until the colour of solution changes to grey-blue or blue. Note the volume (ml) of potassium hydroxide (or sodium hydroxide) (1 mol/L) VS required as *A*, perform a blank determination and note the volume (ml) of potassium hydroxide (or sodium hydroxide) (1 mol/L) VS required as *B*. Calculate the hydroxyl value from the expression:

$$\text{Hydroxyl value} = \frac{(B-A) \times 56.1}{W} + D$$

Where *W* is the weight of the substance being examined, g;
D is the acid value of the substance being examined.

Determination of iodine value Iodine value is the weight of iodine in g, required to halogenate 100 g of fat, fatty oil or other related substances. Weigh accurately a quantity of the substance (g), equivalent to 25/maximum iodine value of the substance being examined, in a 250 ml dry iodine flask. Dissolve it in 10 ml of chloroform, add 25 ml of iodine bromide solution, accurately measured, stopper the flask, mix well and allow to stand in a dark place for 30 minutes. Then add 10 ml of freshly prepared potassium iodide TS and 100 ml of water, mix well. Titrate with sodium thiosulfate (0.1 mol/L) VS with constant shaking until the colour changes to pale yellow, add 1 ml of starch IS, continue to titrate until the blue colour just disappears. Note the volume (ml) of sodium thiosulfate (0.1 mol/L) VS as *A*. Perform a blank determination, and note the volume (ml) of sodium thiosulfate (0.1 mol/L) VS as *B*. Calculate the iodine value from the expression:

$$\text{Iodine value} = \frac{(B-A) \times 1.269}{W}$$

Where *W* is the weight of the substance being examined, g.

Determination of peroxide value The peroxide value is the number that expresses in milliequivalents of active oxygen the quantity of peroxide contained in 1000 g of the substance. Unless otherwise specified, place accurately weighed 5 g of the substance being examined in a 250 ml iodine flask fitted with a ground-glass stopper. Add 30 ml of a mixture of 2 volumes of chloroform and 3 volumes of glacial acetic acid. Shake to dissolve the substance and add 0.5 ml of saturated potassium iodine TS. Shake for exactly 1 min, then add 30 ml of water. Titrate with sodium thiosulfate (0.01 mol/L) VS, adding the titrant slowly with continuous vigorous shaking, until the yellow colour is almost discharged. Add 5 ml of starch IS and continue the titration, shaking vigorously, until the blue colour is discharged. Note the volume (ml) of sodium thiosulfate (0.01 mol/L) VS as *A*. Carry out a blank test under the same conditions, and note the volume (ml) of sodium thiosulfate (0.01 mol/L) VS as *B* and weight of substance being examined (g) as *W*. The volume of sodium thiosulfate (0.01 mol/L) VS used in the blank titration must not exceed 0.1 ml. Calculate the peroxide value from the expression:

$$\text{peroxide value} = \frac{10(A-B)}{W}$$

Heating test Heat about 50 ml of the substance being examined, in a beaker, on a sand bath to about 280°C at a rate of 10°C per minute. Note the change in colour or other character of the oil.

Foreign matter Dissolve about 20 g, accurately weighed, in 20 ml of petroleum ether (boiling range $60-90^{\circ}\text{C}$), in a conical flask. Filter through a dry and weighed sinter-glass filter (if necessary, add more volume of petroleum ether to facilitate filtration). Wash the residue and filter with petroleum ether, dry to constant weight at 105°C and weigh accurately. The weight increased represents the content of

Water and volatile matter Weigh accurately about 5 g of the substance being examined in a bottle dried to constant weight previously, weigh accurately, dry at 105°C for 40 minutes, allow to cool in desiccator and weigh accurately. Repeat the drying at 105°C for further 20 minutes, cool and weigh again until the difference of two successive weighings is not greater than 0.001 g. The loss on drying is the content of water and volatile matter in the substance being examined.

Annotations *Preparation of iodine bromide solution* Dissolve completely 13.0 g of powdered iodine in 1000 ml of glacial acetic acid by warming in a dry glass-stoppered flask. Add promptly 2.5 ml (or 7.8 g) of bromine, stopper the flask and mix well. In order to check the quantity of bromine added, two titrations may be performed.

(1) Before the addition of bromine, pipette 20.0 ml of the solution, titrate with sodium thiosulfate (0.1 mol/L) VS, note the volume (ml) required as A.

(2) After the addition of bromine, pipette 20.0 ml of the solution, add 10 ml of freshly prepared potassium iodide TS, titrate with sodium thiosulfate (0.1 mol/L) VS, note the volume (ml) required as B. B is slightly less than 2 A. Iodine bromide solution should be kept in a well-closed container and protected from light.

VII J Assay of Vitamin A

The potency of vitamin A, expressed in units, is determined by measuring the absorbance of a test preparation at the specified wavelength, 1 Unit is equivalent to 0.344 μg of alltrans retinol acetate or 0.300 μg of alltrans retinol.

Since other materials present in the preparation, such as the oil used for dilution and some of the impurities in vitamin A, may be contributing to the absorbance of vitamin A, the measured absorbance must be corrected. Under the conditions described below, the irrelevant absorption of nonvitamin A substances can be precluded by applying a special equation for the calculation of results.

The correction equation used involves 3 points measurements, one is absorption at the maximum wavelength, the other 2 points are absorption on the two sides of the absorption peak. Since the accuracy of results depends on the precision of measurement, it is essential that the wavelength scale of the spectrophotometer should be checked before the assay.

The assay should be carried out as fast as possible and care must be taken to avoid exposure to actinic light.

Synthetic vitamin A and vitamin A in cod-liver oil are usually present in the form of ester. If the preparation being examined contains only a small amount of impurities interfering with the assay procedure and complies with the requirements mentioned in method 1, it can be dissolved directly and used for the assay, otherwise it should be saponified and extracted to eliminate any possible interference in the assay.

Method 1 Dissolve an accurately weighed quantity of the substance being examined in cyclohexane to produce a solution of 9-15 units per ml. Find out the wavelength of maximum absorption, measure the absorbances at the following listed wavelengths (Appendix IV A). Calculate the relative absorbances from the ratio of absorbances at each wavelength to the absorbance at 328 nm, and calculate the value of $E_{1\%}^{1\text{cm}}$ at 328 nm.

Wavelength/nm	Relative absorbance
300	0.555
316	0.907
328	1.000
340	0.811
360	0.299

If the wavelength of maximum absorption lies between 326 and 329 nm, and the observed relative absorbances are within ± 0.02 of those listed in the table, the potency of vitamin A in units per g can be calculated from the expression:

$$E_{1\%}^{1\text{cm}}(328\text{ nm}) \times 1900$$

If the wavelength of maximum absorption lies between 326 and 329 nm, but the relative absorbances exceed ± 0.02 of those listed in the table, the absorbance at 328 nm can be corrected as follows:

$$A_{328}(\text{corr.}) = 3.52 (2 A_{328} - A_{316} - A_{340})$$

If the corrected absorbance at 328 nm is within 97%-103% of the uncorrected absorbance, the potency of vitamin A should still be calculated from the uncorrected absorbance. If the corrected absorbance is within 85%-97% of the uncorrected absorbance, the potency of vitamin A should be calculated from the corrected absorbance.

If the corrected absorbance exceeds 85%-97% of the uncorrected absorbance, or the absorption wavelength is not within 326-329 nm, the preparation being examined should be assayed by method 2.

Method 2 Place an accurately weighed quantity (not more than 2 g) of the substance being examined equivalent to not less than 500 Units of total vitamin A in a saponification flask. Add 30 ml of ethanol and 3 ml of 50% (g/g) potassium hydroxide solution. Boil on a water bath for 30 minutes under a reflux condenser. Allow to cool and rinse the inner wall of the condenser with 10 ml of water. Transfer the saponified liquid to a separator (use glycerin starch paste as the lubricant for the stopcock of the separator). Wash the flask with 60-100 ml of water subdivide in several portions, add the washings to the separator and extract with 4 quantities (60, 40, 40 ml and 40 ml) of peroxide-free ether successively, shaking for 5 minutes in each extraction. Combine the ether extracts and wash with several 100 ml portions of water by swirling gently to avoid emulsification until the water layer does not become red on the addition of phenolphthalein IS. Filter the ether layer through a funnel containing anhydrous sodium sulfate and absorbent cotton wool. Wash the funnel with ether and combine the washings and the filtrate in a 250 ml volumetric flask, dilute with ether to volume and mix well. Transfer an accurately measured quantity of the ethereal solution into an evaporating dish, warm the dish on a water bath at low temperature until the volume of ethereal solution is reduced to 5 ml. Place the dish in a vacuum desiccator and remove the remaining ether by suction. Dissolve the residue immediately in isopropanol, measured accurately, to produce a solution of 9-15 Units per ml. Find out the wavelength of maximum absorption and measure the absorbances at 300 nm, 310 nm, 325 nm and 334 nm (Appendix IV A). If the wavelength of maximum absorption lies between 323 nm and 327 nm and the ratio of A_{300}/A_{325} does not exceed 0.73, the absorbance at 325 nm can be corrected as follows:

$$A_{325}(\text{corr.}) = 6.815 A_{325} - 2.555 A_{310} - 4.260 A_{334}$$

The potency of vitamin A in units per g can be calculated

$$E_{1\text{cm}}^{1\%}(325\text{ nm, corr.}) \times 1830$$

except that, when the corrected absorbance is within 97%-103% of the uncorrected absorbance, the potency of vitamin A should be calculated from the uncorrected absorbance. If the wavelength of maximum absorption does not lie between 323 nm and 327 nm or the ratio of A_{300}/A_{325} exceeds 0.73, it is necessary to measure accurately another quantity (equivalent to 300-400 Units of vitamin A) from the 250 ml of ethereal extract obtained after saponification. Evaporate the ether under reduced pressure to about 5 ml and continue the evaporation to dryness under a current of nitrogen. Dissolve the residue immediately in exact 3 ml of methanol, measure accurately 500 μl and inject into a column system for purification described under method II in Assay of Vitamin D (Appendix VII K). Accurately collect the eluate containing vitamin A and evaporate to dryness under a current of nitrogen. Continue the procedure described above beginning at the words "Dissolve the residue immediately in isopropanol...", and calculate the content of vitamin A.

Annotations (1) *Glycerin starch paste* To 22 g of glycerin add 9 g of soluble starch and heat at 140°C for 30 minutes with stirring, allow to cool.

(2) *Peroxide-free ether* Carry out the test for peroxide as described under the monograph of Anaesthetic Ether. If the reagent fails to comply with the requirements, shake it with 5% sodium thiosulfate solution, allow to stand, separate the ether layer. Wash the ether layer with water and distil, discard the initial and final aliquots of the distillate, each about 5% of the total volume. Examine the remaining distillate for peroxide, it should comply with the requirement.

VII K Assay of Vitamin D

High performance liquid chromatographic method (Appendix V D) is used for determination of vitamin D and *pre*-vitamin D content (includes vitamin D₂ and D₃) and calculated with reference to the total amount of vitamin D in units of activity, each unit is equivalent to 0.025 μg of vitamin D. The method is applicable to the assay of vitamin D in drug substances, preparations, vitamin A and D preparations, and cod liver oil. Throughout this assay, protect the solutions containing, or derived from the substance being examined and the reference standard from the atmosphere and light, preferably operate under inert gas and in darksome room.

Method 1 is used for assay of the substance being examined that no retinol and impurities which interfere the determination; otherwise it should be treated according to Method 2 before assay; if the impurities still interfere the determination even after the treatment by Method 2, proceed the assay by Method 3.

Method 1

Stock solution of reference substance Dissolve 25 mg of vitamin D₂ or D₃ CRS, accurately weighed, according to the kind of vitamin D of the substance being examined, in 80 ml *iso*-octane by ultrasonication within one minute without heating, make up volume to 100 ml with *iso*-octane in an amber coloured volumetric flask, mix well, fill with nitrogen, and keep below 0°C.

For the assay of vitamin D₂, a vitamin D₃ CRS solution should be also prepared for the system suitability test.

Internal standard solution Prepare a solution of 1 mg of

Chromatographic system and system suitability test Use a column packed with silica gel and *n*-hexane-*n*-amyl alcohol (997 : 3) as the mobile phase, the wavelength of detector is 254 nm. Measure about 5 ml of vitamin D₃ CRS stock solution in a glass stoppered flask, pass nitrogen in it to form an inert gas blanket, stopper tightly, put it in a water bath of 90°C for 1 hour, then cool quickly to room temperature, add 5 ml of *n*-hexane and mix well. Fill the solution in a 1 cm quartz cell, incline the cell at 45°. Excite under two 8 W ultraviolet lamps of 254 nm and 365 nm wavelength each at a distance of 5-6 cm for 5 minutes to convert some vitamin D₃ to *pre*-vitamin D₃, *trans*-vitamin D₃, and tachysterol D₃. Inject this solution into chromatographic column for five times, the standard deviation of peak areas of vitamin D₃ is not more than 2.0%; the resolution between *pre*-vitamin D₃ (the relative retention time with respect to vitamin D₃ is about 0.5) and *trans*-vitamin D₃ (the relative retention time with respect to vitamin D₃ is about 0.6), and that between vitamin D₃ and tachysterol D₃ (the relative retention time with respect to vitamin D₃ is about 1.1) should be larger than 1.0.

Determination of correction factor Accurately measure 5 ml of each of the CRS stock solution and internal standard solution, dilute to 50.00 ml with *n*-hexane, mix well. Inject a suitable volume into the chromatograph column and calculate the correction factor of vitamin D (f_1). Accurately measure another 5 ml of the CRS stock solution into a 50 ml volumetric flask, add a grain of 2,6-di-*tert*-butyl-*p*-cresol crystal, pass nitrogen and stopper the flask. Put it in a water bath of 90°C for 1.5 hours, cool quickly to room temperature; add accurately 5 ml of internal standard solution, dilute to volume with *n*-hexane and mix well. Inject a suitable volume into the chromatographic column, calculate the correction factor for conversion of *pre*-vitamin D to vitamin D (f_2):

$$f_2 = (A_s \times m_i - f_1 \times m_s \times A_{i1}) / (A_{i2} \times m_s)$$

Where A_s is the peak area of internal standard, m_i is the content of CRS, f_1 is the correction factor of vitamin D, m_s is the content of internal standard, A_{i1} is the peak area of vitamin D, and A_{i2} is the peak area of *pre*-vitamin D.

Assay Inject a quantity of the solution of substance being examined prepared as specified in the monograph, calculate the total content of vitamin D (m_t) from the content of vitamin D and *pre*-vitamin D:

$$m_t = (f_1 \times A_{i1} + f_2 \times A_{i2}) \times m_s / A_s$$

Where A_{i1} is the peak area of vitamin D, A_{i2} is the peak area of *pre*-vitamin D, m_s is the quantity of internal standard added, and A_s is the peak area of internal standard.

Method 2

Place an accurately weighed quantity (not more than 2 g) of the substance being examined equivalent to not less than 600 Units of total vitamin D in a saponification flask. Add 30 ml of ethanol, 0.2 g of ascorbic acid, and 3 ml of 50% (g/g) potassium hydroxide solution (if the substance being examined is 3 g, add 4 ml). Boil on a water bath for 30 minutes under reflux. Allow to cool and wash the inner wall of the condenser with 10 ml of water. Transfer the saponified liquid to a separator. Wash the flask with 60-100 ml of water in portions, add the washings to the separator and extract with 3 quantities (60, 40, 40 ml) of peroxide-free ether. Combine the ether extracts and wash with several portions of 100 ml of water cautiously to avoid emulsification until the water layer does not become red on the addition of phenolphthalein IS, allow to stand until the layers are separated completely. Discard the aqueous layer, to the ethereal layer add several pieces of dry filter paper strip and

the ether solution in a flask, wash the separator and filter paper with a few ml of ether and combine it into the flask, evaporate the ether at low temperature to about 5 ml. Remove the residual ether with a stream of nitrogen. Immediately dissolve the residue in exact 3 ml of methanol by ultrasonication. Transfer the solution into a centrifuge tube and centrifugalize, the supernatant liquid is used as test solution A.

Fractionating collection of vitamin D by high performance liquid chromatography Accurately measure 500 μ l of test solution A into the column packed with octadecylsilane bonded silica gel, using a mixture of methanol-acetonitrile-water (50 : 50 : 2) as the mobile phase and the wavelength of detector is 254 nm. Observe the chromatogram that the peak of vitamin D is overlapped with the peak of *pre*-vitamin D, and they are separated from the peak of vitamin A and other peaks due to impurities. Accurately collect the total fractions of mobile phase containing the total amount of vitamin D and *pre*-vitamin D into a flask, remove the mobile phase quickly with a stream of nitrogen. Accurately add a suitable volume of internal standard solution (not less than 2 ml, which contains 50-140 Units of vitamin D per ml, the proportion of internal standard and vitamin D in weight by weight is about 4:1) immediately, stopper tightly, dissolve it by ultrasonication, used as test solution B.

Assay Perform the method of Assay described under Method 1, the injection volume is 100-200 μ l.

Method 3

Preparation of the test solution Prepare test solution A according to the method described under the individual monography. Perform the fractionating collection of vitamin D as described under Method 2, after the mobile phase is removed with nitrogen stream, add immediately 2 ml of *iso*-octane to dissolve the residue, pass nitrogen to drive off the air in the flask, stopper tightly. Put in a water bath of 90°C for 1.5 hours, evaporate immediately the solvent with nitrogen stream in 2 minutes and add accurately 2 ml of *n*-hexane to dissolve the residue. This is used as the test solution C.

Preparation of reference solution Accurately measure a quantity of the CRS stock solution above method 1, dilute to produce a solution of 50 Units/ml of vitamin D in *iso*-octane, accurately measure 2 ml into a flask and proceed the treatment as described under Preparation of test solution beginning at the words "pass nitrogen to drive...".

Assay The parameters are described under Method 1, inject 200 μ l, accurately measured, of the CRS solution and the test preparation alternately, calculate vitamin D content by external standard method from their peak areas.

Appendix VIII

VIII A Limit Test for Chlorides

Test preparation Unless otherwise specified, weigh a quantity of the substance being examined as prescribed under individual monographs, dissolve it in about 25 ml of water (if the solution is alkaline, neutralize with nitric acid dropwise). Add 10 ml of dilute nitric acid and filter if necessary, transfer the solution to a 50 ml Nessler cylinder, add water to produce 40 ml and mix well.

Reference preparation Transfer a volume of sodium chloride standard solution as prescribed under individual monographs to a 50 ml Nessler cylinder, add 10 ml of dilute nitric acid and sufficient water to produce 40 ml, mix well.

Procedure To each of the Nessler cylinders described above add 1.0 ml of silver nitrate TS, dilute with water to 50 ml and mix well. Allow to stand in the dark for 5 minutes, compare the opalescence produced by viewing down the vertical axis of the cylinders against a black background. If the test preparation is coloured, unless otherwise specified, place two aliquots of the test preparation in Nessler cylinders separately, to one cylinder add 1.0 ml of silver nitrate TS, mix and allow to stand for 10 minutes, filter the content of the cylinder repeatedly until the filtrate is perfectly clear, then add the prescribed volume of standard sodium chloride solution to the filtrate, use it as the reference preparation. To the other cylinder add 1.0 ml of silver nitrate TS, use it as the test preparation. Dilute the test preparation and the reference preparation with water to 50 ml, mix well and allow to stand in the dark for 5 minutes, compare the opalescence as described above.

Sodium chloride standard solution Dissolve 0.165 g of sodium chloride in water in a 1000 ml volumetric flask, and dilute to the volume, mix well (stock solution). Transfer 10 ml of the stock solution, accurately measured, into a 100 ml volumetric flask immediately before use, dilute with water to the volume and mix well (each ml is equivalent to 10 µg of Cl).

Annotations The filter paper used in this test, if necessary, should be previously washed with water containing nitric acid until the washing is free from chlorides.

VIII B Limit Test for Sulfates

Test preparation Unless otherwise specified, weigh a quantity of the substance being examined as prescribed under individual monographs, dissolve it in about 40 ml of water, neutralize the solution with hydrochloric acid and filter if

add 2 ml of dilute hydrochloric acid and mix well.

Reference preparation Transfer a volume of potassium sulfate standard solution as prescribed under individual monographs to a 50 ml Nessler cylinder, dilute with water to about 40 ml, add 2 ml of dilute hydrochloric acid and mix well.

Procedure To each of the Nessler cylinders described above add 5 ml of 25% barium chloride solution, dilute with water to 50 ml and mix well, allow to stand for 10 minutes and compare the opalescence produced by viewing down the vertical axis of the cylinder against a black background. If the test preparation is coloured, unless otherwise specified, place two aliquots of the test preparation in Nessler cylinders separately, to one cylinder add 5 ml of 25% barium chloride solution, mix well and allow to stand for 10 minutes, filter the content of the cylinder repeatedly until the filtrate is perfectly clear, then add the prescribed volume of potassium sulfate standard solution to the filtrate and use it as the reference preparation. To the other cylinder add 5 ml of 25% barium chloride solution, use it as the test preparation. Dilute the test preparation and the reference preparation with water to 50 ml, mix well and allow to stand for 10 minutes, compare the opalescence as described above.

Potassium sulfate standard solution Dissolve 0.181 g of potassium sulfate in water in a 1000 ml volumetric flask, and dilute to the volume, mix well (each ml is equivalent to 100 µg of SO₄).

VIII C Limit Test for Sulfides

Apparatus Use the same apparatus as shown in Fig. 20 under Limit Test for Arsenic (Appendix VIII J, method 1), except that there is no lead acetate cotton wool in tube C and a lead acetate test paper is placed between D and E instead of mercuric bromide test paper.

Sodium sulfide standard solution Dissolve 1.0 g of sodium sulfide in 200 ml of water, transfer 50 ml of the solution, accurately measured, into an iodine flask, add 25.0 ml of iodine (0.05 mol/L) VS and 2 ml of hydrochloric acid, mix well. Titrate with sodium thiosulfate (0.1 mol/L) VS until the end point is nearly reached, add 2 ml of starch IS and continue the titration until the blue colour disappears. Perform a blank determination and make any necessary correction. Each ml of iodine (0.05 mol/L) VS is equivalent to 1.603 mg of S. Dilute an accurately measured volume of the sodium sulfide solution with water to produce a solution containing 5 µg of S per ml. This standard solution should be freshly prepared.

Standard sulfide stain Transfer 1 ml of sodium sulfide standard solution, accurately measured, into flask A, add 10 ml of water and 10 ml of dilute hydrochloric acid. Fit

paper on its top. Immerse the flask in a water bath at 80-90°C for 10 minutes, a stain is produced on the test paper.

Procedure Unless otherwise specified, place a quantity of the substance being examined as prescribed under individual monographs in flask A, add 10 ml of water (or ethanol for oily substances) and 10 ml of dilute hydrochloric acid. Fit tube C into flask A immediately proceed as directed above, any stain produced is not more intense than the standard stain.

VIII D Limit Test for Selenium

Selenium standard solution Dissolve an accurately weighed quantity of sodium selenite of known purity in nitric acid solution (1→30) to produce a solution of 1.00 mg Se per ml. Transfer 5 ml of this solution, accurately measured, into a 250 ml volumetric flask, dilute with water to the volume and mix well; transfer 5 ml of this solution, accurately measured, into a 100 ml volumetric flask, add water to the volume and mix well (each ml is equivalent to 1 µg of Se).

Reference preparation Place 5 ml of the selenium standard solution, accurately measured, in a 100 ml beaker, add 25 ml of nitric acid solution (1→30) and 10 ml of water, mix well.

Test preparation Unless otherwise specified, weigh a quantity of the substance being examined as prescribed under individual monographs. Carry out the method for oxygen flask combustion (Appendix VII C) in a 1000 ml combustion flask, using 25 ml of nitric acid solution (1→30) as the absorbing liquid. After the combustion of organic matter is completed, transfer the absorbing liquid and washings to a 100 ml beaker.

Procedure Treat the two preparations concomitantly as follows: adjust pH to 2.0 ± 0.2 with ammonia TS, transfer to a separator, wash the beaker with successive small quantities of water and add the washings to the same separator, dilute with water to 60 ml. Add 1 ml of hydroxylamine hydrochloride solution (1→2) and 5.0 ml of diaminonaphthalene TS, mix well and allow to stand at room temperature for 100 minutes. Add 5.0 ml of cyclohexane, shake vigorously for 2 minutes, allow to separate and discard the aqueous layer. Remove any trace of water in the cyclohexane layer with anhydrous sodium sulfate and measure its absorbance at 378 nm (Appendix IV A). The absorbance of the test preparation is not greater than that of the reference preparation.

Annotations *Determination of Se in sodium selenite* Place about 0.1 g of sodium selenite, accurately weighed, in an iodine flask, dissolve it in 50 ml of water, add 3 g of potassium iodide and 10 ml of hydrochloric acid solution (1→2), insert the stopper and allow to stand for 5 minutes. Add 50 ml of water and titrate with sodium thiosulfate (0.1 mol/L) VS until the colour changes from reddish brown to orange red. Add 2 ml of starch IS and continue the titration until the colour changes from blue to violet-red. Each ml of sodium thiosulfate (0.1 mol/L) VS is equivalent to 4.324 mg of Na_2SeO_3 or 1.974 mg of Se.

VIII E Limit Test for Fluorides

fluoride previously dried for 1 hour at 105°C, accurately weighed, in water in 100 ml volumetric flask and dilute to volume, mix well. Dilute 20 ml, accurately measured, of the solution with water in another 100 ml volumetric flask to volume and mix well. Each ml is equivalent to 20 µg of F.

Test solution Carry out the method for oxygen flask combustion (Appendix VII C), using a quantity of the substance being examined equivalent to about 2.0 mg of fluorine, accurately weighed, and 20 ml of water as the absorbing liquid. Shake for further 2-3 minutes after combustion and absorption are complete, rinse the stopper, platinum wire and gauze with water. Combine the washing liquids with the absorbing liquid in an 100 ml volumetric flask, dilute with water to volume and mix well.

Procedure To each 2 ml of the fluoride standard solution and the test solution, accurately measured, in 50 ml volumetric flasks separately add 10 ml of alizarin fluorine blue TS, mix well, add 3.0 ml of a solution of 12% sodium acetate in dilute acetic acid and 10 ml of cerous nitrate TS respectively, mix well and allow the solutions to stand in the dark for 1 hour. Carry out the method of colourimetry (Appendix IV A), using absorption cells, measure the absorbances at 610 nm and calculate the content of F.

VIII F Limit Test for Cyanides

Method 1

Apparatus Use the same apparatus as shown in Fig. 20 under Limit Test for Arsenic (Appendix VIII J, method 1), except that there is no lead acetate cotton wool in tube C and an alkaline ferrous sulfate paper (freshly prepared by moistening a piece of filter paper with 1 drop each of ferrous sulfate TS and sodium hydroxide TS) is placed between D and E instead of mercuric bromide test paper.

Procedure Unless otherwise specified, place a quantity of the substance being examined as prescribed under individual monographs in flask A, add 10 ml of water and 3 ml of 10% tartaric acid solution. Fit tube C immediately into the mouth of flask A with the alkaline ferrous sulfate test paper on its top. Boil gently for 1 minute, remove the test paper, add 1 drop each of ferric chloride TS and hydrochloric acid, no green or blue colour is developed within 15 minutes.

Method 2

Apparatus See Fig. 18, A is a 200 ml glass-stoppered conical flask, B is a 5 ml beaker which can be placed into the flask A.

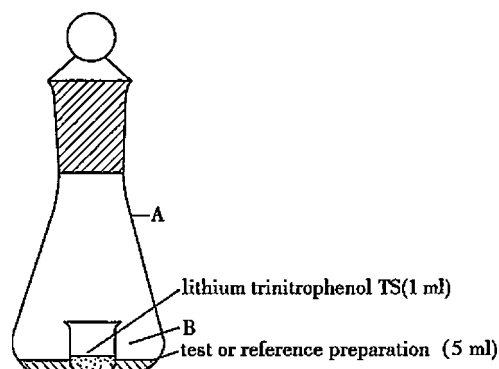


Fig. 18

Potassium cyanide standard solution Weigh accurately 25 mg of potassium cyanide into a 100 ml volumetric flask, dissolve it in water and dilute to volume, mix well. Measure accurately 5 ml of this solution to a 250 ml volumetric flask, dilute with water to volume and mix well (each ml is equivalent to 2 µg of CN).

This standard solution should be freshly prepared.

Procedure Unless otherwise specified, place a quantity of the substance being examined as prescribed under individual monographs in flask A, add sufficient water to produce 5 ml and mix well. Place 1.0 ml of lithium trinitrophenol TS in the beaker, stopper the flask and allow to stand overnight in a dark place. Remove the beaker, add 2.0 ml of water to the solution in the beaker and mix well. Measure its absorbance at 500 nm (Appendix IV A), the absorbance does not exceed that of a solution obtained in the same manner with a volume of potassium cyanide standard solution as prescribed under individual monographs.

VIII G Limit Test for Iron

Unless otherwise specified, dissolve a quantity of the substance being examined as described under individual monographs in water to 25 ml. Transfer the solution to a 50 ml Nessler cylinder, add 4 ml of dilute hydrochloric acid and 50 mg of ammonium persulfate. Dilute with water to about 35 ml, add 3 ml of 30% ammonium thiocyanate solution and sufficient water to produce 50 ml, mix well. Compare the colour produced with that of a reference preparation containing a volume of standard iron solution as prescribed under individual monographs and subjected to the same treatment.

If the colour of the test preparation is of a different shade as compared with that of the reference preparation, transfer each preparation to a separator and extract with 20 ml of *n*-butanol. Transfer each of the *n*-butanol layers to a 50 ml Nessler cylinder, add *n*-butanol to 25 ml and compare the colour of the two solutions.

Iron standard solution Dissolve 0.863 g of ferric ammonium sulfate $\text{FeNH}_4(\text{SO}_4)_2 \cdot 12\text{H}_2\text{O}$, accurately weighed, in water in a 1000 ml volumetric flask, add 2.5 ml of sulfuric acid, dilute with water to volume and mix well. This is the stock solution.

Transfer 10 ml of the stock solution, accurately measured, to a 100 ml volumetric flask immediately before use, add water to volume and mix well (each ml is equivalent to 10 µg of Fe).

VIII H Limit Test for Heavy Metals

The term "heavy metals" refers to those metals that react with thioacetamide or sodium sulfide under the specified conditions to produce a coloured compound.

Lead standard solution Dissolve 0.160 g of lead nitrate in 5 ml of nitric acid and 50 ml of water in a 1000 ml volumetric flask, dilute to volume with water, mix well (stock solution).

Transfer 10 ml of the stock solution, accurately measured, to a 100 ml volumetric flask, dilute with water to volume and mix well (each ml is equivalent to 10 µg of Pb). This

All glassware used for the preparation and preservation of standard lead solution should be free from lead.

Method 1

Unless otherwise specified, use two 25 ml Nessler cylinders. To cylinder A add the specified volume of lead standard solution and 2 ml of acetate BS (pH 3.5), dilute with water or other solvent as specified under individual monographs to 25 ml. To cylinder B add 25 ml of the test preparation containing a quantity of the substance being examined as specified under individual monographs.

If the original test preparation is coloured, it may be matched by the addition of a few drops of dilute caramel solution or other suitable solution to cylinder A.

To each cylinder add 2 ml of thioacetamide TS and mix well, allow to stand for 2 minutes, compare the colour produced by viewing down the vertical axis of the cylinders against a white background. The colour produced in cylinder B is not more intense than that produced in cylinder A.

If the colour cannot be matched by the addition of caramel solution, dissolve the double amount of the substance being examined and the reagent, in water or other solvent as specified under individual monographs to produce 30 ml of test preparation. Divide the test preparation into two equal portions and transfer to Nessler cylinders A and B. To cylinder B add sufficient water or other solvent as specified under individual monographs to produce 25 ml. To cylinder A add 2 ml of thioacetamide TS, mix well and allow to stand for 2 minutes, filter through filter membrane of 3 µm in porosity. To cylinder A add the prescribed volume of lead standard solution and dilute with water of other solvent as specified under individual monographs to produce 25 ml. Then add 2 ml of thioacetamide TS to cylinder B and 2 ml of water to cylinder A and compare the colour as described above.

If the substance being examined contains a ferric salt which interferes with the test, 0.5-1.0 g of ascorbic acid should be added to each cylinder.

Unless otherwise specified, evaporate the same quantity of the same reagents to dryness in a porcelain dish. Dissolve the residue in 2 ml of acetate buffer (pH 3.5) and 15 ml of water. Transfer the solution to a Nessler cylinder, add the specified quantity of lead standard solution and water to 25 ml. The solution is used as reference solution for the test solution which is prepared by using more than 1.0 ml of hydrochloric acid or equivalent amount of dilute hydrochloric acid, 2 ml of ammonia TS or by treating with other reagents.

Method 2

Unless otherwise specified, use the residue obtained from the Determination of Residue on Ignition, add 0.5 ml of nitric acid, evaporate to dryness, heat until nitrous oxide fumes are no longer evolved (or alternatively, ignite a quantity of the substance being examined in a crucible until thoroughly charred, cool, moisten the residue with 0.5-1.0 ml of sulfuric acid, ignite at a low temperature until sulfurous acid fumes are no longer evolved, add 0.5 ml of nitric acid, evaporate to dryness, heat until nitrous oxide fumes are no longer evolved and ignite at 500-600°C until the incineration is complete). Cool, add 2 ml of hydrochloric acid, evaporate to dryness on a water bath, add 15 ml of water, followed by ammonia TS dropwise until the solution is neutral to phenolphthalein IS, then add 2 ml of acetate BS (pH 3.5) and warm to effect dissolution. Transfer the resulting solution to Nessler cylinder B, dilute with water to 25 ml and proceed as described under method 1. The reference preparation should be prepared as follows. Place the same quantity of the same reagents used for the preparation of test solution in a porcelain dish and evaporate to dryness, dissolve in 2 ml of acetate BS (pH

3.5) and 15 ml of water, transfer to the Nessler cylinder A and add the specified volume of standard lead solution, dilute with water to 25 ml.

Method 3

Unless otherwise specified, dissolve a quantity of the substance being examined in 5 ml of sodium hydroxide TS and 20 ml of water. Transfer the solution to a Nessler cylinder, add 5 drops of sodium sulfide TS and mix well, the colour produced is not more intense than that of a reference preparation containing the specified volume of lead standard solution and treated in the same manner.

Method 4

Apparatus The filter holder is composed of tightly sealed upper and lower parts with screw thread, washer, filter membrane and nylon pad web (as Fig. 19).

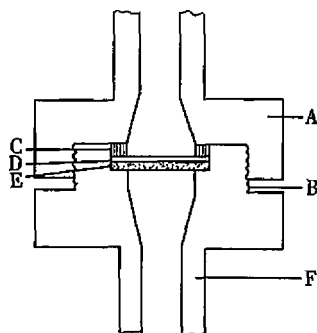


Fig. 19

A is the upper cap part of the filter holder, the entrance may be fitted with a 50 ml syringe; B is joint; C is washer (external diameter is 10 mm, internal diameter is 6 mm); D is filter membrane with 10 mm in diameter and 3.0 μ m of porosity, soaked in water for more than 24 hours before use; E is nylon pad web (porosity diameter is not required) with 10 mm in diameter; F is the lower part of the filter holder, the exit is fitted with a suitable rubber tube.

Lead standard stain Measure accurately a quantity of lead standard solution to a small beaker, dilute to 10 ml with water or other solvent as specified under individual monographs, add 2 ml of acetate BS (pH 3.5) and 1.0 ml of thioacetamide TS, mix well, allow to stand for 10 minutes. Transfer to the above filter holder with a 50 ml syringe and filter it on applying an even pressure (filter rate is about 1 ml per minute), then place the filter membrane on a piece of filter paper and dry it.

Procedure Transfer 10 ml of the test preparation prepared as described under individual monographs and proceed as described under Lead standard stain, beginning with the words "add 2 ml of acetate BS (pH 3.5)". Any stain produced is not more intense than the standard stain.

If the test preparation is coloured or turbid, filter it previously with filter membrane. If the filter membrane is contaminated, replace it with another filter membrane and repeat the filtration until the filter membrane remains uncontaminated. Proceed as described under Lead standard stain, beginning at the words "add 2 ml of acetate BS (pH 3.5)", using 10 ml of filtrate, and compare the stain as described above.

VIII J Limit Test for Arsenic

Arsenic standard solution Dissolve 0.132 g of arsenic trioxide in 5 ml of 20% sodium hydroxide solution in a 1000 ml volumetric flask, neutralize with dilute sulfuric acid and add 10 ml in excess, dilute with water to volume and mix well, as a stock solution.

Transfer 10 ml of the stock solution, accurately measured, to a 1000 ml volumetric flask immediately before use, add 10 ml of dilute sulfuric acid, dilute with water to volume and mix well (each ml is equivalent to 1 μ g of As).

Method 1 (Gutzeit's method)

Apparatus (as Fig. 20). A is a 100 ml conical flask with standard ground joint; B is a standard hollow ground glass stopper connected to glass conduit C (external diameter 8.0 mm, internal diameter 6.0 mm), the total length of B and C is about 180 mm, D is a plastic screw, the upper part of which has an aperture 6.0 mm in diameter and the lower part of which has an aperture 8.0 mm in diameter; E is a plastic screw cap which has an aperture 6.0 mm in diameter. A wad of lead acetate cotton wool weighing about 60 mg is packed into tube C to a depth of about 60-80 mm. A disc of mercuric bromide test paper is placed between the contacting surfaces of D and E.

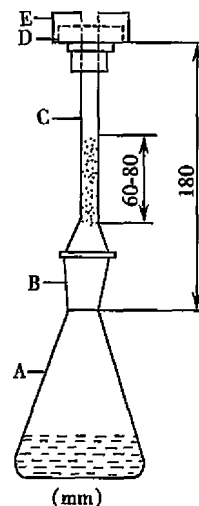


Fig. 20

Arsenic standard stain Place 2 ml of standard arsenic solution, accurately measured, in flask A, add 5 ml of hydrochloric acid and 21 ml of water. Then add 5 ml of potassium iodide TS and 5 drops of acid stannous chloride TS, allow to stand at room temperature for 10 minutes and add 2 g of zinc granules. Insert the stopper B and conduit C into the mouth of flask A and immerse the flask in a water bath at 25-40°C for 45 minutes. Remove the mercuric bromide test paper.

Use arsenic standard solution instead of the substance being examined and treat it in the same manner described under the individual monographs, prepare arsenic standard stain as described above, if the substance being examined needs to be destroyed organically before carrying out the limit test for arsenic.

Procedure Transfer the test preparation prepared as described under individual monographs to flask A and

proceed as described under Arsenic standard stain, beginning with the words "Then add 5 ml of potassium iodide TS..." Any stain produced is not more intense than the standard stain.

Method 2 (Silver diethyldithiocarbamate method)

Apparatus (as Fig. 21) A is a 100 ml conical flask with standard ground joint; B is a standard hollow ground glass stopper connected to glass conduit C (at one end, the external diameter is 8.0 mm and the internal diameter is 6.0 mm; the other end is in length of 180 mm, in external diameter of 4 mm and in internal diameter of 1.6 mm, the internal diameter of sharp end is 1 mm). D is a glass tube with flat bottom (length 180 mm, internal diameter 10 mm, and with a graduation at 5.0 ml). A wad of cotton wool previously moistened with lead acetate TS and dried weighing about 60 mg is packed into conduit C to a depth of about 80 mm, and measure accurately 5 ml of silver diethyldithiocarbamate TS in tube D.

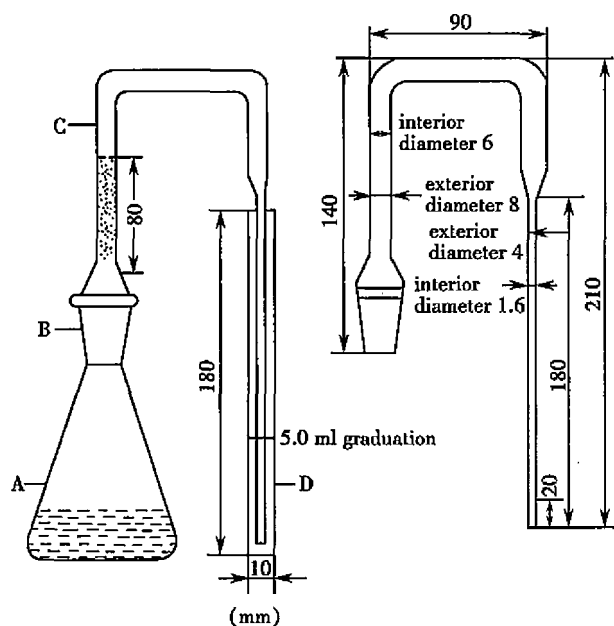


Fig. 21

Standard arsenic reference solution Transfer 5 ml of arsenic standard solution as described under Method 1 to flask A, accurately measured, add 5 ml of hydrochloric acid and 21 ml of water. Then add 5 ml of potassium iodide TS and 5 drops of acid stannous chloride TS, allow to stand at room temperature for 10 minutes and add 2 g of zinc granules. Connect conduit C into flask A immediately, and allow the evolved arsine to enter tube D. Immerse the flask A in a water bath at 25-40°C for 45 minutes. Remove tube D, add chloroform to the graduation, mix well.

Use arsenic standard solution instead of the substance being examined and treat in the same manner described under the individual monographs, prepare arsenic standard stain as described above, if the substance being examined needs to be destroyed organically before carrying out the limit test for arsenic.

Procedure Transfer the test preparation prepared as described under individual monographs to flask A and proceed as described under standard arsenic reference solution, beginning with the words "Then add 5 ml of potassium iodide TS..."

Compare the above two solutions against a white background. Any colour produced by the test preparation is

reference solution. If necessary, determine the absorbance at the wavelength of 510 nm, using silver diethyldithiocarbamate TS as the blank (Appendix IV A).

Annotations (1) Make sure that a blank test produces no arsenic stain or only a barely visible stain.

(2) The preparation of standard stain and test stain must be carried out concomitantly.

(3) The zinc granules should be arsenic free and the size is such that they will pass through a No. 1 sieve. The quantity used should be increased and the reaction time should be extended up to 1 hour, if the granules are of larger size.

(4) Lead acetate cotton wool is prepared by immersing 1.0 g of absorbent cotton in 12 ml of a mixture of equal volumes of lead acetate TS and water. Drain off excess liquid and make the cotton wool fluffy, allow it to dry at a temperature below 100°C and preserve in a well closed glass container.

VIII K Limit Test for Ammonium

Unless otherwise specified, place a quantity of the substance being examined as prescribed under individual monographs in a distillation flask, add 200 ml of ammonia-free distilled water and 1 g of magnesium oxide, heat to distill, introduce the distillate to a 50 ml Nessler cylinder containing 1 drop of dilute hydrochloric acid TS and 5 ml of ammonia-free distilled water. When the volume of the distillate is about 40 ml, stop distillation, add 2 ml of alkaline mercuric potassium iodide TS, mix well, allow to stand for 15 minutes. Compare the colour produced with that of a reference solution containing 2 ml of ammonium chloride standard solution treated in the same manner.

Ammonium chloride standard solution Place 31.5 mg of ammonium chloride, accurately weighed, in a 1000 ml volumetric flask, dissolve it in water and dilute to volume, mix well (each ml is equivalent to 10 µg of NH₄).

VIII L Determination of Loss on Drying

Mix the substance being examined thoroughly, if it is in the form of large crystals, reduce them to a size of about 2 mm by crushing. Place about 1 g or the amount specified under individual monographs of the substance being examined in a tared, shallow weighing bottle, previously dried to constant weight at 105°C, unless otherwise directed.

The substance being examined should be evenly distributed to form a layer of not more than 5 mm in thickness, or not more than 10 mm in the case of bulky material. When the loaded bottle is placed in the drying chamber of desiccator, remove the stopper and put it beside the bottle, or leave it on the bottle in half open position. Upon the opening of the drying chamber or desiccator, the bottle should be closed promptly. If the substance is dried by heating, allow it to cool to room temperature in a desiccator before weighing.

If the substance melts at a lower temperature than the specified drying temperature, maintain the bottle with its content below the melting temperature until most of the water is removed, then dry it under the specified conditions.

If a vacuum desiccator or constant temperature vacuum desiccator is to be used, a pressure of 2.67 kPa (20 mmHg) or less should be maintained unless otherwise directed. The

chloride, silica gel or phosphorus pentoxide. Phosphorus pentoxide is often used in a constant temperature vacuum desiccator at 60°C, unless otherwise specified. The desiccants should be kept fully effective.

VIII M Determination of Water

Method 1 (Karl Fischer's Method)

A. Volumetric titration

This method is based on the quantitative reaction of water with a solution of sulfur dioxide and iodine in pyridine and methanol. The apparatus used should be dry and moistureproof. The determination of water is preferably carried out in a low humidity environment.

(1) *Preparation of Karl Fischer reagent* Place 110 g of iodine, previously dried in a desiccator over sulfuric acid for more than 48 hours, in a dry stoppered conical beaker, add 160 ml of anhydrous pyridine and cool, shake to effect complete dissolution. Add 300 ml of anhydrous methanol and weigh the conical beaker. Keep the conical beaker cold in an ice bath and keep the atmospheric moisture excluded from the system, pass dry sulfur dioxide into the conical beaker until the increase of weight is 72 g, add anhydrous methanol to produce 1000 ml. Stopper tightly and mix well, allow to stand for 24 hours protected from light.

This reagent should be preserved in tightly closed containers, protected from light and stored in a cool and dry place, standardized before use.

(2) *Standardization of Karl Fischer reagent* Standardize with a water determination apparatus directly or place about 30 mg of redistilled water, accurately weighed, in a dry stoppered flask, add 2-5 ml of anhydrous methanol. Titrate with Karl Fischer reagent until the colour changes from pale yellow to reddish brown. The end-point may also be determined electrometrically by dead-stop titration (Appendix VII A). Perform a blank titration and calculate the water equivalent of the reagent in mg of water per ml by the formula:

$$F = \frac{W}{A-B}$$

in which F is the water equivalent of the reagent, W is the weight of redistilled water in mg, A is the volume, in ml, of the reagent consumed in the titration of water and B is the volume, in ml, of the reagent consumed in the blank titration.

(3) *Procedure* Weigh accurately a quantity of the substance being examined which is anticipated to consume 1-5 ml of Karl Fischer reagent and determine with a water determination apparatus directly or place in a dry stoppered flask, add 2-5 ml of anhydrous methanol, titrate with Karl Fischer reagent with continuous shaking or stirring until the colour changes from pale yellow to reddish brown. The end-point may also be determined electrometrically by dead-stop titration (Appendix VII A). Perform a blank titration and calculate the percentage of water in the substance being examined by the formula:

$$\frac{(A-B)F}{W} \times 100$$

in which A and B are the volumes in ml of the reagent consumed in the titration of water in the substance being examined and in the blank titration respectively; F is the

weight of the substance being examined in mg.

B. Coulometric titration

This method is also based on the Karl Fischer reaction and using dead-stop titration (Appendix VII A) to determine the content of water. However, compared with volumetric titration, iodine is not added in the form of a volumetric solution from the titration tube but is produced in an iodide-containing solution by anodic oxidation. When all the water has been consumed an excess of iodine occurs, which can make the platinum electrodes polarize, thus indicating the endpoint. According to Faraday's law, the amount of iodine produced is directly proportional to the electric quantity passed through, so the total amount of water can be determined by measuring the total amount of electric quantity consumed. This method is predominantly used for substances with a very low water content (0.1% to 0.0001%). It is particularly suited to chemically inert substances like hydrocarbons, alcohols, and ethers. All the apparatus used must be dry and atmospheric moisture is excluded from the system. Procedure should be operated in a dry place.

Karl Fischer reagent Prepare or purchase the titration reagent according to the requirements of Karl Fischer's coulometric titrator. Calibration of the instrument is not necessary.

Procedure Moisture is eliminated from the system by pre-electrolysis, transfer quickly a quantity of test specimen estimated to contain 0.5-5 mg of water, accurately measured, into the anolyte solution. Perform coulometric titration to the electrometric endpoint. Read the water content of the specimen directly from the instrument's display, and calculate the percentage of water in the substance. One mg of water is equivalent to 10.72 Coulomb of electric quantity.

Method 2 (Toluene distillation method)

Apparatus As Fig. 22. The apparatus consists of a 500 ml round bottom flask (A), a graduated receiving tube (B) and a reflux condenser (C) approximately 40 cm in length. All parts of the apparatus should be cleaned and dried in an oven.

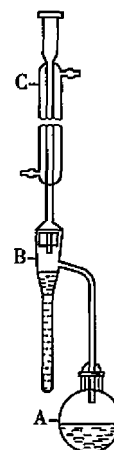


Fig. 22

Procedure Place a quantity of the substance being examined which is anticipated to yield about 1-4 ml of water and accurately weighed, in the flask A, add about 200 ml of toluene and dry and clean unglazed porcelain or a few glass beads if necessary. Assemble the apparatus and fill the receiving tube B with toluene through the condenser. Heat the flask gently, when toluene begins to boil, adjust the

second. When the volume of water in the receiving tube does not increase any more, rinse the inside of condenser with toluene and push down the toluene adhering to the wall with a brush or other suitable tools. Continue the distillation for 5 minutes, cool to room temperature and disconnect the apparatus. Push down any droplet of water adhering to the wall of the receiving tube with a copper wire wetted with toluene. Allow to stand until water is completely separated from toluene in the receiving tube (a small amount of methylene blue may be added to facilitate observation). Record the volume of water distilled and calculate the percentage of water in the substance being examined.

Annotations Toluene used in this procedure should be saturated with water and distilled.

VIII N Determination of Residue on Ignition

Place 1.0-2.0 g or the quantity specified under individual monographs of the substance being examined, accurately weighed, in a suitable crucible (If the substance being examined contains alkali metals or fluorine element, the platinum crucible should be used). Previously ignited to constant weight. Heat gently until it is thoroughly charred, cool and moisten the residue with 0.5-1 ml of sulfuric acid, unless otherwise directed. Heat gently until white fumes are no longer evolved and then ignite at 700-800°C until the incineration is complete. Cool in a desiccator and weigh accurately, ignite again at 700-800°C to constant weight. If the residue is to be used in the limit test for heavy metals, the ignition temperature should be controlled at 500-600°C.

VIII O Limit Test for Readily Carbonizable Substances

Use two colour matching tubes with same inner diameter, A and B. To tube A add 5 ml of the colour reference solution specified under individual monographs. To tube B add 5 ml of sulfuric acid (94.5%-95.5%) and then add the specified quantity of the substance being examined in small portions, shake the mixture thoroughly after each addition until solution is complete. Allow to stand for 15 minutes and compare the colour of the two solutions by viewing transversely against a white background, unless otherwise specified. The colour produced in tube B is not more intense than that of the solution in tube A.

Solid substances should be finely powdered before the test. When heating is necessary to effect dissolution of the substance being examined, mix it with sulfuric acid in a test tube, heat to dissolve, allow to cool, transfer the solution to a colour matching tube and compare the colour as described above.

VIII P Determination of Residual Solvents

Residual solvents in pharmaceuticals are defined as organic

manufacture of drug substances or excipients, or in the preparation of medicinal products, but not completely removed in manufacturing process. The limits of general residual solvents in pharmaceuticals are listed in table 1. Unless otherwise specified, the limits of Class 1, Class 2 and Class 3 residual solvents, should comply with the requirement of table 1; as to other solvents, based on knowledge of the manufacture process, appropriate limits should be set to ensure complying with the requirements of product specifications, good manufacturing practices (GMP) or other quality-based requirements. Carry out the method for gas chromatography (Appendix V E).

Chromatographic column

1. Capillary column

Unless otherwise specified, the capillary column with the similar polarity coating can be substituted each other.

(1) *non-polar column* Coated with 100% dimethylpolysiloxane.

(2) *polar column* Coated with polyethylene glycol (PEG-20 M).

(3) *moderate polar column* Coated with (35%) diphenyl-(65%) methylpolysiloxane, (50%) diphenyl-(50%) dimethylpolysiloxane, (35%) diphenyl-(65%) dimethylpolysiloxane, (14%) cyanopropylphenyl-(86%) dimethylpolysiloxane, (6%) cyanopropylphenyl-(94%) dimethylpolysiloxane.

(4) *lower polar column* Coated with (5%) phenyl-(95%) methylpolysiloxane, (5%) diphenyl-(95%) dimethylpolysiloxane.

2. Packed column

Use porous polymer beads of divinylbenzene-ethylvinylbenzene cross-linked with 0.25-0.18 mm in diameter or other suitable packing material as the stationary phase.

System suitability

(1) The number of theoretical plates of the capillary column is not less than 5000; the number of theoretical plates of the packed column is not less than 1000, calculated with reference to the peak due to the solvent being examined.

(2) In the chromatogram, the resolution between the peaks of the solvent being examined and its neighbouring substance is greater than 1.5.

(3) When internal standard method is used, carry out 5 replicate injections for each of the standard solutions, the relative standard deviation (RSD) of the peak area ratio of the solvent being examined to internal standard is not more than 5%; when external standard method is used, the RSD of the peak areas of the solvent being examined is not more than 10%.

Test solution preparation

1. Headspace injection

Unless otherwise specified, dissolve 0.1-1 g, accurately weighed, of the substance being examined in water, as to the water-insoluble substances, using N, N-dimethylformamide, dimethyl sulfoxide or other appropriate solvents. The principle of selection of the appropriate solvent is based on the solubility of the substance being examined and the residual solvents being controlled and the selected solvent should not interfere with the determination of the residual solvent being controlled. Prepare the test solution based on the limit of residual solvent specified in the monograph, the concentration should meet the requirement of quantitative determination.

2. Direct injection

Weigh accurately a quantity of the substance being examined,

test solution based on the limit of residual solvent specified in the monograph, the concentration should meet the requirement of quantitative determination.

Reference solution preparation

Weigh accurately a quantity of the organic solvent specified in the monograph, use the same method and solvent as that of test solution preparation to prepare the reference solution. For limit test, the concentration of the reference solution is based on the limits of residual solvents in the limit test. For quantitative determination to ensure accuracy of quantitative result, the concentration of reference solution is based on the actual content of residual solvent in the substance being examined. In general, it is better that the peak area of reference solution is not more than two times of the peak area of test solution. If necessary, the concentration of test solution or reference solution should be readjusted.

Procedure

Method 1 The method of isothermal temperature capillary column headspace injection.

When the number of organic solvents being examined is just a few and the difference of polarity of them is small, this method can be used.

Chromatographic conditions Usually maintain the temperature of column at 40-100°C; use nitrogen as the carrier gas, velocity of carrier gas is 1.0-2.0 ml/min; the equilibration temperature of headspace oven is 70-85°C when water is used as the solvent, the equilibration time of headspace vial is 30-60 minute; the injector temperature is 200°C or 250°C if flame ionization detector (FID) is used.

Procedure

Inject the reference solution and test solution, not less than two times respectively, measure the peak area of the solvent being examined.

If there are unknown organic solvents in the chromatogram, prescreen can be carried out according to table 2.

Method 2 The method of programmed temperature capillary column headspace injection.

When several organic solvents with different polarity are to be determined, this method can be used.

Chromatographic conditions If using non-polar chromatographic system, maintain the temperature of the column at 30°C for 7 min, then raise the temperature at a rate of 8°C per min to 120°C and maintain it at 120°C for 15 min. If using polar chromatographic system, maintain the temperature of the column at 60°C for 6 min, then raise the temperature at a rate of 8°C per min to 100°C and maintain it at 100°C for 20 min; nitrogen is used as the carrier gas, velocity of carrier gas is 1.0-2.0 ml/min; when water is used as the solvent, the headspace oven equilibration temperature is 70-85°C, the equilibration time of headspace vial is 30-60 minute; the injector temperature is 200°C or 250°C if flame ionization detector (FID) is used.

The temperature program can be adjusted based on the residual solvents specified in the monograph.

Procedure

Inject the reference solution and test solution not less than two times respectively, then measure the peak area of the solvent being examined.

If there are unknown organic solvents in the chromatogram, prescreen can be carried out according to table 3.

Method 3 Direct injection of solution.

Use packed column, or capillary column of appropriate polarity.

Procedure

Inject the reference solution and test solution two or three

being examined.

Calculation

(1) *limit test* Unless otherwise specified, determine based on the concentration of the test solution specified in the monograph. When internal standard method is used, the ratio of peak area of the residual solvent in the test solution to peak area of the internal standard is not more than the ratio of standard solution. When external standard method is used, the peak area of residual solvent being examined in test solution is not more than the corresponding peak area in standard solution.

(2) *quantitative determination* The content of residual solvents can be calculated by internal standard method or external standard method.

Annotations

(1) Unless otherwise specified, the selection of headspace conditions should as follows

A. The choice of headspace oven equilibration temperature depends on the boiling point of the residual solvents of the substance being examined. As to the residual solvents of high boiling point, the headspace oven equilibration temperature is also high; but at the same time attention should be paid to the thermal degradation ability of the substance to be examined, avoiding the interference of thermal degradation products.

B. The equilibration time of headspace is usually 30-45 min to ensure that the test solution has enough time to reach equilibrium. The equilibration time of headspace should not be too long, the hermeticity of the headspace vial may become worse, if excess 60 min, the accuracy of quantitation may decrease.

C. For reference solution and test solution the same headspace conditions should be used.

(2) Validation of the quantitative method

When headspace injection is used, the substance being examined and standard substance are in the matrix that are not completely the same, so the matrix effect should be taken into account. Standard addition method can eliminate the matrix effect, so usually standard addition method is adopted to validate accuracy of quantitation method. If the results of standard addition test and other quantify methods have discrepancy, the result of standard addition test is preferred.

(3) Elimination of the interference peak

The unknown impurity or the thermal degradation products in the substance being examined can interfere the examination of residual solvents. The interference effects include two kinds, the first kind results from the unknown impurity or the thermal degradation products in the substance being examined having the same retention time as the residual solvent being examined (co-elution); the second kind is caused by the thermal degradation product having the same structure as the residual solvent being examined (e.g. methoxyl produces methanol when thermal degradation occurs). When the residual solvent exceeds the limit, but it is not sure whether some unknown impurities or volatile heat-degradation compounds interfere the determination, experiments should be carried out to exclude the interference. As to the first kind interference effect, the general method adopted is to examine the same substance being examined using a chromatographic system with opposite polarity, then compare the results of the two different chromatographic systems. If the results are the same, then there is no co-elution interference; if the results are different, then there is co-elution interference. As to the second kind interference effect, the general method adopted is to examine the residual solvent-free reference substance.

The stainless steel pipeline and injection liner of ordinary gas chromatography instrument have strong sorption to nitrogenous alkaline substance such as amine, which result in the decrease of sensitivity, so the inert silicon steel or nickel steel pipeline should be used; when the method of direct injection of solution is used, the test solution should not be acidic, because the residual solvent being examined can react with acid that make it difficult to evaporate.

Usually use lower polar column or column that the packing materials have been treated with alkaline previously to examine nitrogenous alkaline substance. Better results may be obtained if the column specially designed for analysis of amines is used.

As to the nitrogenous alkaline substance that is not readily

detected by gas chromatography, such as N-methylpyrrolidone, other appropriate procedures can be used, such as ion chromatography.

(5) Selection of detector

Electron capture detector has high sensitivity for the halogen residual solvents, such as chloroform.

(6) Different laboratories may use different methods to examine the same substance. If the result is at brim edge of eligible or not eligible, the results of internal standard test and standard addition test are preferred.

(7) The following residual solvents are not readily detected by the headspace injection conditions, such as formamide, 2-ethoxyethanol, 2-methoxyethanol, ethylene glycol, N-methylpyrrolidone, etc.

Table 1 General residual solvents in pharmaceutical products and limits

solvents	limit/%	solvents	limit/%	solvents	limit/%	solvents	limit/%
Class 1 solvents (solvents to be avoided)		Class 2 solvents (solvents to be limited)		Class 3 solvents (solvents that should be limited by GMP or other quality-based requirements)		Class 3 solvents (solvents that should be limited by GMP or other qualitybased requirements)	
Benzene	0.0002	2-Ethoxyethanol	0.016	Acetic acid	0.5	Methylethyl ketone	0.5
Carbon tetrachloride	0.0004	Ethyleneglycol	0.062	Acetone	0.5	Methylisobutyl ketone	0.5
1,2-Dichloroethane	0.0005	Formamide	0.022	Anisole	0.5	2-Methyl-1-propanol	0.5
1,1-Dichloroethene	0.0008	Hexane	0.029	1-Butanol	0.5	Pentane	0.5
1,1,1-Trichloroethane	0.15	Methanol	0.3	2-Butanol	0.5	1-Pentanol	0.5
Class 2 solvents (solvents to be limited)		2-Methoxyethanol	0.005	Butyl acetate	0.5	1-Propanol	0.5
Acetonitrile	0.041	Methylbutyl ketone	0.005	tert-Butylmethyl ether	0.5	2-Propanol	0.5
Chlorobenzene	0.036	Methylcyclohexane	0.118	Cumene	0.5	Propyl acetate	0.5
Chloroform	0.006	N-Methylpyrrolidone	0.053	Dimethyl sulfoxide	0.5	Class 4 solvents(solvents for which no adequate toxicological data was found) ^①	
Cyclohexane	0.388	Nitromethane	0.005	Ethanol	0.5	1,1-Diethoxypropane	
1,2-Dichloroethene	0.187	Pyridine	0.02	Ethyl acetate	0.5	1,1-Dimethoxymethane	
Dichloromethane	0.06	Sulfolane	0.016	Ethyl ether	0.5	2,2-Dimethoxypropane	
1,2-Dimethoxyethane	0.01	Tetralin	0.01	Ethyl formate	0.5	Isocatane	
N,N-Dimethylacetamide	0.109	Tetrahydrofuran	0.072	Formic acid	0.5	Isopropyl ether	
N,N-Dimethylformamide	0.088	Toluene	0.089	Heptane	0.5	Methylisopropyl ketone	
1,4-Dioxane	0.038	1,1,2-Trichloroethene	0.0080	Isobutyl acetate	0.5	Methyltetrahydrofuran	
		Xylene ^②	217	Isopropyl acetate	0.5	Petroleum ether	
				Methyl acetate	0.5	Trichloroacetic acid	
				3-Methyl-1-butanol	0.5	Trifluoroacetic acid	

① usually 60% m-xylene, 14% p-xylene, 9% o-xylene with 17% ethyl benzene

② Manufacturers should supply justification for residual levels of these solvents in pharmaceutical products.

Table 2 The retention time (RRT) reference value of the residual solvents relative to methyl ethyl ketone under isothermal conditions

Non-polar column		Polar column	
Organic solvent	Relative retention time(RRT)	Organic solvent	Relative retention time(RRT)
Column temperature:40°C		Column temperature:60°C	
Methanol	0.540	Pentane	0.562
Ethanol	0.615	Hexane	0.581
Acetonitrile	0.640	Ethyl ether	0.589
Acetone	0.668	Isopropyl ether	0.605

continue

Non-polar column		Polar column	
Organic solvent	Relative retention time(RRT)	Organic solvent	Relative retention time(RRT)
Ethyl ether	0.727	1,1-Dichloroethene	0.647
Ethyl formate	0.736	Cyclohexane	0.647
Pentane	0.739	Isooctane	0.657
1,1-Dichloroethene	0.749	Heptane	0.673
Methyl acetate	0.780	Methylcyclohexane	0.687
Dichloromethane	0.785	1,1-Dimethoxymethane	0.711
Nitromethane	0.819	Acetone	0.763
1-Propanol	0.869	Methyl acetate	0.764
tert-Butylmethyl ether	0.942	Ethyl formate	0.821
Methylethyl ketone	1.000	1,1,1-Trichloroethane	0.868
2-Butanol	1.065	Methanol	0.897
Isopropyl ether	1.127	Tetrahydrofuran	0.910
Hexane	1.130	Methyltetrahydrofuran	0.916
Ethyl acetate	1.131	Ethyl acetate	0.948
Chloroform	1.163	Isopropyl acetate	0.973
Tetrahydrofuran	1.232	Methylethyl ketone	1.000
2-Methyl-1-propanol	1.236	2-Propanol	1.049
1,1,1-Trichloroethane	1.431	1,2-Dimethoxyethane	1.062
Methylisopropyl ketone	1.436	Dichloromethane	1.073
1,2-Dimethoxyethane	1.464	Ethanol	1.074
Isopropyl acetate	1.522	Chloroform	1.084
1-Butanol	1.533	Methylisopropyl ketone	1.094
Benzene	1.560	Benzene	1.140
Methyltetrahydrofuran	1.606	Propyl acetate	1.257
Carbon tetrachloride	1.610	1,1,1-Trichloroethane	1.342
Cyclohexane	1.615	Methylisobutyl ketone	1.450
Isooctane	1.975	Isobutyl acetate	1.452
1,1,1-Trichloroethane	1.989	Acetonitrile	1.478
Propyl acetate	2.127	2-Butanol	1.487
Heptane	2.134	1-Propanol	1.599
Methylcyclohexane	2.461	Toluene	1.660
Methylisobutyl ketone	2.487	Butyl acetate	1.668
3-Methyl-1-butanol	2.517	1,4-Dioxane	1.859
Toluene	3.247	1,2-Dichloroethane	1.868
1-Pentanol	3.307	Cumene	2.968
		Pyridine	3.327

Note: 1. The data in this table is the results of non-polar SPB-1 column (30 m×0.32 mm×1.0 μm) and polar HP-FFAP column (25 m×0.32 mm×0.52 μm)

Table 3 the retention time (RRT) reference value of the residual solvents relative to methyl ethyl ketone under programmed temperature conditions

Non-polar column			Polar column		
order	Organic solvent	RRT	order	Organic solvent	RRT
1	Methanol	0.453	1	Pentane	0.611
2	Ethanol	0.539	2	Hexane	0.630
3	Acetonitrile	0.565	3	Ethyl ether	0.640
4	Acetone	0.595	4	Isooctane	0.657
5	2-Propanol	0.628	5	Isopropyl ether	0.657
6	Pentane	0.667	6	tert-Butylmethyl ether	0.670
7	Ethyl ether	0.669	7	Heptane	0.673
8	Ethyl formate	0.683	8	Cyclohexane	0.702
9	1,1-Dimethoxymethane	0.700	9	1,1-Dimethoxymethane	0.711
10	Methyl acetate	0.720	10	Methylcyclohexane	0.747
11	Dichloromethane	0.723	11	Acetone	0.816
12	Nitromethane	0.780	12	Methyl formate	0.824
13	1-Propanol	0.849	13	Methyl acetate	0.830
14	tert-Butylmethyl ether	0.931	14	Tetrahydrofuran	0.908
15	Methylethyl ketone	1.000	15	Methyltetrahydrofuran	0.917
16	2-Butanol	1.095	16	Ethyl acetate	0.949
17	Isopropyl ether	1.169	17	Isopropyl acetate	0.972
18	Hexane	1.171	18	Methanol	0.976
19	Chloroform	1.178	19	Methylethyl ketone	1.000
20	Ethyl acetate	1.179	20	2-Propanol	1.052
21	Tetrahydrofuran	1.283	21	1,2-Dimethoxyethane	1.064
22	2-Methyl-1-propanol	1.324	22	Dichloromethane	1.073
23	1,2-Dichloroethane	1.413	23	Chloroform	1.088
24	1,2-Dimethoxyethane	1.561	24	Ethanol	1.088
25	Methylisopropyl ketone	1.566	25	Methylisopropyl ketone	1.100
26	Benzene	1.658	26	Benzene	1.146
27	Isopropyl acetate	1.679	27	Propyl acetate	1.262
28	1-Butanol	1.696	28	1,1,2-Trichloroethene	1.356
29	Cyclohexane	1.736	29	2-Butanol	1.364
30	Methyltetrahydrofuran	1.740	30	Methylisobutyl ketone	1.449
31	1,1,2-Trichloroethene	2.028	31	Isobutyl acetate	1.459
32	1,4-Dioxane	2.030	32	Acetonitrile	1.480
33	Isooctane	2.054	33	1-Propanol	1.628
34	Heptane	2.163	34	Toluene	1.696
35	Propyl acetate	2.164	35	1,2-Dichloroethane	1.857
36	Pyridine	2.320	36	1,4-Dioxane	1.888
37	Methylcyclohexane	2.334	37	Butyl acetate	1.898
38	Methylisobutyl ketone	2.352	38	Methylbutyl ketone	2.011
39	3-Methyl-1-butanol	2.370	39	2-Methyl-1-propanol	2.102
40	Toluene	2.617	40	1-Butanol	2.798

continue

Non-polar column			Polar column		
order	Organic solvent	RRT	order	Organic solvent	RRT
41	1-Pentanol	2.635	41	Nitromethane	3.101
42	Methylbutyl ketone	2.668	42	Cumene	3.215
43	Isobutyl acetate	2.731	43	Pyridine	3.542
44	Butyl acetate	2.953	44	3-Methyl-1-butanol	3.791
45	Chlorobenzene	3.152	45	Chlorobenzene	3.893
46	Anisole	3.561	46	1-Pentanol	4.404
47	Cumene	3.653	47	Anisole	5.536
48	Tetralin	5.132	48	Tetralin	8.204

Note: The data in this table is only for reference

VII Q Thermal Analysis

Thermal analysis is a group of technique in which the physical-chemical properties of a substance being examined are precisely recorded as a function of temperature according to a controlled temperature program. And the physical variation, i.e. crystalline structure inversions, fusion, evaporation, dehydration or the chemical changes, i.e. decomposition, oxidation etc., and the accompanied variation of temperature, energy and weight are studied.

Absorption or release of energy accompanies phase change or chemical reaction when a substance is heated or cooled. According to the phase rule, temperature during phase inversion (i.e. melting and boiling point) keeps constant. A pure substance has a specific phase inversion temperature and enthalpy change (ΔH). These constants can be used for qualitative analysis, and the variation or variation extent of the measured values from them can indicate the purity of a substance being examined.

Thermal analysis is widely used in the studies of polymorphism, phase inversion, crystal water, crystalline solvent, and decomposition of a substance, and purity, consistency and stability of a drug.

1. Thermogravimetry

Thermogravimetry (TG) is a technique in which the weight of a substance being examined is determined as a function of temperature according to a controlled temperature program. The thermogravimetry curve is recorded as a graph with weight on the ordinate, and temperature (T) or time (t) on the abscissa. TG curve is usually in the shape of a stair, for the temperature during phase inversion (i.e. loss of crystal water or crystalline solvent, decomposition etc.) keeps constant, and the range in which the weight of the substance being examined keeps unchanged is called as plateau. It is easy to discriminate the absorbed water from the crystal water contained in a substance being examined, and the molecular ratio of crystal water can be calculated from the weight loss percentage between plateaus.

Usually, when heated, loss of absorbed water is a gradual process, while loss of crystal water occurs only at a specific temperature point or range (relevant with heating rate) where TG is in the stair shape due to the jump of weight loss.

Thermogravimetry can be used to measure the loss on drying of certain drugs.

Calorimetry

When heated simultaneously, temperature difference (ΔT) is produced between the substance being examined and the heat-inert reference material due to the energy effect resulted from certain physical or chemical changes of the former. As a function of temperature (or time) according to a controlled temperature program, differential thermal analysis (DTA) and differential scanning calorimetry (DSC) measure the temperature difference and the conveyed energy difference (dQ/dT), separately, between the substance being examined and the reference material. Power-compensated differential scanning calorimeter automatically calibrate the heating power conveyed to the substance being examined to compensate the energy effect, and keep the temperature constant between the substance being examined and the reference material. That means there is no extra energy transfer between the substance being examined and the reference material ($\Delta T=0$). This is why the quantitative accuracy of differential scanning calorimetry is better than that of differential thermal analysis.

The shape of DTA curve is similar to that of DSC, with temperature or time on the abscissa for both curves, but on the ordinate ΔT for the former, dQ/dT for the latter. On both curves, there are specific endothermic or exothermic peaks corresponding to a certain substance being examined.

DTA and DSC can be used to measure the following parameters.

1) **Inversion Temperature** DTA and DSC objectively record the temperature where the substance state inverse. For example, fusion curve indicates the initial and peak temperatures within fusion process. However, both temperatures may not be accordant with the melting point measured by the method of Appendix VI C. It is necessary to calibrate the temperature scale of the instrument precisely with a standard substance.

2) **Inversion Enthalpy** The area of endothermal or exothermic peak is directly proportional to the enthalpy change expressed as the following equation.

$$M \cdot \Delta H = K \cdot A$$

Where M is the mass;

ΔH is the inversion enthalpy of a unit mass;

A is the measured peak area;

K is the instrument constant.

The instrument constant K can be determined using a standard substance with a known ΔH , then the experimental inversion enthalpy of a substance being examined can be calculated from the above equation.

3) **Purity** Theoretically, a pure solid substance melts at a specific temperature point or infinity narrow temperature

enthalpy ΔH_f). Any broadening of melting range or lowering of melting point means purity decrease. Lowering of melting point induced by impurity can be expressed as the following Van't Hoff equation,

$$\frac{dT}{dX_2} = \frac{RT^2}{\Delta H_f} \cdot (k-1) \quad (1)$$

Where T is the thermodynamic temperature, K;
 X_2 is the concentration (molar fraction) of impurity;
 ΔH_f is the molar fusion enthalpy of pure substance;
 R is the gas constant;
 k is the distribution coefficient of impurity between the solid and liquid phases at fusion.

If no solid solution forms at fusion, k is equal to 0 and the equation (1) can be integrated to give:

$$X_2 = \frac{(T_0 - T_m) \Delta H_f}{RT_m^2} \quad (2)$$

Where T_0 is the melting point of pure substance, K;
 T_m is the measured melting point of the substance being examined, K.

ΔH_f , T_0 , and T_m can be experimentally measured, then the content of impurity can be calculated by the equation (2).

3. Procedure The thermal analysis techniques of thermogravimetry, differential thermal analysis and differential scanning calorimetry are given by each instrumental instruction in detail. To obtain an objective and reproducible thermogram as possible, it is appropriate to process a preliminary examination over a wide temperature range (from room temperature to a temperature 10-20°C higher than decomposition temperature or melting point) at a higher heating rate (10-20°C per minute), then replicate the examination deliberately over a narrow temperature range at a lower heating rate (e.g. 1°C per minute if necessary) to obtain a satisfactory result of thermal analysis.

A thermal analysis report should be attached with a complete description of the determination conditions, including instrument model, calibrated temperature value, sampling amount and granularity of the substance being examined, atmosphere pressure, direction and rate of temperature change and the sensitivity of instrument.

It is needed to point out that purity determination using Van't Hoff equation is based on the assumption that impurity does not lead to formation of solid solution. Application of the equation in accurately measuring the purity is limited, especially when the substance being examined is polymorphism or decomposes at fusion point.

VIII R Total Organic Carbon in Water for Pharmaceutical Use

Total organic carbon (TOC) determination is an indirect measure of organic substances present in water for pharmaceutical use. TOC determination can also be used to monitor the performance of various operations in the preparation of medicines.

The organic substances present in water for pharmaceutical use are generally from water source, water supply system including purification, storage and distribution, and the velum growth in water system. TOC can indicate the content of the organic substances in water for pharmaceutical use.

A variety of acceptable methods is available for determining TOC. Rather than prescribing a given method to be used, this general chapter describes the procedures used to qualify

tests. A standard solution is analysed at suitable intervals, depending on the frequency of measurements; the solution is prepared with a substance that is expected to be easily oxidisable (for example, sucrose) at a concentration adjusted to give an instrument response corresponding to the TOC limit to be measured. The suitability of the system is determined by analysis of a solution prepared with a substance expected to be oxidisable with difficulty (for example, 1,4-benzoquinone).

The various types of apparatus used to measure TOC in water for pharmaceutical use have in common the objective of completely oxidising molecules in the sample water to produce carbon dioxide followed by measurement of the amount of carbon dioxide produced, the result being used to calculate the carbon concentration in the water.

The apparatus used must discriminate between organic and inorganic carbon, the latter being present as carbonate. The discrimination may be effected either by measuring the inorganic carbon and subtracting it from the total carbon, or by purging inorganic carbon from the sample before oxidation. Purging may also entrain organic molecules, but such purgeable organic carbon is present in negligible quantities in water for pharmaceutical use.

Apparatus Use a calibrated instrument and verify the system suitability at suitable intervals using standard solutions as described below. The apparatus must have a limit of detection specified by the manufacturer of 0.05 mg or less of carbon per liter.

TOC water Use highly purified water complying with the following specifications:

- conductivity; not greater than $1.0 \mu\text{S} \cdot \text{cm}^{-1}$ at 25°;
- total organic carbon; not greater than 0.10 mg/L.

TOC water used, standard solution prepared and system suitability solution should share the same container.

Glassware preparation Use glassware that has been scrupulously cleansed by a method that will remove organic matter. Use TOC water for the final rinse of glassware.

Standard solution

Sucrose standard solution Unless otherwise specified, accurately weigh some sucrose, dried at 105° to a constant weight, and dissolve in TOC water to obtain a solution containing about 1.20 mg of sucrose per liter (0.50 mg of carbon per liter).

1,4-benzoquinone standard solution Unless otherwise specified, accurately weigh some 1,4-benzoquinone, and dissolve in TOC water to obtain a solution having a concentration of 0.75 mg of 1,4-benzoquinone per liter (0.50 mg of carbon per liter).

Test solution Using all due care to avoid contamination, collect water to be tested in an airtight container leaving minimal head space. Examine the water with minimum delay to reduce contamination from the container and its closure.

TOC water control Use TOC water obtained at the same time as that used to prepare the standard solution and the system suitability solution.

Control solutions In addition to the TOC water control, prepare suitable blank solutions or other solutions needed for establishing the base for calibration adjustments following the manufacturer's instructions; run the appropriate blanks to zero the instrument.

System suitability Run the following solutions and record the responses: TOC water (r_w); standard solution (r_s); system suitability solution (r_{ss}). Calculate the percentage response

$$\frac{r_{ss} - r_w}{r_s - r_w} \times 100$$

The system is suitable if the response efficiency is not less than 85% and not more than 115% of the theoretical response.

Procedure Run the test solution and record the *response* (r_u). The test solution complies with the test if r_u is not greater than

$$r_s - r_w.$$

The method can also be applied using on-line instrumentation that has been adequately calibrated and shown to have acceptable system suitability. The location of instrumentation must be chosen to ensure that the responses are representative of the water used.

Appendix IX

IX A Colour of Solution

The colour of solution and its difference from the specified colour can, to some extent, demonstrate the purity of drug. Colour of Solution is a method for testing the colour of a solution, by comparing the colour of solution of drug with that of the reference solutions specified, or, measuring the absorbance at the specified wavelength.

A solution which is termed "colourless" specified in an individual monograph means that the colour of solution of drug is the same as that of the solvent being used for the preparation of the solution, and a solution which is termed "almost colourless" means that the colour of solution of drug is less intense than that of a reference solution, prepared by diluting reference solution No. 1 with same volume of water.

Method 1

Unless otherwise specified, dissolve a quantity of the substance being examined specified in an individual monograph with water in a 25 ml Nessler cylinder, dilute with water to 10 ml. Place in another Nessler cylinder 10 ml of reference solution of specified tint and colour. View down vertically the cylinders against a white background, or view horizontally against a white background in diffused light. The colour in the cylinder containing the test solution is not more intense than that in the cylinder containing the reference solution. If the colour in the cylinder containing the test solution is, or is almost, the same as that in the cylinder containing the reference solution, or the tint between cylinders is not consistent, so that it is unable to estimate the result by naked eye, Method 3 (Colour Difference Meter Method) should be used, and the result should be accorded for justifying.

Potassium dichromate standard solution as reagents

Dissolve 0.4000 g of reference potassium dichromate, previously dried to constant weight at 120°C and accurately weighed, in water in a 500 ml volumetric flask and dilute with water to volume, shake thoroughly. Each ml of the solution contains 0.800 mg of $K_2Cr_2O_7$.

Cupric sulfate standard solution as reagents

Dissolve about 32.5 g of cupric sulfate in a quantity of hydrochloric acid solution (1→40) to produce 500 ml. Transfer 10 ml of the solution, accurately measured, to an iodine flask, add 50 ml of water, 4 ml of acetic acid and 2 g of potassium iodide. Titrate with sodium thiosulfate (0.1 mol/L) VS, add 2 ml of starch IS towards the end point of the titration and continue to titrate until the blue colour disappears. Each ml of sodium thiosulfate (0.1 mol/L) VS is equivalent to 24.97 mg of $CuSO_4 \cdot 5H_2O$. Dilute the rest of cupric sulfate solution with hydrochloric acid solution (1→40) to contain 62.4 mg of $CuSO_4 \cdot 5H_2O$ per ml, based on the above assay result.

Cobaltous chloride standard solution as reagents

Dissolve about 32.5 g of cobaltous chloride in a quantity of hydrochloric acid solution (1→40) to produce 500 ml. Transfer 2 ml of the solution, accurately measured, to a flask, add 200 ml of water, mix well. Add ammonia TS until the solution turns from pink to green colour, add 10 ml of acetic acid-sodium acetate BS (pH 6.0), heat to 60°C and then add 5 drops of xylenol orange IS. Titrate with disodium edetate (0.05 mol/L) VS until the solution turns to yellow. Each ml of disodium edetate (0.05 mol/L) VS is equivalent to 11.90 mg of $CoCl_2 \cdot 6H_2O$. Dilute the rest of cobaltous chloride solution with hydrochloric acid solution (1→40) to contain 59.5 mg of $CoCl_2 \cdot 6H_2O$, based on the above assay result.

Preparation of stock reference solutions Prepare the following stock Reference Solutions, using the 3 Standard Solutions.

Preparation of stock reference solutions (expressed in ml)

Colour	Cobaltous chloride standard solution	Potassium dichromate standard solution	Cupric sulfate standard solution	Water
yellowish green(YG)	1.2	22.8	7.2	68.8
yellow(Y)	4.0	23.3	0	72.7
orange yellow(OY)	10.6	19.0	4.0	66.4
orange red(OR)	12.0	20.0	0	68.0
brownish red(BR)	22.5	12.5	20.0	45.0

Preparation of reference solutions Prepare the following reference solutions, using the Stock Reference Solutions.

Preparation of reference solutions (expressed in ml)

Number of reference solution	1	2	3	4	5	6	7	8	9	10
Stock Reference Solution	0.5	1.0	1.5	2.0	2.5	3.0	4.5	6.0	7.5	10.0
Water	9.5	9.0	8.5	8.0	7.5	7.0	5.5	4.0	2.5	0

Method 2

Unless otherwise specified, dissolve a quantity of the substance being examined specified in an individual monograph with water to produce a solution of 10 ml. filter if necessary. Measure the absorbance at the wavelength specified, it gives not more than the required value.

Method 3 (Colour Difference Meter Method)

This is a method describing and analyzing the colour of a solution quantitatively by direct measurement of its tristimulus values of transmittance using colour difference meter. Using this method for determination recognition when it is difficult to identify the colour difference between a test specimen and a reference solution visually. Colour difference between a test specimen and a reference solution is achieved by comparing their tristimulus values directly or by comparing them with those of water respectively.

According to the modern colour vision theory, there are three kinds of colour-sensitive pyramidal cells in retina of human eyes, which are sensitive to red, green and blue respectively. The colour vision procedure can be divided into two steps. Firstly, the three kinds of independent colour-sensitive pyramidal substances in retina absorb light radiation of various wavelengths of spectrum selectively and at the same time each by itself produces the reaction of white in the strong light or of black without stimulation outside. Then these three reactions combine again in the course of nerve stimulation transmission from the pyramidal receptors to the vision centre, resulting in three pairs of opposite neural reactions, i.e., red or green, yellow or blue, and white or black reaction. At last various senses of colours are formed in the vision centre of the pallium.

All colours in nature can be composed of a mixture of proper ratio of red, green and blue, the three primary colours, which are called the three kinds of receptor cells in human eyes. So a new concept, the tristimulus values, (X , Y , and Z), can be defined as three primary source stimulation values to match the colour being examined in the given three-colour system. Through extensive colour-matching experiments with human subjects having normal colour vision (who are called standard observers or standard eyes), distribution coefficients ($\bar{x}(\lambda)$, $\bar{y}(\lambda)$ and $\bar{z}(\lambda)$) have been measured for each visible wavelength (380-780 nm) which stimulates each pyramidal receptor to give the relative data. The curve of the combined distribution coefficients is called the spectral tristimulus values curve of the CIE 1931 standard colourimetric observer (as Fig. 23).

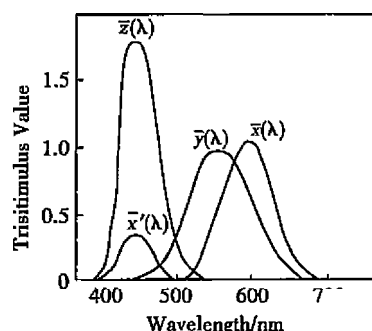


Fig. 23 The spectral tristimulus values curve of CIE 1931 standard colourimetric observer (the visual field being 10°)

The relationships between the distribution coefficient and the tristimulus values are given in following equations:

$$X = K \int S(\lambda) P(\lambda) \bar{x}(\lambda) d\lambda$$

$$Y = K \int S(\lambda) P(\lambda) \bar{y}(\lambda) d\lambda$$

$$Z = K \int S(\lambda) P(\lambda) \bar{z}(\lambda) d\lambda$$

$$Z = K \int S(\lambda) P(\lambda) \bar{z}(\lambda) d\lambda$$

Where K is the normalization coefficient;
 $S(\lambda)$ is the relative spectral power distribution of the illuminant;
 $P(\lambda)$ is either the spectral reflectance or spectral transmittance produced by the colour object;
 $\bar{x}(\lambda)$, $\bar{y}(\lambda)$ and $\bar{z}(\lambda)$ are the distribution coefficients of standard observers;
 $d\lambda$ is the wavelength interval, usually of 10 nm or 5 nm.

Once the tristimulus values of a colour have been determined, they may be used to calculate the coordinates of the colour in an idealized three-dimensional colour space. Many sets of colour equations named as the colour express system have been developed to define the space, such as the CIE 1931-XYZ colour express system, the CIE 1964 supplemental standard chroma system, the CIE 1976 $L^*a^*b^*$ colour space or the CIE Lab uniform colour space, the Hunter colour express system, etc.

In order to understand and compare conveniently, the CIE Lab uniform colour space is often used to describe colour and colour difference. It is constructed by a right-angle coordinate labelled by $L^*a^*b^*$ respectively. Every point in the three-dimensional-colour coordinate represents a colour and the geometrical distance between the point and the reference point illustrates the difference between the two colours (as Fig. 24 and Fig. 25). The same distance means the same colour difference. When the instrumental method is applied to compare the colour of a test preparation with that of a standard, the parameter needed to be compared is the difference, in the visually uniform colour space, between the colour of the blank and that of the test specimen or standard.

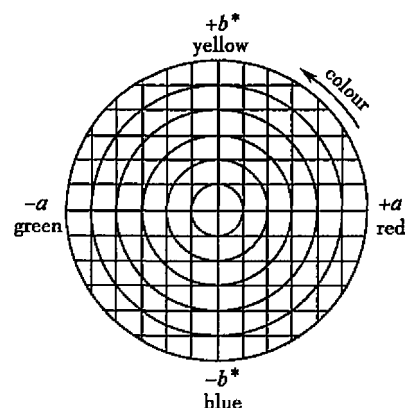


Fig. 24 The $L^*a^*b^*$ chromaticity diagram

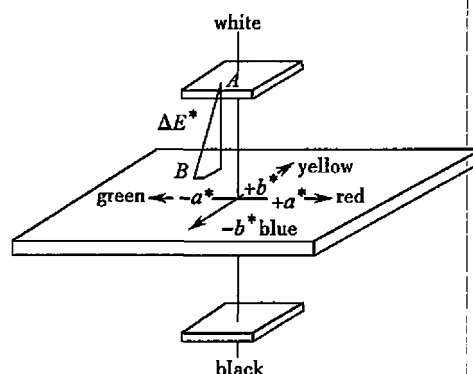


Fig. 25 The $L^*a^*b^*$ colour space and the colour difference ΔE^*

In the CIE *Lab* uniform colour space, the relationships of among colour coordinates L^* , a^* and b^* , the tristimulus values X , Y and Z and the colour difference ΔE^* are defined by

$$\text{Luminosity Index } L^* = 116 \times (Y/Y_n)^{1/3} - 16$$

$$\text{Chromaticity Index } a^* = 500 \times [(X/X_n)^{1/3} - (Y/Y_n)^{1/3}]$$

$$\text{Chromaticity Index } b^* = 200 \times [(Y/Y_n)^{1/3} - (Z/Z_n)^{1/3}]$$

$$\text{Colour Difference } \Delta E^* = \sqrt{(\Delta L^*)^2 + (\Delta a^*)^2 + (\Delta b^*)^2}$$

Where X , Y and Z are the tristimulus values of the test specimen, X_n , Y_n and Z_n are the tristimulus values of the absolutely diffuse reflection material, and X/X_n , Y/Y_n and Z/Z_n should be more than 0.008856. ΔE^* , ΔL^* , both Δa^* and Δb^* are the colour difference, the luminosity index difference, and the chromaticity index differences of the test specimen and the standard respectively. The colour of the test specimen is brighter than that of the standard when ΔL^* is positive, and deeper or more saturated when Δa^* and Δb^* are both positive.

Briefly, the operating principle of colour difference meter is to simulate the sense of sight system of human eyes and turn the tristimulus values of spectral data into the mathematical expression of the colour through its inner analogy integrating optical system, then calculate L^* , a^* , b^* and ΔE^* . Fig. 26 is the working schematic diagram of a colour difference meter. Instrumental methods can provide accurate and precise measurements of colour and colour differences with the same spectral power distribution of the standard light source as that of the light source used in common colour observation (e.g., in daylight) and with the same photo-electrical response receptor as the colour vision of the observers (e.g., the visual field is 10° .) The provided data are more objective that do not drift with time, place and individuals.

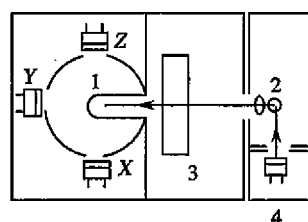


Fig. 26 The photometry system diagram of the colour difference meter

- 1—Integrating sphere; 2—light source;
3—transmissive sample;
4—photo-electric tube for balance

1. General requirements of the instrument The instrument is commonly a photo-electric integrating colour difference meter. The illumination and observation condition is $0/d$ or $d/0$, the light source is D65, and the visual field is 10° . It can detect the tristimulus values X , Y and Z and calculate L^* , a^* , b^* , ΔE^* , the hue and the hue number of the test solution directly.

For the measurement of the spectral transmittance of clear liquids, the colour of solutions changes with the thickness of the layer measured. Unless otherwise specified, a cell of 1 cm should be used.

To ensure the reliability of the measurement, the instrument should be calibrated at regular intervals. Colourless materials such as water or air should be used as a standard and assigned a transmittance of 1.000 at all wavelengths during the calibration.

The tristimulus values of water or air are $X=94.81$, $Y=100.00$, and $Z=107.32$ under the conditions of the light source being D65 and the visual field being 10° at room temperature.

2. Determination Unless otherwise specified, the colour difference meter should be calibrated with water firstly. Then detect the solutions of the test specimen and the standard which are prepared as directed in the individual monograph. The colour difference ΔE^* between the solutions of the test specimen and water should not be more than that between the solutions of the standard and water. If there are two tints specified in the individual monograph, and the actual tint of the solution of the test specimen is between the two standard tints specified, and difficult to judge, the colour difference ΔE^* between the solutions of the test specimen and water should not be more than the mean value of the colour differences between the solution of the two standard tints and water $[\Delta E^* \leq (\Delta E_1^* + \Delta E_2^*)/2]$.

IX B Clarity of Solution

Clarity of Solution is a method for testing of clarity or opalescence of a solution. Place the solution of the substance being examined and reference suspension of appropriate concentration into separate matched, flat-bottomed test tubes, 15-16 mm in diameter, of colourless, transparent, neutral hard glass, accurately measured. Compare the contents of the test tubes after 5 minutes in preparation of the reference suspension against a black background by viewing under diffused light down the vertical axes of the tubes. Or otherwise place the tubes under the light source of the illuminating shade chamber of 1000 lx, view horizontally through the tubes.

A solution which is termed "clear" means that the clarity of solution of the substance being examined is the same as that of the solvent being used for the preparation of the solution, or its opalescence is not more pronounced than that of reference suspension No 0.5.

Preparation of opalescence reference standard stock solution

Dissolve 1.00 g of hydrazine sulfate, previously dried to constant weight at 105°C , in 100 ml volumetric flask with

with water to volume, shake thoroughly and allow to stand for 4-6 hours. Mix the solution with equal volume of 10% urotropine solution, shake thoroughly and allow to stand for 24 hours at 25°C , protected from light. The suspension is stable for 2 months in a cool place, protected from light. Shake thoroughly before use.

Preparation of opalescence reference standard solution Dilute 15.0 ml of Opalescence Reference Standard Stock Solution with water in 1000 ml volumetric flask and make up to volume, shake thoroughly. Transfer a quantity to a 1 cm cell, measure the absorbance at 550 nm (Appendix IV A), the absorbance is 0.12-0.15. The solution should be used within 48 hours of preparation. Shake thoroughly before use.

Preparation of reference suspension Prepare the following reference suspensions using the Opalescence Reference Standard Solution and water. This solution should be freshly prepared. Shake thoroughly before use.

Reference suspension No.	0.5	1	2	3	4
Opalescence reference standard solution/ml	2.50	5.0	10.0	30.0	50.0
Water/ml	97.50	95.0	90.0	70.0	50.0

IX C Test for Particulate Matter in Injections

The test for Particulate Matter is applied to determine the size and number of particulate matter in injections for intravenous injection that are in solutions. Prior to this test, the injection should comply with the visible particles test.

This test consists of light obscuration and microscopic test. Unless otherwise specified, light obscuration test is preferably used. If the test result using light obscuration test does not comply with the requirements or this test is not applicable for the sample, microscopic test should be followed to reach a conclusion on conformance to requirements.

Light obscuration test is not suitable for the preparations having increased viscosity, or the preparation which is apt to crystallization or the injections which will produce air bubbles when drawn into the sensor. If the viscosity of the preparation to be tested is sufficiently high so as to preclude its examination by either test method, a quantitative dilution with an appropriate diluent may be made to decrease viscosity, as necessary to allow the analysis to be performed.

Test environment Perform the test in an environment that does not contribute any significant amount of particulate matter. Test preparation should be carried in a laminar flow cabinet. The glassware and other required equipment should be clean and particle free. The water or other suitable solvent used in the test should be filtered through a filter with a porosity of not more than $1.0\ \mu\text{m}$.

Place a 50 ml volume of water or other suitable solvents for the test of particulate matter in a sample container, determined as directed under test procedure. For light obscuration test it should meet the requirements that not more than 10 particles of greater than $10\ \mu\text{m}$ in size and not more than 2 particles of greater than $25\ \mu\text{m}$ in size are observed in the combined 10 ml of solvent. For microscopic test it should meet the requirements that not more than 20 particles of greater than $10\ \mu\text{m}$ in size and not more than 5 particles of greater than $25\ \mu\text{m}$ in size are observed in the combined 50 ml of solvent. Otherwise, the water or other suitable solvents for the test of particulate matter, glassware and test environment are not suitable for particulate analysis. In this case, repeat the preparatory steps until conditions of analysis are suitable for the test.

1. Light obscuration particle count test

When particles in solution pass through a narrow testing area, the incident light at right angle with direction of fluid is weakened by obscuring of insoluble particles, therefore the output signal of sensor reduced. The variations of signal are proportional to the cross-sectional areas of particles. Light obscuration method for insoluble particles in injections are based on the principle mentioned above.

Test apparatus Usually consists of sample-feeding device, sensor and data processor.

The range of particular size determination is from 2 to $50\ \mu\text{m}$ and the concentration of particles for measurement is 0-5000 particulates per ml.

Instrument calibration The instrument should be calibrated every 6 months.

(1) *Sample volume* Transfer a volume of water for the test

to a container after the instrument equilibrated, and weigh. Withdraw through the sample-feeding device a certain volume of the water, and weigh the container again. Obtain the sample volume by calculating the difference of the two weights. Test for 3 times consecutively. Each volume obtained should be within $\pm 5\%$ of the volume specified, and the mean value should be within $\pm 3\%$ of the volume specified. The results should comply with the requirements mentioned above if it is calibrated by the other suitable methods.

(2) *Particle counting* Prepare a suspension containing 1000-1500 particles of standard particles having average diameters of $10\ \mu\text{m}$ or $25\ \mu\text{m}$ per ml and the relative standard deviation of the size distribution of the standard particles used is not more than 5%. Degas by ultrasonication (at 80-120 watts) for 30 seconds or by allowing to stand. Turn on the stirrer and agitate the sample gently to homogenize it. Withdraw and obtain the particle counts for three consecutive samples, disregarding the first count. The average of second and third counts should be within $\pm 20\%$ of the limits of number of particles.

(3) *Sensor resolution* Prepare a suspension containing 1000-1500 particles per ml of standard particles having average diameter of $10\ \mu\text{m}$ (standard deviation of mean diameter is not more than $1\ \mu\text{m}$) and the relative standard deviation of the size distribution of the standard particles used is not more than 5%. Degas by ultrasonication (at 80-120 watts) for 30 seconds or by allowing to stand. Turn on the stirrer and agitate the sample gently to homogenize it (taking care not to introduce air bubbles), determine the particles at $10\ \mu\text{m}$ and $12\ \mu\text{m}$ channel. The ratio of the difference count of two channels and the accumulative count of $10\ \mu\text{m}$ channel is not less than 68%. If the instrument calibration does not comply with the requirements, repeat the calibration steps after adjusting the instrument until it is well done.

Note Self-test can be conducted if the instrument is attached by the self-test software.

Procedure

(1) *Intravenous injection with a labelled volume of 25 ml or larger* Unless otherwise specified, wash the outside walls of the container of the injection being examined with water. Mix the contents by inverting the container 20 times and carefully open the container immediately. Pour a portion of specimen to wash the bottleneck and sample container, transfer the specimen in the sample container, degas by ultrasonication (at 80 to 120 watts) for 30 seconds or by allowing to stand, then place it on the sample-feeding device (or directly place the specimen on the sample-feeding device without stirring after degas). Turn on the stirrer or swirl gently by hand to homogenize the sample (avoid introducing air bubbles), withdraw a minimum of three aliquots, each not less than 5 ml in volume, record the data. Determine a minimum of another two specimens as the same way. Discard the data from the first portion of each specimen, calculate the average of consecutive counts.

(2) *Intravenous injection with a labelled volume of less than 25 ml* Unless otherwise specified, wash the outside walls of the container of the injection being examined with water. Mix the contents by inverting the container 20 times. Degas by ultrasonication (at 80 to 120 watts) for 30 seconds or by allowing to stand. Carefully open the container then place it on the sample-feeding device without stirring. Withdraw directly a suitable volume without introducing air bubbles, record the data. Determine a minimum of another two specimens as the same way. Discard the data from the

consecutive counts.

An appropriate method also can be used to combine the contents of 3 or more units to obtain a volume of not less than 20 ml into the sample container in the laminar flow cabinet. Degas by ultrasonication (at 80 to 120 watts) for 30 seconds or by allowing to stand, then place it on the sample-feeding device. Turn on the stirrer or swirl gently by hand to homogenize the sample (avoid introducing air bubbles), withdraw a minimum of three aliquots, each not less than 5 ml in volume into the light obscuration counter sensor, record the data. Discard the data from the first portion of each specimen, calculate the number of particles in each container by average the consecutive counts.

(3) *Sterile powder for intravenous injection or concentrated solution for injection* Unless otherwise specified, wash the outside walls of the container of the injection being examined with water. Carefully remove the cover, accurately add a quantity of water for particulate matter or appropriate solvent, replace the closure carefully and gently agitate the container to ensure the contents dissolved (for concentrated solution for injection, operate directly). Degas by ultrasonication (at 80 to 120 watts) for 30 seconds or by allowing to stand. Carefully open the container then place it on the sample-feeding device without stirring. Withdraw directly a suitable volume without introducing air bubbles, record the data. Determine a minimum of another two specimens as the same way. Discard the data from the first portion of each specimen, calculate the average of consecutive counts.

An appropriate method also can be used, wash the outside walls of 3 or more containers of the injection being examined with water in the laminar flow cabinet. Carefully remove the cover, accurately add a quantity of water for particulate matter or appropriate solvent respectively, gently agitate the container to ensure the contents dissolved (for concentrated solution for injection, operate directly). Combine the solution of each container to obtain a total volume of not less than 20 ml into the sample container. Degas by ultrasonication (at 80 to 120 watts) for 30 seconds or by allowing to stand, then place it on the sample-feeding device. Turn on the stirrer or swirl gently by hand to homogenize the sample (avoid introducing air bubbles), withdraw a minimum of three aliquots, each not less than 5 ml in volume, record the data. Discard the data from the first portion of each specimen, calculate the number of particles in each container by average the consecutive counts.

Evaluation

(1) *Intravenous injection with a labelled volume of 100 ml or larger* Unless otherwise specified, each ml of the injection contains not more than 25 particles that are greater than 10 μm and not more than 3 particles that are greater than 25 μm .

(2) *Intravenous injection with a labelled volume of less than 100 ml, sterile powder for intravenous injection and concentrated solution for injection* Unless otherwise specified, each container of the specimen contains not more than 6000 particles that are greater than 10 μm and not more than 600 particles that are greater than 25 μm .

2. Microscopic particle count test

Test apparatus Usually consists of laminar flow cabinet, microscope, microporous membrane filter, filtration apparatus and Petri dish.

Laminar flow cabinet HEPA-filter having a pore of 0.45 μm , the direction of airflow is from inside to outside. The wind speed and the particles in the cabinet should be

Microscope Use a suitable binocular microscope with big visual field, equipped with an objective micrometer with a calibrated ocular micrometer (0.05-0.1 mm per grid). The coordinate axis can move up and down, left and right, move scope should larger than 30 mm. The microscope is equipped with an illuminator which the incident angle of light and the strength of light can be adjusted. It can give a magnification of 100 \times during examination.

Microporous membrane The membrane is 25 mm or 13 mm in diameter with pores of 0.45 μm in effective diameter, it is white in colour and grids with partition of 3 mm has been printed on one side. It should be washed with water for particular matter until free from particular matter of an effective diameter greater than 25 μm , and not more than 5 particles greater than 10 μm are left on the membrane.

Preparation Before Examination When test environment meets the requirements, rinse the filter under the cabinet with water for particulate matter or other suitable solvent. Rinse the membrane with water for particulate matter or other suitable solvent, then place it on the filter holder with a blunt forceps, invert the fixed filter and wash the inner wall of the filter repeatedly with water for particulate matter or other suitable solvent. Allow to drain and place the filter on a suction flask.

Procedure

(1) *Intravenous injection with a labelled volume of 25 ml or larger* Unless otherwise specified, wash the outside walls of the container of the injection being examined with water. Under the cabinet mix the contents by inverting the container 20 times and carefully open the container immediately. Transfer 25 ml of specimen to the pretreated filter (25 mm in diameter of membrane) gently along the inner wall of the filter, allow to stand for 1 minute and filter under gentle suction. Release the vacuum and wash the inner walls of the filter with 25 ml of water for particulate matter, remove the washings by suction. Release the vacuum and remove the membrane with the forceps. Place the membrane on a Petri slide, using a very thin layer of glycerin, if necessary, to hold the membrane flat and in its place. Allow the membrane to dry and place the covered slide on the micrometer stage of the microscope. Examine the membrane under 100 \times magnification with the incident light at a suitable angle and adjust the microscope to see the grid clearly. Count the number of particles that are greater than 10 μm , and those greater than 25 μm in effective diameter.

(2) *Intravenous injection with a labelled volume of less than 25 ml* Unless otherwise specified, wash the outside walls of the container of the injection being examined with water. Mix the contents by inverting the container 20 times carefully under the cabinet. Carefully open the container immediately. Withdraw all solutions in each container directly with an appropriate method. Transfer the specimen to the pretreated filter (13 mm in diameter of membrane) gently along the inner wall of the filter, proceed as directed for procedure (1) above.

(3) *Sterile powder for intravenous injection or concentrated solution for injection* Unless otherwise specified, prepare specimen as directed under procedure (3) in light obscuration particle count test, proceed as directed for procedure (1) above.

Evaluation

(1) *Intravenous injection with a labelled volume of 100 ml or larger* Unless otherwise specified, each ml of the injection contains not more than 12 particles that are greater than 10 μm and not more than 2 particles that are greater

(2) *Intravenous injection with a labelled volume of less than 100 ml, Sterile powder for intravenous injection and concentrated solution for injection* Unless otherwise specified, each container of the specimen contains not more than 3000 particles that are greater than 10 μm and not more than 300 particles that are greater than 25 μm .

IX D Crystallinity

Solid substance may be classified as two forms: crystalline and noncrystalline. The following methods are used to test its crystallinity.

Method 1 (polarizing microscope method) Generally crystals have optical anisotropism except isometric crystal system. The transparent crystals exhibit the phenomena of birefringence when the light passes through them. Mount a few particles of the specimen on a clean glass slide, add a quantity of liquid paraffin. Examine the mixture under a polarizing microscope; the particles exhibit the phenomena of birefringence, extinction positions and optical crystalline characteristics specified in the individual monograph when the microscope stage is revolved.

Method 2 (X-ray powder diffraction) Crystalline materials present characteristic diffraction decorative pattern (sharply diffraction pattern), while noncrystalline materials, broad dispersion diffraction pattern. The test method is described under X-ray Powder Diffraction (Appendix IX F).

IX E Determination of Particle Size and Particle Distribution

The following procedures are used for the determination of particle size or particle distribution. The method 1 and method 2 are used for the determination of particle size or size limit in pharmaceutical preparation. The method 3 is used for the determination of particle distribution in drug substance or pharmaceutical preparation.

Method 1 (microscopy)

The particle size determined by this method is expressed as the length of particles observed under a microscope.

Standardization of ocular micrometer Standardization of ocular micrometer is carried out to ascertain the value of each unit of the ocular micrometer for each optical combination (objective, ocular, and tube length).

Place the stage micrometer on the stage of the microscope. Focus the illuminator and the scale of the stage micrometer. Adjust stage micrometer until the image is in the centre of the field of view. Take out the ocular. Unscrew the cover of the ocular, and insert the ocular micrometer within the tube of the ocular by placing it on the shelf which is about halfway between the upper and lower lenses of the ocular. The engraved surface must be faced upper. Screw the cover of the ocular, and place the ocular back to the tube of the ocular. The image of the stage micrometer and the scale of the ocular micrometer can be observed in the same field of view. Make the lines on the two micrometers parallel each other and the extreme left line (marking 0) on each scale coincide by adjusting the stage micrometer and rotating the ocular. Find the second lines which coincide, and count the

ratio. The value (μm) of each unit of the ocular micrometer for the objective, with which it is used, will be judged based on the ratio. As the value for each unit of the stage micrometer is 10 μm , the value of each unit of the ocular micrometer can be calculated by the following equation:

$$\frac{10 \times \text{the number of included units of the stage micrometer}}{\text{the number of included units of the ocular micrometer}}$$

When two objectives with different magnification are to be used, it is necessary to ascertain the value of each unit of the ocular micrometer for each objective with which it is used.

Procedure Thoroughly mix the substance being examined. For the substance with high viscosity, a suitable quantity of glycerin solution (1 \rightarrow 2) specified in the individual monograph may be added. Introduce 1-2 drops of the substance being examined onto a slide as specified in the appendix of the dosage form or in the individual monograph, cover a cover glass, and press gently to make the particles spread uniformly. Prevent formation of bubbles. For the substance being examined which is semisolid, it can be spread directly onto a slide. Immediately examine the slide under a microscope, in the whole field of view, using 50-100 \times magnification. No agglomeration occurs and none of the particles has a dimension of 50 μm or greater than it specified in the individual monograph. Examine the slide again under a microscope, in the field of view specified in the appendix of the dosage form or in the individual monograph, using 200-500 \times magnification. Record the total number of particles observed and the number of particles having the specified dimension. Calculate the percentage.

Method 2 (sieving)

Single sieve Place a quantity of the substance being examined, as specified in the individual monograph, upon the specified No. sieve with a close-fitting receiving pan and cover. Shake the sieve in a rotary horizontal direction for not less than 3 minutes, and gently tap on the sieve frequently in vertical direction. Weigh accurately the amount in the receiving pan, and calculate the percentage.

Two sieves Place the accurately weighed content of 5 single-dose units or of 1 multiple-dose unit upon the sieve specified in the appendix of the dosage form or in the individual monograph. Shake the sieve in a left-to-right horizontal direction by gently tapping on the sieve for 3 minutes. Weigh accurately the amount remaining on the smaller No. sieve and passing through the larger No. sieve. Calculate the percentage of the fraction.

Method 3 (Laser Diffraction)

Laser diffraction particle size analysis is based on the scientific phenomenon that particles in a laser beam scatter laser light at angles that inversely proportional to the size of the particles. There is a direct relationship between the distribution of the scattered light energy and the particle size distribution. Mie theory or Fraunhofer Approximation Theory is used to obtain the size distribution of the particles. The size range of this method is 0.02-3500 μm .

1. Instrument

Laser diffraction analyzer; The intensity of the laser source should be stable and the electronic background and optical background should be automatically eliminated.

"Standard reference material" with certain distribution and eigenvalues [$d(0.1)$, $d(0.5)$, $d(0.9)$] can be used for verification of the analyzer. Relative Standard Deviation (RSD) is generally used to express the size distribution of "standard reference material". For samples where the coefficient of variation of the particle size distribution is less than 50% (or ratio of diameter of largest to smallest particle

performed. The deviation of $d(0.5)$ of the "standard reference material" from the eigenvalue should be less than 3%, and the RSD of the five measurements should not exceed 3%. The deviation of the $d(0.1)$ and $d(0.9)$ of the "standard reference material" from the eigenvalue should be smaller than 5%, and the RSD of the measurements should not exceed 5%. As for the "standard reference material" with size below $10\text{ }\mu\text{m}$, the deviation of the measured $d(0.5)$ from the eigenvalue should be less than 6%, and the RSD of the paralleled tests should not exceed 6%; the deviation of the $d(0.1)$ and $d(0.9)$ from the eigenvalue should be less than 10%, and the RSD of the paralleled tests should not exceed 10%.

2. Procedure

Either wet dispersion unit or dry dispersion unit can be chosen according to the properties and solubility of the material for test. Wet method can be used for measurement of the suspended materials or the materials that are not soluble in the dispersion media. Dry method is used for measuring water-soluble materials or solid materials without any suitable dispersion media.

Wet method The lower size limit is usually 20 nm .

The suitable dispersion method should be chosen according to the properties of the material for test so that sample can be dispersed into stable suspended solution. Generally, such physical dispersion methods as ultrasonication and stirring can be used. When necessary, certain amount of chemical additive or surfactant can be added, so that the sample can be dispersed in a stable system. Thus, the sample can evenly and stably pass through the cell window, so as to get the accurate results.

Only when the electrical double layer potential (Zeta Potential) is in a certain range, can the dispersion system be in a stable state. Therefore, when the dispersion system of the material for test is prepared, attention should be paid to the measurement of Zeta Potential of the system, so as to assure the repeatability of the measurement.

Normally the amount of sample for test is displayed as obscuration. The optimal obscuration is between 8% and 20%. For the most advanced analyzer the lower limit can be down to 0.2%.

Dry method The lower size limit is usually 200 nm .

Generally, sample path should be obturated to prevent the sample from absorbing moisture. The velocity biasing should be eliminated from selecting dry powder feeder and sample cell. According to how easily the material can be dispersed, the air pressure applied for sample dispersion should be able to be adjusted, so that particles with different sizes can pass through the cell window evenly and stably at the same speed, thus assuring the accuracy of results.

For chemical drug substance, the ejective dispersion unit shall be used. A proper amount of metal balls can be added into the unit. The vibration feeding rate, the air pressure (usually $0.0\text{--}0.4\text{ MPa}$), and the gap of sample tray should be adjusted to control the dispersion and the amount of the sample that passes through the analyzer.

The amount of sample for dry measurement should reach 0.5%–5% in obscuration.

Annotations

(1) The setting of optical parameters is related to the size distribution of the sample. The refractive index and absorption index affect slightly to those particles with size above $10\text{ }\mu\text{m}$, and they affect considerably to those particles with size below $10\text{ }\mu\text{m}$. When measuring the size distribution of different drug substances and products, currently there is no mature theory available for guiding the setting of the optical parameters of the instrument, so that the setting can

be used to verify the instrument.

(2) For measurement of coloured material, emulsion, and particles smaller than $10\text{ }\mu\text{m}$, the Mie Theory should be the best general solution so as to reduce measuring errors. Fraunhofer Approximation Theory should not be used in this regard.

(3) When measuring the broad size distribution samples, it is recommended to use the whole size range analyzer with wide dynamic detector instead of analyzer with separate size range to reduce the measurement errors.

IX F X-Ray Powder Diffraction

Every crystal form of a compound produces its own characteristic X-ray diffraction pattern. These diffraction patterns can be derived either from a single crystal or from a powdered specimen (containing numerous crystals) of the material. The spacings between and the relative intensities of the diffracted maxima (spots or lines) can be used for qualitative and quantitative analysis of crystalline materials. Powder diffraction techniques are most commonly employed for routine identification and the determination of relative purity of crystalline materials. The principal use of single-crystal diffraction data is for the determination of molecular weight and analysis of crystal structure at the atomic level.

A solid substance can be classified as being crystalline, non-crystalline, or a mixture of the two forms. In crystalline materials, the molecular or atomic species are ordered periodically in a three dimensional array, called a lattice, within the solid particles. This lattice structure is lacking in non-crystalline material, which sometimes are referred to as glasses or amorphous solids.

The relatively random arrangement of molecules in non-crystalline substances makes them poor coherent scatterers of X-rays, resulting in broad, diffuse maxima in diffraction patterns. Their X-ray patterns are quite distinguishable from crystalline specimens, which give sharply defined diffraction patterns.

Many compounds are capable of crystallizing in more than one type of crystal lattice. At any particular temperature and pressure, only one crystalline form (polymorph) is thermodynamically stable. Since the rate of phase transformation of a metastable polymorph to the stable one can be quite slow, it is not uncommon to find several polymorphs of crystalline pharmaceutical compounds existing under normal handling conditions.

In addition to exhibiting polymorphism, many compounds form crystalline solvates in which the solvent molecule is an integral part of the crystal structure. Just as every polymorph has its own characteristic X-ray patterns, so does every solvate.

A collimated beam of monochromatic X-ray is diffracted in various directions when it impinges upon a rotating crystal or randomly oriented powdered crystal. The crystal acts as a three-dimensional diffraction grating to this radiation. The condition that diffraction can occur should conform to the Bragg equation:

$$d_{hkl} = \frac{n\lambda}{2 \sin \theta}$$

Where d_{hkl} denotes the interplanar spacings and θ is the angle of diffraction. The principal radiation sources utilized for X-ray diffraction are vacuum tubes with copper, molybdenum, iron, and chromium as anodes; copper X-rays are employed most commonly for organic substances. For each of these radiations there is an element that will filter off K_α radiation and permit the K_β radiation to pass (nickel is used in the

case of copper radiation). In this manner the radiation is practically monochromatized. The choice of radiation source to be used depends upon absorption characteristics of the material and not producing fluorescence by atoms present in the specimen.

Only a limited number of Bragg planes are in a position to diffract when monochromatized X-ray passes through a single crystal. But a beam passing through a very large number of small, randomly oriented crystals produces continuous cones of diffracted rays from each set of lattice planes. The diffraction patterns can be recorded by photographic films, radiation detectors, image board or planar detectors such as inductance coupling detectors etc. When film is used the Bragg angle can be measured easily from a film for determination, the diffraction intensities can be read by microphotometer. When radiation detector or planar detector is employed the angle, the intensities and d spacing all can be conveniently read by the powder diffractometer.

There are a varieties of factors that affect diffraction intensities. Generally the amplitude of a diffracted X-ray beam from any set of planes is dependent upon the following structural factors of the crystal and the experimental conditions. The former includes: ① position of each atom in the unit cell; ② the respective atomic scattering factors; and ③ the absorption of the X-radiation by the specimen and the polarizing factors. The latter includes: ① the intensity and wavelength of the incident radiation; ② the volume, the crystalline degree and the density of crystalline specimen; ③ the experiment temperature; and ④ the experimental arrangement utilized to record the intensity data.

Sample preparation and associated experimental techniques In general, the shapes of many crystalline particles tend to give a specimen that exhibits some degree of preferred orientation in the specimen holder. This is especially evident for needle-like or plate-like crystals. Preferred orientation in the specimen influences the relative intensities of various diffraction. In an attempt to improve randomness in the orientation of crystallites, the specimen may be ground carefully in a mortar to a fine powder.

In order to accurately measure the Bragg angle, a small amount of standard substance can be mixed into the specimen. Every d value of the standard substance is measured in the diffraction pattern and compared to literature values, so the diffraction data and the diffractometer can be calibrated.

In quantitative analysis of materials, a standard curve method is commonly used. The internal standard used should have approximately the same density as the specimen and similar absorption characteristics. More important, its diffraction pattern should not overlap to any extent with that of the material to be analyzed. As the X-radiation can be absorbed by the matrix, standard curve should be made in a quantity of matrix similar to that in which the substance will be analyzed. In favorable cases, the ratio of amount of the substance being analyzed to that of matrix is not more than 10%. Due to its poor quantification accuracy, the method is only used for some of specific quantification, such as the determination of the crystalline degree and the relative quantification for different polymorphs of a homogeneous compound.

Identification of crystalline materials can be accomplished by comparison of X-ray powder diffraction patterns obtained for known materials with those of the unknown. The diffraction angle (2θ), the intensity ratio and the d spacing are used in the comparison. Agreement between sample and reference should be within the calibrated precision of the diffractometer for diffraction angle, while relative intensities between sample and reference may vary up to 20%. For identification,

transformation may be induced by grinding pressure, resulting in change of diffraction pattern; (2) Sometimes the differences in the diffraction patterns of different polymorphs are relatively minor, and must be very carefully evaluated before a definitive conclusion is reached.

For most organic crystals, it is appropriate to record the diffraction pattern to include values for 2θ that range from near 0° to 40° . For inorganic salts, it may be necessary to extend the 2θ region scanned to well beyond 40° .

IX G Determination of Osmolality

The phenomenon that a solvent diffuses through a semi-permeable membrane from a solution of low concentration to a higher concentration solution is called osmosis. The pressure that is needed to prevent osmosis is called osmotic pressure. Biomembrane, such as cell membrane or capillary wall of the body, has the properties of a semi-permeable membrane, thus the osmotic pressure must be considered for injection and eye drops. The declaration of osmolar concentration on the label of intravenous replenishment liquid, nutrient (s), electrolyte (s) or osmotic diuretic agents, such as Monnitol Injection, are required to inform the clinical doctors.

The units of osmolar concentration are usually expressed as milliosmoles (mOs mol) of solute per kilogram of solution. The ideal milliosmole concentration may be determined according to the formula:

$$\begin{aligned} & \text{Milliosmole concentration (mOs mol/kg)} \\ &= \frac{\text{weight of solute (g/kg)}}{\text{molecular weight (g)}} \times n \times 1000 \end{aligned}$$

Where n is the number of ions or chemical species produced when the solute is dissolved. In ideal solutions, for example, $n=1$ for glucose, $n=2$ for sodium chloride or magnesium sulfate, $n=3$ for calcium chloride, $n=4$ for sodium citrate.

Deviation from ideal condition is usually slight in solutions within the physiological range and for more dilute solutions, but for highly concentrated solutions, the actual osmolarities may be appreciably lower than ideal values. For example, the ideal osmolality of 0.9% Sodium Chloride Injection is $2 \times 1000 \times 9/58.4 = 308$ mOs mol/kg, but in fact, its n is slightly less than 2, and the actual measured osmolality is 286 mOs mol/kg. The theoretical osmolality of a complex mixture, such as Protein Hydrolysate Injection, can not be readily calculated, so the actual measured value is usually used.

Apparatus It is difficult to directly measure osmolality, but more convenient to measure the freezing point, so osmolality is often determined by measuring the depression of freezing point. In ideally dilute solution, the depression of freezing point should conform to the following equation: $\Delta T_f = K_f \cdot m$, where ΔT_f is the depression value of freezing point, K_f is the depression constant of freezing point ($K_f=1.86$ when the solvent is water), m is the weight mole concentration. Osmolality is calculated by $P_o = K_o \cdot m$, where P_o is osmolality, K_o is the constant of osmolality, and m is the weight mole concentration. Due to the same meaning of concentration in the two formula mentioned above, osmolality can be determined by measuring the depression of freezing point. Osmometer is generally designed according to the principle of the depression of freezing point.

An osmometer consists of a test tube containing the solution

and a pair of resistor sensitive to temperature (thermistors). When measuring, immerse the sensor into the solution in the glass tube, lower the tube into the cooling system and the temperature of the cooling system is decreased until the solution is super-cooled. The measured freezing point is converted to a measurement value by instrument.

Procedure Determine the zero point by using a certain volume of water (prepared freshly), calibrate the osmometer using reference solutions whose osmolality range is close to that expected for the solution being examined, then measure the osmolality of the solution being examined. When the osmolality of the solution being examined is beyond the range limit of the osmometer, dilute it with appropriate solvent to a measurable range of osmolality. If the sample is a solid, dissolve it in an appropriate solvent and then determine.

Preparation of reference solution for calibration of osmometer Dissolve a quantity, accurately weighed, of sodium chloride (primary reference substance) previously dried for 40 to 50 minutes at 500-650°C and cooled to room temperature in a desiccator contain in silica gel, as described in the Table, as required, in 1 kg of water, mix well.

Reference solution for calibration of osmometer

Weights of sodium chloride in 1 kg of water(g)	Milliosmole concentration (mOsmol/kg)	The depression of freezing point (°C)
3.087	100	0.186
6.260	200	0.372
9.463	300	0.558
12.684	400	0.744
15.916	500	0.930
9.47	600	.6
22.380	700	1.302

Determination of milliosmole concentration ratio The ratio of milliosmole concentration of the test sample to that of 0.9% (W/V) sodium chloride solution is called milliosmole concentration ratio. Determine the milliosmole concentration of the test sample (O_T) and that of the reference solution (O_S) respectively, calculate the milliosmole concentration ratio by the following equation:

$$\text{milliosmole concentration ratio} = \frac{O_T}{O_S}$$

Preparation of reference solution for measurement of milliosmole concentration ratio Weigh accurately 0.900 g of sodium chloride (primary reference substance), previously dried for 40-50 minutes at 500-650°C and cooled to room temperature in a desiccator containing silica gel, into a 100 ml volumetric flask, dissolve in water and dilute to volume, mix well.

For the preparation of injections or eye drops containing sodium chloride, osmolality is often measured instead of the assay of sodium chloride if the function of sodium chloride is mainly to regulate the osmotic pressure.

IX H Test for Visible Particles in Injections

Visible particles are defined as insoluble substance that present in injections or eye drops and can be observed under the required conditions by visual test. Their size or length

Injections or eye drops should be produced according to the Good Manufacture Practice (GMP). All of the products should be detected respectively by suitable methods before released, and the unacceptable products are eliminated synchronously.

There are two methods for the test for visible particles-lamp test and light scattering method. Lamp test is commonly used, but light scattering method also may be used especially some products that unsuitable for lamp test, such as the containers are coloured transparent glass or the colour of the solutions being examined is too dark to observe, should be detected by light scattering method.

During the test is carrying out in laboratory, must prevent to introduce foreign visible particles. All procedures must be performed under hygienic class 100, preferably in a laminar-air-flow cabinet, if the containers of samples being examined are unsuitable for detected (opaque or unshaped), and need to transfer the contents into other appropriate glass containers.

1. Lamp test

This test is carried out in a darkroom.

Apparatus See the following figure (Fig. 27):

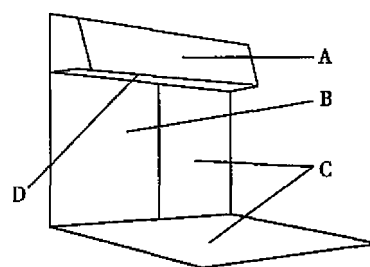


Fig. 27

A-a light source of daylight lamp with panel for obstructing from light; The intensity of illumination is adjustable between 1000-4000 lx.

B-a non-glare black background.

C-a non-glare white background and the bottom (supply with test for coloured particles).

D-a glare white background (inboard of light baffle).

Requests for inspector Inspector's visions of distant and near distance should be 4.9 or more than 4.9 (vision after correcting defects should be 5.0 or more than 5.0); Inspector is also not colour blindness.

Procedure Unless otherwise specified, take 20 containers being examined randomly. First remove any adherent labels from the containers, clean the outer surfaces, then gently swirl and invert each individual container in order to force the visible particles that present in solutions being examined floating (Caution: ensuring that air bubbles are not introduced). If necessary, transfer the solutions being examined into other clean and transparent appropriate glass containers. Hold the bottle-neck of the container at the edge of light baffle and gently invert the container, meanwhile observe the presence of any particles in it, and retain appropriate distance to inspectors' eyes (common distance is 25 cm) with visual method respectively under black background and white background.

The intensity of illumination should be 1000-1500 lx for the colourless injections or eye drops; The intensity of illumination should be 2000-3000 lx for the samples which with coloured glass or transparent plastic containers and coloured solutions being examined; For the suspensions for injections or eye drops only detect coloured mass, cilia etc.

Criteria

Solutions for injection i.v., concentrated solutions for injection and eye drops All of the 20 containers should be free from visible particles. If visible particle has been found in not more than 1 container, repeat the procedure for a further 20 containers, and none visible particles could be found.

Suspensions for injection or eye drops All of the 20 containers should be free from coloured mass, cilia etc.

Injections not used for i.v., Power for injections and Sterile raw material for injection Comply with the related requirements of the drug surveillance administration of State Council.

2. Light scattering method

When a beam of monochromatic colour laser pass through the solution being examined, the insoluble substances in the solution cause the light scattering. The scattering energy is related to the size of insoluble substance. This method is intended to measure the light scattering energies caused by insoluble substance in solutions and then compare the energies with liminal value which preseted to check out the visible particles.

The light scattering energies caused by insoluble substance can be analyzed base on the series of the images collected. Suppose the light scattering energies is E , it is processed opto-electrical signal change over, became a corresponding stereopicture with the height of pyramid is H and the diameter is D and a pick-up camera can catches it. The light scattering energies E is a monotonous function for D and H , i.e. $E=f(D, H)$. Meanwhile, suppose the intensity of the light scattering energies is q , the exposure time of take a photograph is T , there is furthermore $E=g(q, T)$. Reasoning can be obtained from the above that the relationship between D with q and D with T is $D=w(q, T)$, remain the relationship of monotonous function. After D has been determined, the light scattering energies can be calculated according to the curve of the function.

Apparatus and Principle The apparatus consists of the rotator for sample bottle, laser photosource, image collecting equipment, data processing system and terminal monitoring system. It also includes the automatic send and deliver devices for the bottle.

The samples are transferred to the rotator by the send device. The rotator must rotate the bottle rounding the perpendicular line in high speed for a while and then stopped sharply. The homogeneous laser beam from laser photosource should evenly illuminates through the solutions being examined. As soon as the turbulent flow in the solutions disappears, but the solution is still rotating due to inertia, the image collecting equipment takes images continuously at specific angle for light scattering energies that resulting from insoluble substances in the rotating solution. The numbers of image should be not less than 75. Data processing system then processes the series of the images. It will assess automatically the insoluble substance more than given size exists or not according to the predefined criteria, or it will display the images on the monitor in order to making decision manually. The results will be recorded at the same time. Then the deliver device will be instructed to differentiate the qualified and unqualified samples automatically.

Standardization for Instrument The instrument should have the automatic calibrating function. The calibration should be carried out using the reference particles before the test. Unless otherwise specified, calibrate the instrument using the reference particles with diameter 40 μm and 60 μm respectively. The curve equation resulting from the

parameter of the reference particle with diameter 50 μm for test criterion.

After the pinel parameter is set according to the 50 μm reference particle, detect the solutions containing the 60 μm reference particle three times, each result should be positive.

Procedure Unless otherwise specified, choice the corresponding test parameters from the menu provided in the instrument according to the strength of samples and adjust the parameters in compliance with the size of the containers. The test must carry out three times. If a container fails the test even one time, change the method to the lamp test for further confirmation except the container is coloured transparent vessel or the colour of the solution being examined is too dark to observe by visual test.

In general conditions, the left and right lines of sampling window should overlap with the edges of the container, the upper line should be a secant line with the curve surface of the solution in the container. Rotating time parameter should be settled longer than the time that the whirlpool in the solution reaches to the bottom of the bottle in order to force the solid substances floating and air bubble broken. Holding time parameter should be set as short as possible but not shorter than the time for the whirlpool calming down in order to avoid the interference of air bubbles meanwhile retain the solid substances in moving state when image collecting equipment start to work. The tightness parameter for holding bottle prefer to same with the diameter of the bottom of the bottle (mm), and it is adjustable based on the qualities of the bottle. If the bottle is not smooth and straight enough to avoid the vibration during rotating, air bubbles would be introduced. In this case the tightness parameter should be increased to decrease the vibration, meanwhile, the rotating time parameter should be increased so ensuring that the whirlpool in the solution reach to the bottom of the bottle.

Injections Unless otherwise specified, take 20 containers being examined randomly. First remove any adherent nontransparent labels from the containers, clean the outer surfaces, then put the samples onto the send device, start the instrument and record the results. All of the 20 containers should be free from visible particles. If it is confirmed that visible particle has been found in not more than 1 container, repeat the procedure for a further 20 containers, and none visible particles could be found.

Eye drops Unless otherwise specified, take 20 containers being examined randomly and transfer the solutions into other clean and diaphanous appropriate glass containers. Put the containers onto the send device, start the instrument and record the results. All of the 20 containers should be free from visible particles. If it is confirmed that visible particle has been found in not more than 1 container, repeat the procedure for a further 20 containers, and none visible particles could be found.

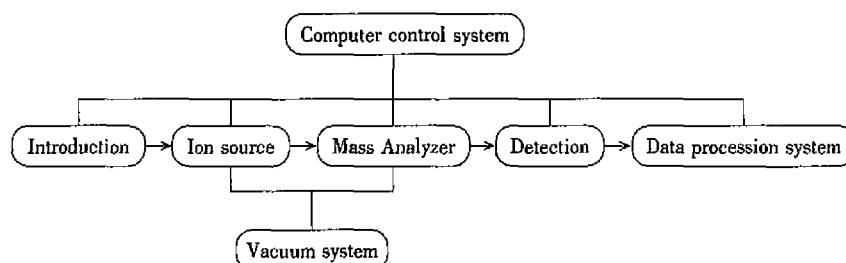
IX J Mass Spectrometry

Mass spectrometry is a method of analysis in which ions obtained by ionizing the analyte are separated according to their mass-to-charge ratios (m/z) and their spectral peak intensities are measured for analytical purpose. Mass is one of the intrinsic attributes of a substance, and different substances give different mass spectra. This attribute can be used for qualitative analysis (including molecular mass and relevant structural information). In addition, spectral peak

represented by a particular peak, and thus can be used for quantitative analysis.

A typical mass spectrometer comprises six parts: vacuum system-by which the vacuum status of each part of the mass and spectrometer is controlled; the sample introduction system-by which the sample is introduced into the suitable part of the ion source with the ionization technique as appropriate; the ion source-by which sample molecules are ionized and the ions produced are focused into an ion beam of certain energy level and in particular geometric shape; the mass analyzer-by which ions of different m/z ratios in the ion beam

origination from the ion source are separated according to factors such as spatial position, time sequence or orbital stability under the action of electromagnetic field (including magnetic field, combination of magnetic and electric fields, high-frequency electric field and high-frequency pulsed electric field etc.); the detector-by which post-separation ion signals are received, detected and recorded; data-processing system-by which the whole equipment is controlled by the computer system and data collection and procession is conducted. The diagrammatic sketch, which shows the operation principle, is as follows:



1. Vacuum System

The vacuum system is composed by mechanical pump and molecular pump. In order to get precise mass value, the collision between the ion and the remain gas molecular of test sample should be as little as possible. The method to realize this aim is letting the ion into the magnetic field under the high vacuum status, where the ion collector collects as many ions as possible and the vacuum extracts the gas molecular of the remaining test sample. To satisfy the test requirement, the pressure of the ion source should be reduced to 10^{-8} - 10^{-7} mmHg, while the pressure of the mass analyzer should be reduced to 10^{-7} - 10^{-8} mmHg.

2. Sample Introduction System and Interface Techniques

Introducing the sample into the mass spectrometer can be achieved by two means, direct introduction and through an interface.

(1) Direct Introduction

Under room temperature and normal pressure, a gaseous or liquid sample is introduced into the ion source by an adjustable spray device in the form of a neutral current. Volatile substances adhered to a solid or dissolved in a liquid can be enriched with the headspace analyzer, captured by the adsorption column, desorbed via temperature-programmed process, and delivered into the mass spectrometer through a capillary.

For solid samples, direct introduction by an insertion probe is usually adopted. The sample is introduced by heating it in a small crucible at the probe tip under the vacuum environment near the ion source, or desorption on a fast heating metallic filament in the ionization chamber, or by laser assisted desorption. Such introduction method, if coupled with electron impact ionization, chemical ionization and field ionization, is applicable to the analysis of materials with poor volatility or thermal stability.

(2) Interface

At present, the interface technique used for various couplings of liquid chromatography with mass spectrometry has undergone more rapid development over other sample introduction systems. This technique delivers chromatographic effluent into the mass spectrometry for ionization and subsequent spectrum analysis. Its major varieties include various types of spraying techniques (electrospray, thermal spray and ion spray), transmission device (particle beam) and particle-induced description (fast atom bombardment) etc.

Sample carried in the chromatographic mobile phase is ejected through a high-voltage (of several thousand volts) needle-shaped ejector and turned into charged droplets. Subsequent to the removal of solvent by drying air, the charged ions enter the mass analyzer directly through a capillary or pinhole. Conventional electrospray interface, suitable only for systems of mobile phase velocity from 1 to 5 $\mu\text{l}/\text{min}$, is used mainly for micro-column liquid chromatography. Since ions can carry multiple charges, the m/z ratios of macromolecular substances fall into the analytical ranges (m/z ratio less than 4000) of most quadrupole or magnetic mass analyzers. Thus, substances with high molecular mass up to several hundred thousand Daltons (Da) can be analyzed.

2) Thermal Spray Interface

Analyte carried in the mobile phase of a volatile buffer (such as ammonium acetate solution) is introduced through a duct of small diameter into the ion source and heated at the same time. Solvent is removed in the duct and the analyte enters the gaseous phase. Neutral molecules, via reaction with gaseous buffer ions (such as NH_4^+), are ionized by chemical ionization, and then delivered into the mass analyzer. The thermal spray interface is suitable for detecting various types of polarized compounds. Since the solvent requires a relatively higher temperature to evaporate, the analyte may be decomposed by heat.

3) Ion Spray Interface

On the basis of electrospray interface, spraying is assisted by gas to increase the mobile phase velocity to 1 ml/min. In electrospray and ion spray techniques, volatile buffer has to be used in mobile-phase system.

4) Particle Beam Interface

Chromatographic effluent is transformed into aerosol. Having its solvent removed in the solvent removal chamber, the neutral analyte molecules obtained are introduced into the ion source and ionized by means of electron impact ionization (EI) or chemical ionization (CI). The resulting spectra are thus classical EI or CI spectra, the former with a wealth of structure information. However, due to limitations with respect to polarity, thermal stability and molecular mass, particle beam interface is best suited for small organic molecules with masses less than 1000 Da.

5) Desorption Technique

In the coupling of microflow liquid chromatography with particle-induced desorption technique (fast atom bombardment), the chromatographic effluent is ionized by fast atom bombardment (FAB) and then analyzed by mass spectrometry.

the commonly used flow rate is 1 to 10 $\mu\text{l}/\text{min}$ and a trace of low-volatility liquid (such as glycerol) has to be added to the mobile phase. The liquid mixture flows through a capillary to a metal target set in the ion source. A liquid membrane is formed after solvent evaporation and is then bombarded by high-energy atoms or ions for ionization. The resulting spectra are similar to those resulted from fast atom bombardment or liquid secondary ion spectrum but the background from the sample matrix greatly reduced.

3. Ion Source

Function of an ion source determine the ionization efficiency and to a great extent the sensitivity of the mass spectrometer. There are two common types of ionization: one being the ionization of the sample in its gaseous phase at the ion source, and the other being the splashing of charged ions from solid surface or solution. In many cases, sample introduction and ionization take place simultaneously.

(1) Electron Impact (EI) Ionization

Upon entry into the ionization chamber, gaseous sample molecules are subject to bombardment by accelerated electron current emitted from tungsten or rhenium filament to produce positive ions. The pressure in the ionization chamber is maintained at the range between 10^{-4} and 10^{-6} mmHg. Energy gained from electron bombardment exceeds the ionization energy of the sample molecules, thus causing ionization or fragmentation of such molecules. EI spectra provide the most abundant structural information for organic compounds, and have a good reproducibility. The study on their fragmentation pattern is also the most comprehensive. A database of standard spectra of tens of thousand of organic compounds has been established for searching.

The drawback is that it is not suitable for samples with poor volatility and thermal stability.

(2) Chemical Ionization (CI)

Reagent gas with certain pressure is admitted to the source and ionized by a high energy electron beam or discharge. The ions resulted react further with reagent gas molecules, or have ion-molecule reaction with sample molecules. Sample molecules are then ionized through exchange of protons. Commonly used reaction gases include methane, iso-butane and ammonia. By chemical ionization, quasi-molecular ions are usually obtained. If proton affinity potential of the sample molecules is greater than that of the reagent gas, $[M+H]^+$ are produced; otherwise, $[M-H]^+$ are generated. Depending on the pressure of the reagent gas, CI ion source falls into three categories, namely atmospheric pressure, medium pressure (0.1-10 mmHg) and low pressure (10^{-6} mmHg). Atmospheric pressure CI ion source is suited to the coupling of chromatography with mass spectrometry, and the sensitivity is improved by two to three orders of magnitude over common CI ion source. Low pressure CI ion source can analyze less volatile samples at lower temperatures, and reagents with low volatility can be used but only in Fourier transform mass spectrometer.

(3) Fast Atom Bombardment (FAB)

The sample is dissolved in a matrix (usually solvents with high boiling points such as glycerol) to form a solution which is then applied to the metal surface for introducing into the FAB ion source. Neutral proton beam of an inert gas (such as xenon) is accelerated by strong electric field and aimed at the sample for bombardment. Associated ions existed in the matrix and the sample ions produced from FAB are both splashed into the gaseous phase and then delivered into the mass analyzer under the action of electric field. When an ion beam of an inert gas (such as caesium and argon) instead of the neutral atom beam is used for bombardment, a liquid secondary ion mass spectrometry will

FAB technique has the advantage of good ionization efficiency and is applicable to polar, poor volatility and thermal stability samples as well as those unsuited to EI or CI. When compared with EI, FAB can obtain stronger molecular ions or quasi-molecular ions; when compared with CI, FAB outperforms in giving more information about spectral peaks of fragment ions, which facilitates structural analysis. The limitation of FAB is the decreased sensitivity for non-polarized samples and the generation of more interference peaks from the matrix when the mass range is low (less than 400). FAB is a surface analysis technique, and care must be taken during sample preparation to optimize the condition of the surface. The adduction of sample molecules and alkaline metal ions, such as $[M+Na]^+$ and $[M+K]^+$, facilitates the formation of ions, as well as the ionization of biological molecules. Therefore, treatment of sample surface with sodium chloride solution may enhance the yield of adduct ions. Such yield can also be enhance by heating the sample in the course of analysis.

(4) Field Ionization (FI) and Field Desorption (FD)

FI ion source is formed by a pair of closely-spaced anode and cathode. By applying a high voltage between the two electrodes, a strong electric field up to 10^7 to 10^8 V/cm is formed around the cathode. Gaseous sample molecules near the cathode are ionized into positive molecular ions, and then accelerated to enter the mass analyzer. Liquid samples (solid samples dissolved with solvents first) can be ionized by FD. A metallic filament is immersed into the sample solution. Upon evaporation of the solvent, the filament, acting as the emitter, is delivered into the ion source. By a weak current applied to provide the energy for sample desorption, the sample molecules are dispersed into the high-field emission zone and ionized. FD is suited to nonvolatile and poor thermal stability samples. Both FI and FD can yield molecular ions easily.

(5) Atmospheric Pressure Ionization (API)

API is the most common ionization technique used in the coupling of liquid chromatograph with mass spectrometry. There are three types of common API ion source, namely atmospheric pressure electrospray ionization (APESI), atmospheric pressure chemical ionization (APCI) and atmospheric pressure photoionization (APPI). APESI, a process by which ions are produced from charged droplets following the removal of solvent, is suited to polar compounds which ionize easily in solutions. Given its capacity to handle multiple charges, it can analyze a wide range of molecular mass, and thus suited to small molecules as well as peptides, proteins and oligonucleotides. APCI, an ionization technique by which samples in gaseous and mobile phase are ionized by means of corona discharge under atmosphere pressure, is suited to considerably volatile samples, like non-polar compounds or compounds with low or medium polarity. Since ions with multiple charges are rarely formed, the analyzable range of molecular mass is subject to the mass range of the mass analyzer. Unlike APCI, APPI substitutes ultra-violet light for corona discharge to ionize gas-phase sample by photochemical action. APPI is suitable for non-polar compounds. In an API setting, the ion source is separated from the highly vacuum mass analyzer. The switch between different API ion sources is therefore very convenient.

(6) Matrix-assisted Laser Desorption Ionization (MALDI)

Sample dissolved in a suitable matrix is deposited on the metal support, and then exposed to ultraviolet or infrared pulsed laser radiation of high intensity to achieve ionization. This technique is mainly used for the analysis of macromolecules with mass up to 100000 Da. Its usage is limited to the ion source of the time-of-flight analyzer.

Plasma is composed of free electrons, ions and neutral atoms or molecules. It is largely a neutrally charged gas with an internal temperature as high as several thousand or even up to ten thousand degree Celsius. The sample, carried by a carrier gas through the centre of the plasma blaze, is evaporated and ionized quickly and introduced into the mass analyzer via an ion-led interface. Under extremely high temperature, the sample is completely evaporated and decomposed, resulting in a high percentage of ionization. It can therefore give relatively higher detection sensitivity for almost all elements. As the molecular structure of the compound will be damaged under such conditions, the use of ICP is limited to elemental analysis.

4. Mass Analyzer

A mass analyzer separates charged ions by their m/z ratios for recording mass and abundance of different ions. The two main technical parameters of a mass analyzer are the detectable range of m/z ratios (mass range) and the resolving power.

(1) Magnetic Sector Analyzer

Ions generated from the ion source are focused into an ion beam under a sector-type magnetic field and through a small slit. After exiting the ion source, the ions are subjected to a magnetic field perpendicular to their forward direction. Under the action of magnetic field, ions of different m/z ratios are deflected with various degree of deviation from their forward direction, resulting in the scattering of the ion beam. Given the difference in m/z ratios, these ions will have specific radius of curvature in their motion paths under the sector field. By varying the strength of the magnetic field, ions passing through the small slit sequentially are detected. Spatial separation of ions is then realized and their mass spectra obtained.

(2) Quadrupole Analyzer

A quadrupole analyzer gets its name from the four parallel metal rods it comprises. The ion beam is focused on the axis parallel to the rods. A direct current (DC) potential of fixed and a radio frequency (RF) potential are applied to the rods, making the two pairs of rods in opposite electrical potential. For given combination of DC and RF potential, ions of a particular m/z ratio travel steadily along the axis, while ions of other ratios are deflected to the sides and lost. By varying the combination of DC and RF potential maintaining a fixed slope, mass scanning can be achieved. A quadrupole analyzer exhibits a relatively higher sensitivity in selected ion analysis.

(3) Ion Trap Analyzer

It consists of a quadrupole-like ring electrode between two endcap electrodes. The endcap electrodes are held either at ground potential or at a DC voltage while RF voltage is applied to the ring electrode. With appropriate voltages, a potential energy trap (ion trap) is formed. The ion trap can capture ions within certain mass range, depending on the RF voltage level. Ions are stored in the trap and when a certain quantity is reached, the RF voltage of the ring electrode will be increased. Ions leaving the trap in descending order of their m/z ratios are detected by the electron multiplier. The current technology can already allow the ion trap analyzer to analyze ions of high m/z ratio, up to several thousand Da. The ion trap analyzer will decrease less sensitivity when a full-scan mode is used. Moreover, a single ion trap can achieve the function of multiple-stage mass spectrometry (MS^n) with a pre-set time sequence.

(4) Time of flight (TOF) Analyzer

Ions of same kinetic energy but different masses are separated according to their flight velocities. For a fixed distance of ion flight, ions of different masses vary in TOF. Ions of smaller

TOF of an ion is proportional to the square root of its m/z ratio. Ions are introduced into the mass spectrometer in discrete packets so that their flights start at the same point and TOF can be measured sequentially. Ion packets are either through a pulsed ionization process or through a gating system in which ions are produced continuously, but are introduced only at given times into the flight tube. Newly developed TOF analyzers, with its wider analyzable mass range and higher mass resolution, are particularly suitable for analysis of biological macromolecules like proteins.

(5) Fourier Transform Analyzer

Under a magnetic field of flux density, ions will move in circular orbits and their paths of movement are restricted by a resonant crossover electric field. When the crossover electric field frequency equals the cyclotron frequency, ions will be accelerated steadily, with the corresponding increases to their path radius and kinetic energy levels. As soon as the electric field disappears, the orbiting ions will create an alternate current on the electrodes and their masses can be obtained by analyzing the signal frequencies. Time and corresponding frequency spectrum are then imputed into the computer for Fourier transformation to produce the mass spectrum. The analyzer has the advantage of high resolution, with a precision as high as one milli-Dalton in the m/z ratio.

5. Tandem Mass Spectrometry (MS/MS) and Coupling Techniques

(1) MS/MS

Two or more mass spectrometers connecting together are called MS/MS. The simplest MS/MS consists of two mass spectrometers; ions will be pre-separated or modified with imparting energy at the first mass analyzer (MS_1) and delivered to the second one (MS_2) for result analysis. The most common type of MS/MS is triple quadrupole MS/MS, with the first quadrupole (Q_1) and the third quadrupole (Q_3) functioning as MS_1 and MS_2 respectively while Q_2 performing the function of bombarding various peaks produced by MS_1 to achieve fragmentation of the precursor ions before their entry into MS_2 for analysis. MS/MS formed by different mass analyzers are now available, such as Q-TOF and TOF-TOF tandems, expanding its application. Ion trap and Fourier transform analyzers can achieve time series MS_n scan at different time sequences.

One of the most basic functions of MS/MS is to determine the relationship between the precursor ions in MS_1 and the product ions in MS_2 . By the scan modes of MS_1 and MS_2 , such as product ion scan, precursor ion scan and neutral loss scan, the relationships between ions of different mass can be identified. Precursor ion fragmentation can be achieved by the following: collision-induced dissociation, surface induced dissociation and laser-induced dissociation. Dissociation without induction is known as metastable dissociation.

MS/MS has many advantages in mixture analysis. Coupling gas chromatography or liquid chromatography with mass spectrometry allows assay to be carried out even without chromatographic baseline separation of the substance. MS/MS can select precursor ions from the sample for analysis, without being interfered by other substances.

MS/MS can be widely used in the pharmaceutical field. Product ion scan can give qualitative information on the precursor ions of the drug's main ingredients, impurities and other substances contained, aiding the identification of unknown substances. It can also be used for identifying the sequence of peptides and amino acid of proteins.

In pharmacokinetical studies involving quantitative analysis of low-concentration samples in complex biological matrices, multiple reaction monitoring (MRM) mode can be used to reduce interference. In the analysis of specific ions of a drug, interfering signals from other compounds in the matrix

MS₂ on fragments of specific ions can reduce such interference. MRM can also perform quantitative analysis of several compounds at the same time. In the study of drug metabolism, neutral loss can be used to search for all the analyte all its ions containing the same functional group that is lost as a neutral fragment, such as the loss of neutral carbon dioxide in carboxylic acids, so that molecules with the common structural features can be identified. If the fragments lost are in the form of ions, the use of precursor ion scan can identify all the precursor ions losing such fragments.

(2) Coupling Techniques

Apart from acting as a sample introduction device for mass spectrometer, chromatography can perform preliminary sample separation and purification. Coupling chromatography with mass spectrometry can, therefore, carry out separation and analysis of complex systems. With the compound's retention time obtained by chromatography and its molecular mass and structural information by mass spectrometry, highly effective identification and assay of the compound in a complex system or mixture can be achieved. Among the coupling techniques available, gas chromatography/mass spectrometry (GC/MS) and high-performance Liquid chromatography/mass spectrometry (HPLC/MS) have been widely used in drug analysis.

1) GC/MS

GC effluent is already in the vapor state and can be admitted into MS directly. As working pressures of GC and MS differ by several orders of magnitude, various gas separators were used between them at the early stage coupling to address the difference in working pressure. With the application of capillary GC and high-speed vacuum pumps, however, GC effluent can now be delivered into MS directly.

2) HPLC/MS

As mentioned earlier before, HPLC/MS interface is mainly used for analysis of substances that cannot be analyzed by GC/MS, or are of poor thermal stability, strong polarity and high molecular mass, such as biological samples (drugs and their metabolites) and biological macromolecules (peptides, proteins, nucleic acids and polysaccharides).

3) Capillary electrophoresis/mass spectrometry (CE/MS)

CE is suitable for separation and analysis of ultra-trace sample (nL volume) and for special purposes (such as chiral enantiomer separation). CE effluent can be introduced into MS directly or can be added to the assisted mobile phase compatible with the mass spectrometer.

4) Supercritical fluid chromatography/mass spectrometry (SFC/MS)

SFC often uses supercritical fluid carbon dioxide as the mobile phase, suitable for separation of substances of low or medium polarity. Coupling SFC with MS can be achieved by the use of a separator between the chromatographic column and the ion source.

5) Inductively coupled plasma/mass spectrometry (ICP/MS)

Coupling ICP to MS with the former acting as the ion source is mainly used for elemental analysis and elemental morphology analysis.

6. data processing and application

Detectors commonly used are photomultipliers and electron multipliers. Signals collected are multiplied and digitalized for feeding into the computer for processing to obtain the mass spectrum.

In a spectrum, the quantity of ions is indicated by abundance, i.e. the number of ions of a given m/z ratio. As it is impossible to determine the "number" of a specific ion, relative abundance is generally used to represent its

base peak, while abundance of other ions is represented by a percentage relative to the base peak. A mass spectrum is produced by m/z ratios and relative intensities of ions within the detectable mass range of the mass spectrometer. In LC/MS and GC/MS, chromatographic retention times of common analytes together with the relative intensities of their ions obtained by MS form the total ion current chromatogram. One can also fix a specific m/z ratio and perform selected-ion monitoring (SIM) on the chromatographic effluent to obtain selected-ion chromatogram. Resolution, sensitivity and mass range are the most important parameters of a mass spectrometer.

1) Resolution

The ion separation capability of a mass spectrometer is called resolution, which is generally defined as the ratio between average peak mass and peak mass difference of two adjacent peaks of the same height with a 10% valley-to-peak height level. Mass spectrometers of low, medium and high resolution refer to resolution at 100 to 2000, 2000 to 10000 and over 10000 respectively.

$$R = \frac{M}{\Delta M}$$

Where, $M = \frac{M_1 + M_2}{2}$, $\Delta M = |M_1 - M_2|$

2) Sensitivity

The sensitivity is the measurement of the relationship between the intensity of the mass peak and the quantity of the test sample. In practice, the quantity of the test sample should be as less as better while the intensity of the mass peak should be as more intensive as better. Generally speaking, there are interaction between the resolution and the sensitivity.

3) Mass range

The mass range means the largest mass number of the ion, which can be measured precisely by the equipment. The obtainment of the largest mass number is directly related with the accelerating voltage. The accelerating voltage forms a inverse ratio with the m/z ratio. The reduction of the accelerating voltage will increase the largest mass number, but it also will reduce the resolution and the sensitivity at the same time.

7. Application

The main applications of mass spectrometry in the pharmaceutical field are qualitative assay, structural analysis and quantitative analysis of drugs.

The loss or gain of one electron by a neutral molecule results in the m/z ratio of molecular ions equaling the molecular mass number. The precise mass number of ions can be obtained by the use of high-resolution mass spectrometer or reference peak matching method, and the molecular formula of the compound can then be worked out. Cleavage of various chemical bonds of the molecular ions produces fragment ions, which aid in structural elucidation and identification.

When used for quantitative analysis, mass spectrometry has advantages in selectivity, precision and accuracy. External or internal standards may be used but the latter has higher precision than the former. The internal standard used in quantitative analysis can be either structural or stable isotope analogs, the former requires a lower cost but the latter yields higher precision and accuracy. When using isotopic substances are used as the internal standard, one has to make sure that the isotopic label are not exchangeable under the sampling separation and ionization condition. The use of FAB and LC/MS (thermal spray and electrospray) in quantitative analysis generally requires stable isotopes as the internal standard. The relative abundance of the analyte and

monitors specific ions of the analyte and the internal standard). When compared to a full scan, SIM exhibits increased selectivity and sensitivity because of the long integration time of ion current. By using the chromatographic peak area or peak height ratio of the analyte and the internal

standard, the calibration curve can be obtained. The analyte quantity can then be worked out based on the chromatographic peak area or peak height ratio of the analyte and the internal standard in the sample.

Appendix X

X A Determination of Disintegration

Disintegration is provided to determine whether the oral solid preparations disintegrate or disperse into fragments or particles within a prescribed time when placed in a liquid medium under the prescribed experimental conditions.

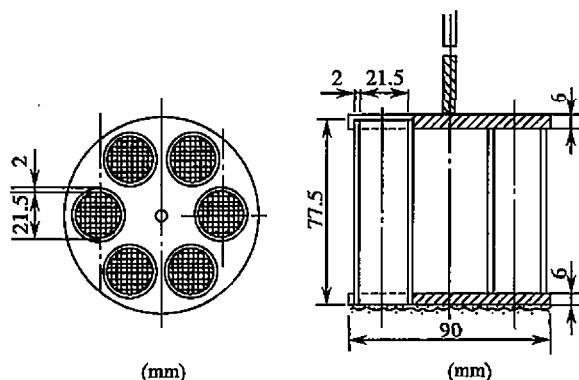
Disintegration is not required for the preparations which, except fragments of undissolved tablet coating or of capsule shell, remains on the screen of the test apparatus. Disintegration can be also considered to be achieved when the residue remained consists of a soft mass having no palpably, unmoistened core, or floats because of light weight.

Disintegration is not required for the preparations which comply with the requirements for Dissolution, Drug release or Disintegration for Suppositories and Vaginal Tablets.

1. Tablets

Apparatus The apparatus mainly consists of a basket-rack assembly with disks and a metallic device capable of raising and lowering the basket in the liquid medium at a constant rate between 30 and 32 cycles per minute through a distance of $55 \text{ mm} \pm 2 \text{ mm}$.

Basket-rack assembly The basket-rack assembly consists of six glass tubes, each $77.5 \text{ mm} \pm 2.5 \text{ mm}$ long, 21.5 mm in internal diameter with a wall of 2 mm in thickness. The tubes are held in a vertical position by two transparent plastic plates, each about 90 mm in diameter and 6 mm in thickness, with six holes, each about 26 mm in diameter. On the top of the upper plastic plate is a stainless-steel plate about 90 mm in diameter and 1 mm in thickness, with six holes each about 22 mm in diameter. Attached to the under surface of the lower plate is a disk of stainless-steel wire gauze about 90 mm in diameter, with apertures of 2.0 mm in internal diameter. A stainless-steel central shaft about 80 mm long is fixed with the upper plastic plate and stainless-steel plate. The stainless-steel plate, the two plastic plates and the wire gauze are fixed together by three screws (as Fig. 28).



Disks The disk is made of a smooth transparent plastic material having a specific gravity of $1.18-1.20$ with $20.7 \text{ mm} \pm 0.15 \text{ mm}$ in diameter, and $9.5 \text{ mm} \pm 0.15 \text{ mm}$ in thickness. It has five holes with 2 mm in diameter, one of the holes is located in the center and the others at an equal distance of 6 mm from the central hole. Equally spaced on the sides of the disk are four V-shaped notches. The dimensions of each notch are such that the upper openings are 9.5 mm wide and 2.55 mm deep and the lower openings are 1.6 mm wide and 1.6 mm deep (as Fig. 29).

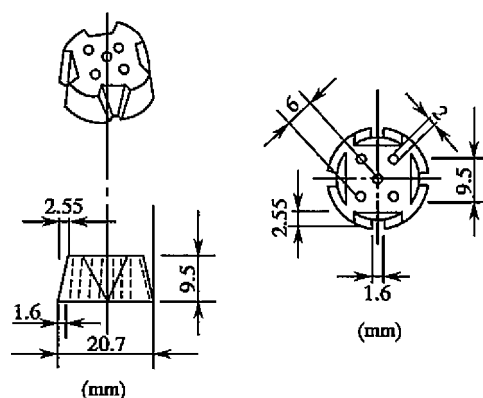


Fig. 29

Procedure The basket is suspended in a water bath preferably using a 1000 ml of beaker, maintained at $37^\circ\text{C} \pm 1^\circ\text{C}$, the volume of the fluid in the vessel is adjusted appropriately so that at the highest point of the upward stroke the wire mesh remains at least 15 mm below the surface of the fluid and descends to a distance not less than 25 mm from the bottom of the vessel on the downward stroke.

Unless otherwise specified, place 1 tablet in each of the six tubes of the basket and operate the apparatus. All of the tablets should disintegrate completely within 15 minutes. If 1 tablet fails to disintegrate completely, repeat the test on 6 additional tablets. All of the tablets should comply with the requirement.

Film-coated tablets Carry out the test as described above. Replacing the water in the beaker with hydrochloric acid ($9 \rightarrow 1000$), all of the tablets should disintegrate within 30 minutes. If any one of the tablets has not disintegrated, repeat the test on additional six tablets; all the tablets should comply with the test.

Sugar-coated tablets Carry out the test as described above. All of the tablets should disintegrate within 60 minutes. If any one of the tablets has not disintegrated, repeat the test on additional six tablets; all the tablets should comply with the test.

Enteric-coated tablets Enteric-coated tablets are tested in the same way as described above using hydrochloric acid solution ($9 \rightarrow 1000$) as the immersion fluid and the tablets should disintegrate within 2 hours.

2 hours. Remove the basket, wash the tablets with a small quantity of water, add a disk to each tube. Repeat the operation using phosphate BS (pH 6.8) as the immersion fluid, all tablets should disintegrate completely within 1 hour. If 1 tablet fails to comply with the test, repeat the operation with additional 6 tablets. All the tablets should comply with the test.

Buccal tablets Unless otherwise specified, buccal tablets are tested in the same way as described above. All of the tablets should disintegrate or dissolve within 30 minutes. If any one of the tablets has not disintegrated, repeat the test on additional six tablets. All the tablets should comply with the test.

Sublingual tablets Unless otherwise specified, sublingual tablets are tested in the same way as described above. All of the tablets should disintegrate and dissolve within 5 minutes. If any one of the tablets has not disintegrated, repeat the test on additional six tablets. All the tablets should comply with the test.

Soluble tablets Unless otherwise specified, soluble tablets are tested in the same way as described above maintained the temperature at 15-25°C. All of the tablets should disintegrate and dissolve within 3 minutes. If any one of the tablets has not disintegrated, repeat the test on additional six tablets. All the tablets should comply with the test.

Colon-located enteric-coated tablets Unless otherwise specified, colon-located enteric-coated tablets are tested in the same apparatus as described under the individual monograph. All of the tablets should not release and disintegrate in the sulfuric acid solution (9→1000) and the phosphoric acid buffer solution with pH value less than 6.8, but release and disintegrate in the phosphoric acid buffer solution with pH value between 7.8 and 8.0 within 1 hour, and the tablet core also disintegrates. If any one of the tablets has not disintegrated, repeat the test on additional six tablets. All the tablets should comply with the test.

Effervescent tablets Effervescent tablets are tested in the following way. Place one tablet in a 250 ml beaker containing 200 ml of water maintained at 15-25°C, numerous gas bubbles are evolved. When the evolution of gas around the tablet or its fragments has ceased the tablets disintegrate, dissolve or disperse in the water so that no agglomerates of particles remain. Unless otherwise specified, the preparation being examined complies with the test if 6 tablets used in the test disintegrate in the manner prescribed within 5 minutes. If any one of the tablets has not disintegrated, repeat the test on additional six tablets. All the tablets should comply with the test.

2. Capsules

Unless otherwise specified, hard capsules or soft capsules are tested comply with the test as described above. If the capsules float on the surface of the water, a disk may be added. The hard capsules should disintegrate within 30 minutes and the soft capsules disintegrate within 1 hour. If one of the capsules has not disintegrated, repeat the test on further six capsules, all the capsules should comply with the test. For soft capsules, replacing the water in the beaker with simulated gastric fluid.

Unless otherwise specified, enteric capsules are tested in the same way as described above using hydrochloric acid solution (9→1000) as the immersion fluid and the capsule shells show no evidence of cracking, disintegrating in 2 hours. Remove the basket, wash the capsules with a small quantity of water, add a disk to each tube. Repeat the operation using simulated intestinal fluid as the immersion fluid, all capsules should disintegrate completely within 1 hour. If 1

with another 6 capsules. All the capsules should comply with the test.

3. Dripping pills

Carry out the test with the same apparatus as described as tablets using the stainless steel wire gauze with apertures of 0.425 mm in internal diameter. Carry out the test as described above using 6 dripping pills, unless otherwise specified. All of the dripping pills disperse completely within 30 minutes, and the coated-dripping pills should disperse completely within 60 minutes. If any one of the dripping pills has not dispersed completely, repeat the test on further six dripping pills, all the dripping pills should comply with the test.

Dripping pills made of gelatin matrix may be tested in simulated gastric fluid.

Annotation Simulated gastric fluid Add about 800 ml of water and 10 g of pepsin to 16.4 ml of dilute hydrochloric acid, mix well, dilute with water to produce 1000 ml.

Simulated intestinal fluid See Phosphate-Pancreatin BS (pH 6.8) (Appendix XV D).

X B Disintegration Test for Suppositories and Vaginal Tablets

The test for disintegration of suppositories and vaginal tablets determines whether a solid dosage form such as suppositories and vaginal tablets can disintegrate, soften, dissolve or disperse under the specified experimental conditions.

1. Suppositories

Apparatus The apparatus is composed of a transparent sleeve and a metal device (as Fig. 30).

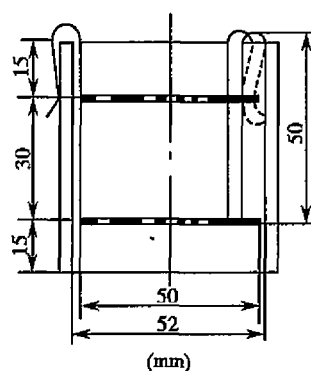


Fig. 30

Transparent sleeve The transparent sleeve is made of glass or suitable plastic, with a height of 60 mm, an internal diameter of 52 mm and an appropriate wall thickness.

Metal device The metal device consists of two stainless steel metal discs and three metal hooks. Each of the disc has a diameter of 50 mm and contains 39 holes, each 4 mm in diameter (as Fig. 31). The discs are separated by a distance of 30 mm. The metal device is attached to the outer sleeve by means of the three equally-spaced hooks.

Procedure Take 3 suppositories being examined and allow to stand at room temperature for 1 hour. Place them on the lower discs of 3 metal devices respectively, then insert the devices into separate sleeves and fix them by means of the hooks. Unless otherwise specified, place each piece of the

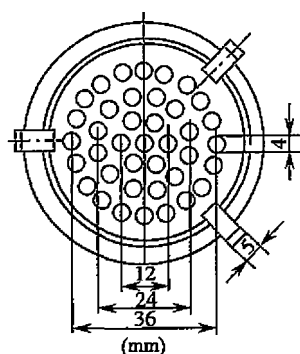


Fig. 31

above apparatus in 3 vessels separately, each containing not less than 4 litres of water at $37.0^{\circ}\text{C} \pm 0.5^{\circ}\text{C}$ and fitted with a slow stirrer and a means of holding the apparatus vertically 90 mm below the surface of water, after each 10 minutes invert each apparatus without allowing it to emerge from the liquid.

Interpretation Unless otherwise specified, all of the fat-based suppositories should disintegrate, soften or have no solid core offering resistance to pressure within 30 minutes; all of the water-soluble suppositories should completely dissolve within 60 minutes. If one of the suppositories fails to comply with the requirements, repeat the test on 3 additional suppositories and all of them should comply with the requirements.

2. Vaginal tablets

Apparatus The apparatus is the same as that used for suppositories except that set the hook-end upside down in the vessel (as Fig. 32).

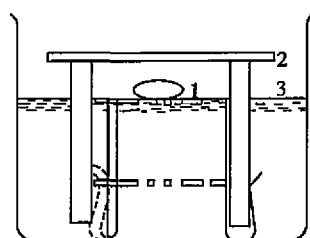


Fig. 32
1—Vaginal tablet; 2—Glass plate;
3—Water surface

Procedure Adjust the water surface level until the holes of the upper metal disc are just covered by a uniform layer of water. Put 3 vaginal tablets being examined on separate upper discs and cover the apparatus with a glass plate to maintain appropriate humidity.

Interpretation Unless otherwise specified, all of the vaginal tablets should dissolve or disintegrate into fragments and pass through the perforated plates or only remain a small amount of soft masses which have no solid core within 30 minutes. If one of the tablets fails to comply with the requirements, repeat the test on 3 additional tablets and all of them should comply with the requirements.

X C Dissolution Test

Dissolution test is used to determine the dissolution rate and

tablets, capsules or granules under the specified conditions. When dissolution test is specified in the monograph, it is understood that disintegration test can be exempted.

Method 1

Apparatus As Fig. 33.

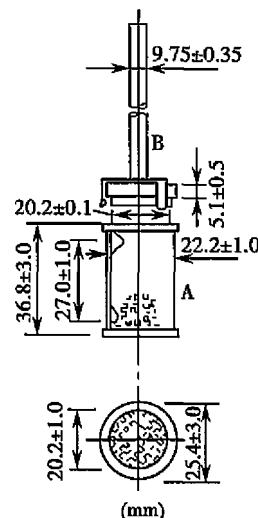


Fig. 33

(1) The basket assembly consists of a basket and a shaft made of stainless steel (The materials should not adsorb, or interfere with the specimen being tested.). The basket (A) is made of stainless steel woven cloth with a nominal aperture of 0.40 mm; the stainless steel wire is 0.25 mm in diameter. The basket is cylindrical, $20.2 \text{ mm} \pm 1.0 \text{ mm}$ in internal diameter, with a metallic flanged rim at each end. The shaft (B) is $9.75 \text{ mm} \pm 0.35 \text{ mm}$ in diameter and is connected to the metallic lid of the basket. The lid has a vent hole, 2.0 mm in diameter and 3 retention springs with 3 tangs on 120° centers. The upper part of the lid has a diameter equal to the outside diameter of the basket and the lower part has a diameter equal to the inside diameter of the basket.

(2) The vessel is cylindrical, made of hard glass or other inert, transparent or brown materials, with a hemispherical bottom and a nominal capacity of 1000 ml, internal diameter $102 \text{ mm} \pm 4 \text{ mm}$, height $168 \text{ mm} \pm 8 \text{ mm}$. A fitted cover may be used to retard evaporation, the cover has a number of holes, the central one is used for the shaft to pass through, and the others are used for the insertion of thermometer and withdrawal of specimens. The vessel is placed in a constant temperature water bath.

(3) The shaft is connected with a motor with a speed regulator capable of maintaining the speed of rotation of the basket within $\pm 4\%$ of that specified in the individual monograph. When the motor is in operation, no part of the assembly, including the environment in which the assembly is placed, contributes any significant motion or vibration beyond that due to the smoothly rotating element. The shaft is positioned so that its axis is not more than 2 mm at any point from the vertical axis of the vessel. The wobble range is not greater than 1.0 mm during the rotation of the basket.

(4) The apparatus with six sets of assembly described above can be used to determine 6 specimens at the same time.

Assay Before test, adjust the apparatus so that the distance between the inside bottom of the vessel and the bottom of the basket is $25 \text{ mm} \pm 2 \text{ mm}$. Unless otherwise specified in the monograph, place 900 ml of de-aerated medium in each of 6 vessels, warm in a water bath to maintain a temperature at $37^{\circ}\text{C} \pm 0.5^{\circ}\text{C}$. Place 1 tablet (capsule or packet) in each of

speed to that specified in the monograph. Lower the baskets into the vessels, start the counting of time when the specimens immerse into the dissolution medium. Unless otherwise specified in the monograph, withdraw an aliquot of solution from a zone midway between the surface of the dissolution medium and the top of the rotating basket, 10 mm apart from the wall of the vessel within the time interval specified, or at each of the times stated (If two or more sampling times are specified, the sum of the volume of the samples withdrawn should be within $\pm 1\%$ of the volume of the dissolution medium. If the sum is greater than 1%, replace the aliquots withdrawn for analysis with equal volumes of fresh dissolution medium at 37°C immediately, or correct for the volume change in the calculation.). Filter immediately through a suitable membrane (The filter, made of inert material, has an appropriate pore size of not more than $0.8\ \mu\text{m}$ in diameter, should cause no significant absorption of the active ingredient from the dissolution solution and contain no materials extractable by the dissolution medium that would interfere with the prescribed analytical procedures). Complete taking and filtering a specimen within 30 seconds. Carry out the assay of active ingredient as directed in the monograph using the successive filtrate and calculate the amount of active ingredient dissolved from each tablet (capsule or packet).

Interpretation Unless otherwise specified in the monograph, the requirements are met if the quantities of active ingredient dissolved from tablets (capsules or packets) conform to one of the following states.

(1) The amount of active ingredient dissolved from each of 6 tablets (capsules or packets) is not less than the specified quantity (Q) calculated on the labelled content.

2. If 1-2 of 6 tablet (capsules or packets) fail the requirement, but not less than $Q-10\%$ and the average amount of active ingredient dissolved is not less than Q .

(3) If 1-2 of 6 tablets (capsules or packets) fail the requirement, and only 1 of tablets (capsules or packets) is less than $Q-10\%$ but not less than $Q-20\%$, and the average amount of active ingredient dissolved is not less than Q , repeat the test on 6 additional tablets (capsules or packets); if 1-3 of the second set of 6 tablets (capsules or packets) are less than Q , and only 1 of tablets (capsules or packets) is less than $Q-10\%$ but not less than $Q-20\%$, and the average amount of active ingredient dissolved is not less than Q .

The 10% and 20% values stated above interpretation are expressed as percentages of the labelled content.

Method 2

Apparatus As Fig. 34.

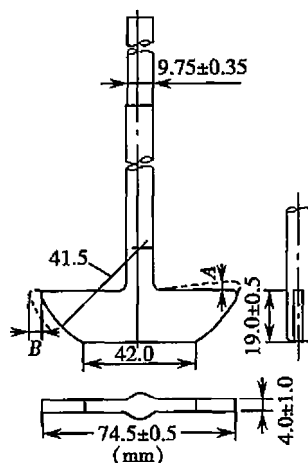


Fig. 34

Use the same assembly as that used in method 1, except that a paddle (A) is used instead of the basket. The paddle is made of stainless steel (as that used in method 1), the paddle blade and the lower part of shaft may be coated with a suitable inert material (such as Teflon). The shaft is positioned so that its axis is not more than 2 mm at any point from the vertical axis of the vessel. The wobble range of A, B is not greater than 0.5 mm during the rotation of the paddle.

Assay Before test, adjust the apparatus so that the distance between the lower edge of the blade and the inside bottom of the vessel is $25\text{ mm} \pm 2\text{ mm}$. Unless otherwise specified in the monograph, place 900 ml of de-aerated medium in each of 6 vessels, warm in a water bath to maintain a temperature of $37^\circ\text{C} \pm 0.5^\circ\text{C}$. Start the motor and adjust the rotational speed to that specified in the monograph. Place 1 tablet (capsule or packet) in each of 6 vessels (If tablet or capsule float, a sinker may be used, as Fig. 35). Start the counting of time when the specimens immerse into the dissolution medium. Unless otherwise specified in the monograph, withdraw an aliquot of the solution from a zone midway between the surface of the dissolution medium and the top of the blade, 10 mm apart from the wall of the vessel within the time interval specified, or at each of the times stated (If two or more sampling times are specified, as described in method 1). Filter immediately through a membrane (as that used in method 1). Complete taking and filtering a specimen within 30 seconds. Carry out the assay of active ingredient as directed in the monograph using the successive filtrate and calculate the amount of active ingredient dissolved from each tablet (capsule or packet).

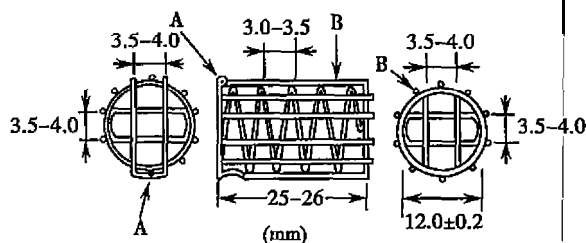


Fig. 35

A: Acid-resistant wire clasp
B: Acid-resistant wire support

Interpretation Unless otherwise specified, proceed as directed for interpretation under method 1.

Method 3

Apparatus As Fig. 36.

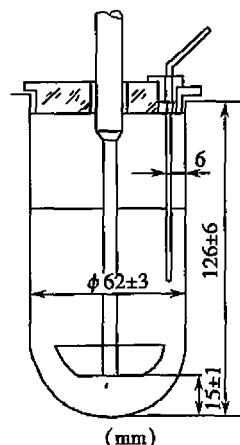


Fig. 36

(1) The paddle, as Fig 37, is made of stainless steel (as that used in method 1); the upper part of the shaft is $9.75 \text{ mm} \pm 0.35 \text{ mm}$ in diameter and the lower part is $6.0 \text{ mm} \pm 0.2 \text{ mm}$ in diameter. The shaft is positioned so that its axis is not more than 2 mm at any point from the vertical axis of the vessel. The wobble rang A, B are not great than 0.5 mm during the rotation of the paddle.

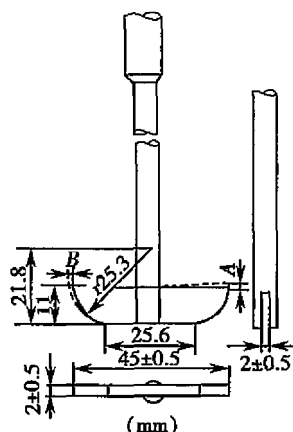


Fig. 37

(2) The vessel is cylindrical, made of hard glass or other inert, transparent or brown materials, with a hemispherical bottom and a nominal capacity of 250 ml, internal diameter $62 \text{ mm} \pm 3 \text{ mm}$, height $126 \text{ mm} \pm 6 \text{ mm}$. The others used are the same assembly as that used in method 1 (2).

(3) The motor is connected with the shaft. The speed of the paddle is maintained within $\pm 1\%$ of that specified in the monograph. The others used are the same assembly as that used in method 2.

Assay Before test, adjust the apparatus so that the distance between the lower edge of the blade and the inside bottom of the vessel is $15 \text{ mm} \pm 2 \text{ mm}$. Unless otherwise specified in the monograph, place 100-250 ml of de-aerated medium in each vessels (a small, loose piece of anticorrosive materials such as metal filament may be attached to capsule that would otherwise float), and the rest of the procedure is the same as described in method 2. Withdraw an aliquot of the solution from a zone midway between the surface of the dissolution medium and the top of the blade, 6 mm apart from the wall of the vessel.

Interpretation Unless otherwise specified, proceed as directed for interpretation under method 1.

Dissolution conditions and attentions

(1) Apparatus Suitability Test Individually test 1 tablet of the dissolution calibrator, according to the operating conditions specified. The apparatus is suitable if the results obtained are within the acceptable range stated in the certificate for the calibrator in the apparatus test.

(2) Dissolution medium Use the dissolution medium specified in the monograph, freshly prepared and de-aerated before use [Dissolved gases can cause bubbles to form, which may change the results of the test. In such cases, dissolved gases should be removed prior to testing. Methods of de-aeration are as follows: Heat the medium, while stirring gently, to about 41°C , and continue stirring under vacuum for about 5 minutes; or continue boiling 15 minutes (about 5000 ml). Other validated de-aeration techniques for removal of dissolved gases may be used, such as ultrasonication or filtration]. If the dissolution medium is a buffered solution, adjust the solution so that its pH is within 0.05 unit of the pH specified in the monograph.

(3) Sampling time Specimens are to be withdrawn only at

the specified time of the monograph. Complete sampling specimens from 6 vessels within 1 minute.

(4) Where capsule shells interfere with analysis, remove the contents of not less than 6 capsules as completely as possible, and dissolve the empty capsule shells in the specified volume of dissolution medium. Perform the analysis as directed in the monograph. Make any necessary correction. Correction factors greater than 25% of the labelled content are unacceptable. If correction factors are not more than 2% of the labelled content, the interference of capsule shells is negligible.

(5) Unless otherwise specified in the monograph, withdraw samples at 45 minutes and the amount of active ingredient dissolved is not less than 70% of the labelled content.

(6) Unless otherwise specified in the monograph, place only 1 tablet (capsule or packet) in each of 6 vessels.

X D Drug Release Test

Drug release test is defined as the rate and degree at which a medicament is released from sustained-release preparation, controlled-release preparation, enteric-coated preparation or transdermal patches in the specified conditions when drug release test is specified in the monograph, it is understood that dissolution test or disintegration test can be exempt. The categories of sustained-release preparation, controlled-release preparation and enteric-coated preparation comply with Appendix XIX D.

Apparatus Unless otherwise specified, use the same assembly that used in dissolution test (Appendix X C).

Method 1 Used for sustained-release preparation or controlled-release preparation.

Assay Carry out the dissolution test accordingly with generally 3 sampling times. Withdraw an aliquot of the solution at the specified site where the specimens are taken after a specified time, and filter immediately through a membrane with pores of less than $0.8 \mu\text{m}$ in diameter. Complete sampling and filtering the specimen within 30 seconds. Replace the aliquots with fresh medium in equal volume immediately. Carry out the assay of active ingredient as directed in the monograph using the successive filtrate and calculate the amount of active ingredient released from each tablet (or capsules).

Interpretation Unless otherwise specified, the requirements are met if the quantities of active ingredient released from tablets (capsules) conform to one of following states.

(1) The amount of active ingredient released from each of 6 tablets (capsules) lies in the specified range, calculated on the labelled content at each test time.

(2) If 1-2 of tablets (capsules) fail the requirement, but not exceed 10% and the average amount of active ingredient released lies in the specified range at each test time.

(3) If 1-2 of tablets (capsules) fail the requirement, and only 1 of tablets (capsules) exceed 10%, but not exceed 20%, and the average amount of active ingredient released lies in the specified range at each test time, repeat the test on 6 additional tablets (capsules); if 1-3 of tablets (capsules) of the total of 12 tablets (capsules) exceed the specified range, and only 1 of tablets (capsules) exceeds 10%, but not exceed 20%, and the average amount of active ingredient released lies in the specified range at each test time.

The 10% and 20% values stated above interpretation are expressed as percentages of the labelled content. Exceeding

the specified range 10% means that the amount of active ingredient released from each tablet is not less than 10% of the lower limit of the specified range, and not more than 10% of the upper limit of the specified range at each time. The amount of active ingredient released at each time includes the amount of active ingredient release at terminal time.

Method 2 Used for enteric-coated preparation.

(1) **The amount released in acid** Unless otherwise specified, place 750 ml of 0.1 mol/L hydrochloric acid solution in each of 6 vessels, which are partially immersed in a suitable water bath that permits to keep the temperature inside the vessel at $37^{\circ}\text{C} \pm 0.5^{\circ}\text{C}$ during the test, adjust the rotational speed and maintain it stable. Carry out the method specified in monograph, place 1 tablet (capsule or packet) in each of 6 dry baskets or 6 vessels, start the motor to operate for 2 hours. Withdraw an aliquot of the solution at the specified site where the specimens are taken after a specified time, and filter immediately through a membrane with pores of less than $0.8\ \mu\text{m}$ in diameter. Complete sampling and filtering the specimen within 30 seconds. Carry out the assay of active ingredient as directed in the monograph using the successive filtrate and calculate the amount of active ingredient release from each tablet (or unit) in acid.

The amount released in buffer solution To the acid solution state above a ml of mol/L sodium phosphate [adjust to pH 6.8 ± 0.05 with 2 mol/L hydrochloric acid solution, if necessary]. Continue to operate the apparatus for 45 minutes, or for the time specified in the monograph, withdraw an aliquot of the solution at the specified site where the specimens are taken after a specified time, and filter immediately through a membrane with pores of less than $0.8\ \mu\text{m}$ in diameter. Complete sampling and filtering the specimen within 30 seconds. Carry out the assay of active ingredient as directed in the monograph using the successive filtrate and calculate the amount of active ingredient release from each tablet (or unit) in buffer solution.

(2) **The amount released in acid** Unless otherwise specified, place 900 ml of 0.1 mol/L hydrochloric acid solution in each of 6 vessels, proceed as directed under method (1) to measure the amount released in acid.

The amount released in buffer solution Drain the acid from each of 6 vessels, and add 900 ml of pH 6.8 phosphate buffer to each of 6 vessels, prepared by mixing 0.1 mol/L hydrochloric acid solution with 2 mol/L sodium phosphate solution (3 : 1), and adjusting with 2 mol/L hydrochloric acid solution or 2 mol/L sodium hydroxide solution to pH 6.8 ± 0.05 , if necessary. Or transferring each of 6 tablets (or units) to 6 other vessels containing 900 ml of phosphate buffer (pH 6.8) respectively, proceed as directed under (1) to measure the amount released in buffer solution.

Interpretation Unless otherwise specified, the requirements are met if the quantities of active ingredient released from tablets (capsules or packets) conform to one of the following states.

The amount released in acid (1) The amount of active ingredient release from each of 6 tablets (or capsules) is not more than 10%, calculated on the labelled content.

(2) If 1-2 of 6 tablets (or capsules) are more than 10%, but the average amount of active ingredient released is not more than 10%.

The amount released in buffer solution (1) The amount of active ingredient release from each of 6 tablets (or capsules) is not less than the specified quantity (Q) of the labelled content. Unless otherwise specified, the value of Q is 70% of the labelled content.

(2) If 1-2 of 6 tablets (or capsules) is less than Q, but not

less than $Q-10\%$, and the average amount of active ingredient released is not less than Q.

(3) If 1-2 of 6 tablets (or capsules) is less than Q, only 1 of tablets (capsules) is less than $Q-10\%$, but not less than $Q-20\%$, and the average amount of active ingredient released is not less than Q, repeat the test on 6 additional tablets (capsules); if 1-3 of tablets (capsules) of the total of 12 tablets (capsules) are less than Q, and only 1 of tablets (capsules) is less than $Q-10\%$, but not less than $Q-20\%$, and the average amount of active ingredient released is not less than Q.

The 10% and 20% values stated above interpretation are expressed as percentages of the labelled content.

Method 3 Used for transdermal patches.

Apparatus Use the paddle and vessel assembly (as Fig. 38) described in the dissolution test for tablets and capsules (Appendix X C, method 2), the disk assembly as Fig. 39.

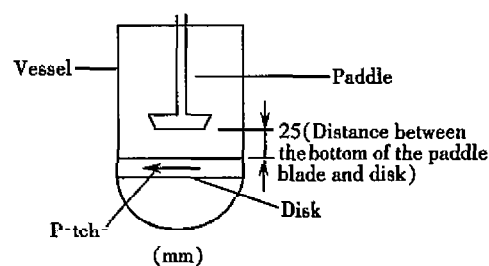


Fig. 38 Paddle Over Disk

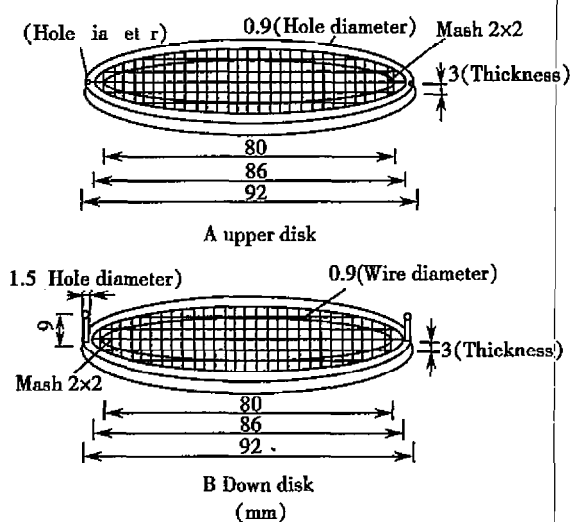


Fig. 39 Disk Assembly

Assay Place the prescribed volume of the dissolution medium in the vessel and equilibrate the medium to $32^{\circ}\text{C} \pm 0.5^{\circ}\text{C}$. Apply the patch in the disk ensuring that the release surface of the patch is as flat as possible and facing up. Place the disk at the bottom of the vessel and the release surface parallel to the bottom of the paddle blade. A distance of $25\ \text{mm} \pm 2\ \text{mm}$ between the paddle blade and the surface of the disk is maintained during the test. Immediately rotate the paddle and withdraw at determined intervals. Withdraw an aliquot of solution from a zone midway between the surface of the dissolution medium and the top of the blade, not less than 1 cm apart from the wall of the vessel. Replace the aliquots withdrawn for analysis with equal volumes of fresh dissolution medium.

Sampling method as same as Method 1.

Interpretation Unless otherwise specified, proceed as directed

for interpretation under method 1.

X E Test for Content Uniformity

Test for content uniformity is expressed as the contents of single ingredient of solid preparations, semi-solid preparations, and unhomogeneous liquid preparations small dosage or comply with the labelled amount. Unless otherwise specified, the labelled amount of each tablet, capsule or sterile powder for injection is not more than 10 mg or the content of the active ingredient is less than 5% of each weight; the labelled amount of each other preparation is less than 2 mg or the content of the active ingredient is less than 2% of each weight; and transdermal patches, are all carried on the test for content uniformity. The products whose effective concentration is relatively close to the concentration for the poison or side reaction or mixing technique is difficult and the labelled amount of each is not more than 25 mg, are also carried on the test for content uniformity. The component which complies with the above requirement is tested for compound preparations. When the test for content uniformity is specified in the monograph, it is understood that the test for weight variation (and of content) can be exempted.

Unless otherwise specified, take 10 tablets (unit) of the substance being examined, as specified in the individual monograph, determine separately the relative content X of each tablet which express 100 as the labelled amount, calculate its mean value \bar{X} , the standard deviation S^D and the absolute value A ($A = |100 - \bar{X}|$) which is the difference between the labelled amount and the mean value: if $A + 1.80 S \leq 15.0$, the substance being examined complies with the test for content uniformity; if $A + S > 15.0$, the substance being examined fails to comply with the test for content uniformity; if $A + 1.80 S > 15.0$ and $A + S \leq 15.0$, then repeat the determination using another 20 tablets. According to the results of first and repeated test, calculate the mean value \bar{X} of 30 tablets, standard deviation S and the absolute value A , the difference between the labelled amount and the mean value: if $A + 1.45 S \leq 15.0$, the substance being examined complies with the test for content uniformity; if $A + 1.45 S > 15.0$, the substance being examined fails to comply with the test for content uniformity.

The limit of the content uniformity should comply with the specifications under the individual monograph. Unless otherwise specified, the single ingredient of oral suspended solution, soft capsule filling with suspended substances, powder inhalation that holds capsules or blisters, and the single ingredient of suspensions for eye, ear and nose, solid or semi-solid preparations; the limit should be $\pm 20\%$; the limit for the transdermal patches and suppositories should be $\pm 25\%$.

If the limit of the test for content uniformity is $\pm 20\%$ or other percentage as specified in the monograph, the 15.0 in the above judge formula should be changed to 20.0 or other

corresponding value, but keep the coefficient in the formula unchanged.

If the method used for test for content uniformity is different to the assay method and the content of each tablet of content uniformity can not get from the response value (such as absorbance), take 10 tablets (units) of substance being examined, as specified in the test for content uniformity in the individual monograph. Use the response value Y from instrumental method (absorbance, peak area etc.) to calculate its mean value \bar{Y} . Determine the content X_A of each tablet which express 100 as the labelled amount by assay method. Calculate the X_A/\bar{Y} to get a proportional coefficient K ($K = X_A/\bar{Y}$). Every response value Y multiply by K to calculate the relative percentage content X ($X = KY$) of each tablet which express 100 as the labelled amount. Calculate \bar{X} , S and A by the method as described above and then identify the results.

X F Minimum Fill

The following tests and specifications apply to solid, semisolid, and liquid dosage forms packed in containers, except those preparations for which the tests for Weight Variation of Contents and Volume in Container are otherwise specified required or radio active pharmaceuticals.

Procedure

Gravimetric method (for containers labelled by weight)
Unless otherwise specified, select 5 containers (or 3 containers if the labelled quantity is more than 50 g), remove the cover and label. Thoroughly clean and dry the outside of the containers by suitable means, and weigh individually and accurately. Accurately remove the contents from each container, wash the container with a suitable solvent. Dry, and again weigh each empty container. Determine the net weight of contents in each container and the average net weight of contents. The results comply with the requirements. If one container fails the requirements, a further 5 (or 3) containers may be tested individually and all must comply.

Volumetric method (for containers labelled by volume)
Unless otherwise specified, select 5 containers (or 3 containers if the labelled quantity is more than 50 ml). Open the containers with caution to avoid any loss of the contents. Take up individually the contents of each container into a dry, previously standardized syringe, or pour into a dry, previously standardized graduated cylinder, if the labelled quantity is more than 50 ml. For viscous liquids, keep the containers upside down for 15 minutes to pour the contents as completely as possible. Measure the volume of the contents in each container, calculate the average volume of contents. The results comply with the requirements. If one container fails the requirements, a further 5 (or 3) containers may be tested and all must comply.

Labelled quantity	Solids, semisolids, liquids		Viscous liquids(volumetric method)	
	Average quantity	Quantity in each container	Average quantity	Quantity in each container
Less than 20 g(ml)	Not less than the labelled quantity	Not less than 93% of the labelled quantity	Not less than 90% of the labelled quantity	Not less than 85% of the labelled quantity
20-50 g(ml)	Not less than the labelled quantity	Not less than 95% of the labelled quantity	Not less than 95% of the labelled quantity	Not less than 90% of the labelled quantity

$$① S = \sqrt{\frac{\sum(X - \bar{X})^2}{n}}$$

continue

Labelled quantity	Solids, semisolids, liquids		Viscous liquids (volumetric method)	
	Average quantity	Quantity in each container	Average quantity	Quantity in each container
More than 50 g(ml)	Not less than the labelled quantity	Not less than 97% of the labelled quantity	Not less than 95% of the labelled quantity	Not less than 93% of the labelled quantity

In the cases of hygroscopic tablets, care must be taken to perform the test quickly enough to prevent moisture absorption (relative humidity is not more than 40%).

X G Test for Tablet Friability

This chapter provides guidelines for the friability determination of compressed, uncoated tablets. The test procedure presented in this chapter is generally applicable to most compressed tablets, and supplements other physical strength measurements, such as tablet crushing strength.

Apparatus Use a drum with an internal diameter of about 286 mm and a depth of 39 mm made of a transparent synthetic polymer with polished internal surfaces, and not subject to static build-up (as Fig. 40). One side of the drum is removable. The tablets are tumbled at each turn of the drum by a curved projection with an inside radius of $80 \text{ mm} \pm 1 \text{ mm}$ that extends from the middle of the drum to the outer wall. The drum is attached to the horizontal axis of a device that rotates at $25 \pm 1 \text{ rpm}$. Thus, at each turn the tablets roll or slide and fall onto the drum wall or onto each other.

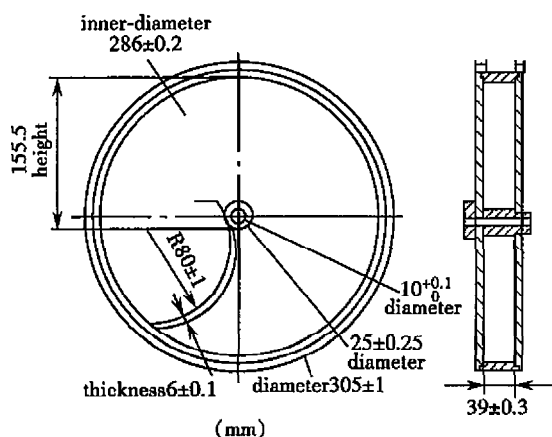


Fig. 40 Tablet friability apparatus

Procedure For tablets weighing up to 0.65 g each, take a 6.5 g of sample; for tablets weighing over 0.65 g each, a 10-tablet sample is sufficient. Place the tablets on a No. 10 sieve and remove any loose dust with the aid of air pressure or a soft brush. Accurately weigh the tablet sample, and place the tablets in the drum. Rotate the drum 100 times, and remove the tablets. Remove any loose dust from the tablets as before and weigh.

Generally, the test is run once. If the results are doubtful or if the weight loss is greater than 1%, the test should be repeated twice and determine the mean of the three tests. A maximum weight loss of not more than 1% of the weight of the tablets being tested is considered acceptable and any tablets broken, chapped and smashed are not picked up.

If tablet size or shape causes irregular tumbling, adjust the drum so that its axis forms a 10° angle with the base and the tablets no longer bind together when lying next to each other, which prevents them from falling freely.

If tablet size or shape causes severe irregular tumbling in the drum, or tablets are produced by special procedure, this

X H Determination of Particle or Droplet Size Distribution of Inhalation Preparations

The particle or droplet size distribution in the spray discharged from inhalation preparations (including inhalation aerosol, dry powder inhalers and inhalation nebulizers), are important characteristics used in judging inhalation performance. While particle size measurement by microscopy, light obscuration, light scattering or light diffraction methods can be used to evaluate the number of particles in the emissions of inhalations in the manufacturing process, whenever possible this test should be replaced with a method to determine the aerodynamic size distribution of the drug aerosol leaving the inhalers for finished products. The particle or droplet size distribution measured by this test is the percentage of the inhalation output having an aerodynamic size less than or equal to that defined in the individual monograph over the amount of each emitted dose.

Apparatus The apparatus is shown figure 41, and the component units are described as follows.

Connect all the component units according to the figure and operate the apparatus at $20-25^\circ\text{C}$. Introduce 7 ml of solvent specified in the individual monograph as the propellant in the first impingement chamber D, and 30 ml of solvent specified in the individual monograph as the entrapping liquid in the second impingement chamber, H. Connect all the component units and ensure that the jet from the assembly G, just touches the bottom of the second impingement chamber. Clip the second impingement chamber and make all the component units tightly collected. Ensure that the assembly is vertical and adequately supported and that component C and E parallel each other. Connect a flowmeter inlet to the fitting F, and a pump to the flowmeter outlet. Place the rubber adapter on the assembly inlet. Insert the inhaler and ensure that the mouthpiece points along the horizontal axis of the throat B, while the container is upturned and in the same vertical plane as the assembly. Switch on the pump, adjust flow control valve to achieve a flow rate at 60 ± 5 liters per minute, switch off the pump, and remove the inhaler. Do not adjust the flow control valve during the operation.

Procedure

1. **Procedure for inhalation aerosols** Select one aerosol container and allow it to stand at $22^\circ\text{C} \pm 2^\circ\text{C}$ for at least 1 hour. Shake thoroughly and fire several discharges to waste. Insert the actuator into rubber adapter, switch on the pump, shake the container for 5 seconds, replace the container in its actuator, discharge once immediately. Remove the container from its actuator, shake for 5 seconds, relocate the container in its actuator and discharge again. Repeat the discharging for 10

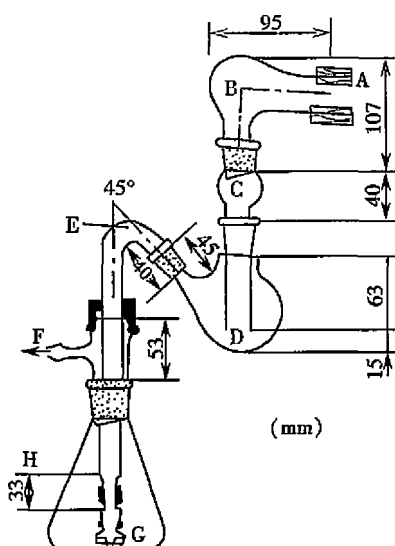


Fig. 41 Devices for aerodynamic size distribution

- A: Rubber adapter for actuator mouthpiece.
 B: Throat, a modified 60 ml round-bottomed flask with 29/32 ground-glass inlet socket and 24/29 ground-glass outlet cone.
 C: Neck.
 D: First impingement chamber, a modified 100 ml round-bottomed flask with 24/29 ground-glass inlet socket and 14/23 ground-glass outlet socket.
 E: Coupling tube, a glass wall tube with 14 ground-glass outlet cone connected to D.
 F: Outlet fitting, connected to a flowmeter, the screw thread inlet connected to E sealed with a plastic screw cap (containing a ring).
 G: Jet assembly, a modified polypropylene filter holder with 4 jets (1.85 mm \pm 0.125 mm in diameter) arranged on a circular disc and with an integral jet spacer peg with 2 mm protrusion (2 mm in diameter).
 H: Second impingement chamber, a 250 ml conical flask with 24 ground-glass inlet socket.
 The dimension tolerance of the glassware is ± 1 mm.

discharging, remove the container, wait for 5 seconds and then switch off the pump. Dismantle the apparatus.

2. Procedure for powder inhalers

(1) Procedure for powder inhalers supplied in capsules Select one capsule, place it in the dry powder inhaler, squeeze the buttons on each side of the inhaler to pierce the two sides of the capsule, switch on the pump. Insert assembled inhaler with a suitable rubber adapter into the throat and ensure that the inhaler is tightly connected to the throat and lines up along the horizontal axis of the throat B. After 10 seconds remove the inhaler, place another capsule in the inhaler. Conduct the determination for 10 or 20 capsules. After the last discharging, switch off the pump and dismantle the apparatus.

(2) Procedure for powder inhalers supplied in blisters Pierce one blister in the inhaler unit. Switch on the pump. Insert the assembled inhaler with a suitable rubber adapter into the throat and ensure that the inhaler is tightly connected to the throat and lines up along the horizontal axis of the throat B. After 10 seconds remove the inhaler, pierce another blister in the inhaler. Conduct the determination for 10 or 20 blisters. After the last discharge, switch off the pump and dismantle the apparatus.

(3) Procedure for powder inhalers supplied in powder reservoir Load the inhaler with a dose by turning the grip or squeezing the inhaler. Switch on the pump. Insert the assembled inhaler with a suitable rubber adapter into the throat and ensure that the inhaler is tightly connected to the throat and line up along the horizontal axis of the throat B.

for 10 or 20 times as specified in the monograph. After the last discharging, switch off the pump and dismantle the apparatus.

3. Procedure for inhalation nebulizers

(1) Procedure for single-dose nebulizers Select one container, and put it into the devices. Switch on the pump of the apparatus and after 10 seconds actuating the nebulizer. Insert the assembled inhaler with a suitable rubber adapter into the throat and ensure that the inhaler is tightly connected to the throat and lines up along the horizontal axis of the throat B. After 60 seconds, stop nebulizing, wait for about 5 seconds and then switch off the pump of the apparatus. Conduct the determination for 10 or 20 containers as specified in the monograph. After the last discharging, switch off the pump and dismantle the apparatus.

(2) Procedure for multiple doses nebulizers Select one container, and put it into the devices. Switch on the pump of the apparatus and after 10 seconds actuating the nebulizer. Insert the assembled inhaler with a suitable rubber adapter into the throat and ensure that the inhaler is tightly connected to the throat and lines up along the horizontal axis of the throat B. After 60 seconds, stop nebulizing, wait for about 5 seconds and then switch off the pump of the apparatus. Conduct the determination for 10 or 20 doses as specified in the monograph. After the last discharging, switch off the pump and dismantle the apparatus.

Evaluation

Using the blank entrapping liquid, wash the filter, F interface, and the inner of the inlet tube to the lower conical flask and its out surface where it projects into the flask. Combine the washings into the second impingement chamber H and dilute with the same solvent to a volume. Determine the quantity of the active ingredient in this solution using the method described under the individual monograph. Calculate the amount of active ingredient collected in lower impingement chamber per discharge by dividing the determination value by 10 or 20, and express the result as a percentage of the labelled content. The percentage is referred as the particle or droplet size distribution of the emitted dose.

X J Determination of Patches Adhesion

Patches are the pharmaceutical preparations which are applied to the skin surface. It is necessary to control the adhesive force of the patches to skin as they could influence the safety and effectiveness of the product directly. Usually the adhesion between the pressure-sensitive adhesive of patches and the skin can be scaled by 3 indices, the tack testing, the maintaining adhesion and the peel strength. The tack exhibits the initial tendency to stick to skin when the pressure-sensitive adhesive contacts with skin softly and short-termly, the so-called handle stickiness. The maintaining adhesion exhibit the cohesive force of the pressure-sensitive adhesive. It is the ability of the pressure-sensitive adhesive resists creep damage induced by durable external shearing force. The peel strength is the cementation index of the pressure-sensitive adhesive.

1. Tack testing

Tack is measured by Bowl Incline Stopping. A series of fitting friction balls under the table roll past the adhesive surface of the inclined plate separately. The tack is evaluated by the biggest friction ball the adhesive surface could cling.

Table The number of friction balls and specification

The number	Diameter/mm	Weight /kg
1	0.794	0.002
2	1.588	0.016
3	2.381	0.055
4	3.175	0.132
5	3.969	0.257
6	4.763	0.440
7	5.556	0.702
8	5.953	0.86
9	6.350	1.03
10	7.144	1.50
11	7.938	2.06
12	8.731	2.66
13	9.525	3.55
14	10.319	4.43
15	11.113	5.64
16	11.509	6.20
17	11.906	6.93
18	12.303	7.5
19	12.700	8.42
20	13.494	10.1
21	14.288	12.0
22	15.081	14.1
23	15.875	16.5
24	16.669	19.1
25	17.463	21.9
26	18.256	25.0
27	19.050	28.4
28	19.844	32.4
29	20.638	36.2
30	22.225	45.2
31	23.019	50.0
32	23.8131	55.5
33	25.400	57.4
34	26.988	80.8
35	28.575	95.5
36	30.163	112.8
37	31.750	131.9
38	33.338	152
39	34.925	175
40	36.513	198.1
41	38.100	227.3
42	41.275	287.57
43	42.863	320.4
44	44.450	361
45	47.625	439.5
46	50.800	538.8

(1) Apparatus

The tack tester consists of inclined plate, base frame and ball meeting box (as Fig 42). A stainless steel plate with about 2 mm thickness is used as the inclined plate (angle of inclination is 45°), two horizontal lines with the interval scale of 10 mm were drawn on it. The top one is the mark of the ball's zero position and the bottom line is the mark of sample's stationary position. The base frame could be adjusted and keep horizon of the tester. The ball meeting box is used to meet the ball rolling down the plate, the inwall of the box is lined with soft abrasives. The number

description in the table above.

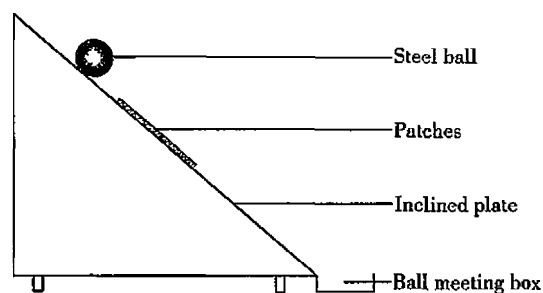


Fig. 42

(2) Procedure

Preliminary, patches should be taken out of the package and put non overlapping to each other under the room temperature for 2 hours.

1) *Preparation work* Clean the surface of inclined plate and friction ball. With the adhesive surface upward, fixed the patch to the inclined plate between the two lines by double faced adhesive tape, and keep flattening. Put the friction ball at the starting line with a tweezer, before the formal test preliminary test may be conducted several times, friction ball's right or left position should be adjusted so that the rolling track will misalign each time. Preselect a bigger friction ball, observe whether the friction ball rolling down could be stuck to the test section (stop moving for more than 5 seconds). From the big to the small, select friction balls of different numbers to carry out the test for several times, until the friction ball with the biggest number which could be stuck to the test section is found. Do the test again on the same sample with the friction ball of the biggest number and the neighboring two, then confirm the biggest one.

2) *Procedure* Take 3 samples, conduct the test with the friction ball of the biggest number to the samples separately. If one of them couldn't stop the friction ball, do the test again with the neighboring smaller one for a change. If it fails again, confirm the friction ball of the biggest number according to the method above.

3) *Interpretation* Comply with the ball number of the friction ball specified in the individual monograph. Among the numbers of the friction ball which is stuck to 3 samples, if 3 all are the same biggest one, or if 2 of them are the biggest one and the other is only the neighboring smaller one, the result is expressed as the biggest ball number; if one of them is the biggest one and the other two are only the neighboring smaller one, then the result is expressed as the ball number of the neighboring smaller one.

2. Measurement of patches' maintaining adhesive force

Apply the patches to the plate surface. Keep the plate verticality, hanging a poise with a standard mass along the length direction of the patches, record the time period the patches slip from starting to dropping out or the distance it slips down in a certain period of time.

(1) Apparatus

1) *Test frame* It consists of a base frame, which could be adjusted to keep horizontal, and a bracket, which is used to hang, and fix the test plate. Test frame keep the acting surface of the test plate to be hangd vertically.

2) *Test plate* Test plate is 1.5-2.0 mm in thick, 125 mm in wide, 125 mm in long. The test plate is made of stainless steel. Snag its surface sidewise softly with waterproof-abrasive paper whose viscosity is P280 as prescribed in GB/T7499-1994, when gentle trace appears on the plate

traces. The test plate should be used after snagging if it is used frequently or not used for a long time. Change the test plate if permanent pollution or scar is found.

3) *Press stick* Press stick is a steel axis coated by rubber.

4) *Loading board* The requirements for the material, dimension and surface are same as test plate.

(2) Procedure

Before the test, removed their bagging materials of the patches and place them non-overlapping to each other under the room temperature for 2 hours.

Dip the cleaning material in the detergent and scrub the test plate and loading board, then towel off carefully with a neat gauze. Repeat this operation more than 3 times, until the acting surface of the plate is clean by visual check. Do not touch the acting surface of the plate with your finger or other things after cleaning. Stick the sample to the middle between the test plate and loading board and the sample is parallel with the end of the plate. Rolling on the sample with press stick. When the sample sticks to the plate, put it under the room temperature for 20 minutes, fix it to the test frame. Record the starting time of the test.

Remove weight at the schedule time, measure the displacement of the sample downslide, or record the time the sample dropping out the plate.

(3) *Interpretation* The displacement or the dropping time should comply with the requirements specified in individual monograph.

The test result is the arithmetic mean of a set of samples' displacement or dropping time

3. Measurement of the peel strength

Conduct this test by 180° peel strength test method.

(1) Apparatus

1) *Testing machine* Sample's breakdown load should be 15%-85% of lacerating machine's full load. The indication error of force should be less than 1%. The machine peels continuously with a lowering speed of 300 mm/min±10 mm/min, usually accompanied by a plotting device record peeling

load automatically.

2) *Test plate* The stainless steel test plate is 1.5-2.0 mm in thick, 50 mm±1 mm in wide, 125 mm±1 mm in long.

3) *Melinex* The PET film is 0.025 mm in thick, about 110 mm in long, 20 mm in wide. The melinex should comply with the requirements of JB1256-77 (6020 PET).

(2) Procedure

Before the test, removed their bagging materials of the patches and place them non-overlapping to each other under the room temperature for 2 hours.

Fix the patches' backface to test plate with double faced adhesive tape and fix the sample to the incline plate with adhesive tape, fix sample with adhesive tape along its up side and down side if necessary, let the test sample be stuck on the plate flat.

Stick sample's adhesive layer to clean melinex, rolling on the sample back and forth with press stick to ensure that there is no air blister at the joining part. Before test, put the sample under the room temperature for 20-40 minutes after sticking. Fold the free end of the melinex 180°, grasp melinex's free end and the test plate to up side and down side separately of the testing machine. Keep the peeling surface and testing machine in line. The testing machine peels continuously with a lowering speed of 300 mm/min±10 mm/min, the peeling curve is drawn by an automatic recording device.

(3) Interpretation

Peel strength should comply with the requirements specified in individual monograph.

The 180° peel strength σ (kN/m) of the patch is calculated according to the following formula,

$$\sigma = \frac{S}{LB} \cdot c$$

In the formula: s is the area under the curve in the numeric area, mm²;

L is the length of the curve in the numeric area, mm;

B is the actual width of the sample, mm;

c is the load of record sheet's unit height, kN/m.

The test result is the arithmetic mean of the peel strength.

Appendix XI

XI A Microbiological Assay of Antibiotics

The activity (potency) of antibiotics may be demonstrated under suitable conditions by their inhibitory effect on microorganisms. The assay is designed on the basis of the principle of parallel line model.

Two general methods are employed, the agar diffusion method and the turbidimetric method.

If the calculated potency is less than 90% or more than 110% of the estimated potency, the assay should be repeated by changing the estimated potency.

Unless otherwise specified, the average percentage of fiducial limits is not more than 5%.

Method 1 Agar diffusion method

The agar diffusion method is a method to determine the potency of an antibiotic to be tested, and is based on comparing the dose response of the preparation being examined that inhibits the growth of a suitable susceptible microorganism and that of the standard preparation of that antibiotic are in the same degree of inhibition expressed by the sizes of the corresponding inhibition zones.

Preparation of Inoculum

Bacillus subtilis suspension Transfer the growth of *Bacillus subtilis* [CMCC(B)63501] from the nutrient agar slant onto a large slant surface, incubate at 35-37°C for 7 days, examine the growth stained by Gram's method microscopically, it contains not less than 85% of spores. Wash off the spores with sterile water and heat at 65°C for 30 minutes.

Bacillus Pumilus suspension Transfer the growth of *Bacillus pumilus* [CMCC(B)63202] from the nutrient agar slant onto a large slant surface, prepare the suspension as described under *Bacillus subtilis* suspension.

Staphylococcus aureus suspension Transfer the growth of *Staphylococcus aureus* [CMCC(B)26003] from the nutrient

agar slant onto a fresh slant surface, incubate at 35-37°C for 20-22 hours. Wash off the growth with sterile water or sterile solution of 0.9% sodium chloride immediately before use.

Micrococcus lutea suspension Transfer the growth of *Micrococcus lutea* [CMCC(B)28001] from the nutrient agar slant onto a large slant surface, incubate at 26-27°C for 24 hours. Wash off the growth with medium III or sterile solution of 0.9% sodium chloride immediately before use.

Escherichia coli suspension Transfer the growth of *Escherichia coli* [CMCC(B)44103] from the nutrient agar slant onto a fresh slant surface, incubate at 35-37°C for 20-22 hours. Wash off the growth with sterile water immediately before use.

Saccharomyces cerevisiae suspension Transfer the growth of *Saccharomyces cerevisiae* (ATTC9763) from medium V slant onto medium IV slant, incubate at 32-35°C for 24 hours. Wash off the growth with sterile water into a tube containing sterile glass beads, shake well.

Klebsiella Pneumoniae suspension Transfer the growth of *Klebsiella Pneumoniae* [CMCC(B)46117] from the nutrient agar slant onto a fresh slant surface, incubate at 35-37°C for 20-22 hours. Wash off the growth with sterile water immediately before use.

Bordetella Bronchiseptica suspension Transfer the growth of *Bordetella Bronchiseptica* [CMCC(B)58403] from the nutrient agar slant onto a fresh slant surface, incubate at 32-35°C for 24 hours. Wash off the growth with sterile water immediately before use.

Reference Preparation The reference substances should be handled as directed in the package inserts. Solutions of the reference substance are prepared using sterile buffers described in Table 1 and diluted immediately before use.

The reference substances, molecular formula and theoretical potency are shown in Table 2.

Test Preparation Dissolve an accurately weighed quantity of the substance being examined in the solvent prescribed under individual monographs and dilute to approximately the same concentration as that of the reference preparation.

Table 1 The Experimental Design of the Agar Diffusion Assay of Antibiotics

Antibiotics	Test Organism	Medium		Sterile buffer solution pH	Concentration Unit/ml	Incubate Condition	
		No.	pH			temp. /°C	time/h
Streptomycin	<i>Bacillus subtilis</i> [CMCC(B)63501]	I	7.8-8.0	7.8	0.6-1.6	35-37	14-16
Kanamycin		I	7.8-8.0	7.8	0.9-4.5	35-37	14-16
Amikacin		I	7.8-8.0	7.8	0.9-4.5	35-37	14-16
Paromomycin		I	7.8-8.0	7.8	0.9-4.5	35-37	14-16
Ribostamycin		I	7.8-8.0	7.8	2.0-12.0	35-37	14-16
Capreomycin	<i>Bacillus pumilus</i> [CMCC(B)63202]	I	7.8-8.0	7.8	10.0-40.0	35-37	14-16
Sulbenicillin		I	6.5-6.6	6.0	5.0-10.0	35-37	14-16
Norvancomycin		VII	6.0	6.0	9.0-43.7	35-37	14-16
Acetylspiramycin ^①		II	8.0-8.2	7.8	5-40	35-37	14-16

continue

Antibiotics	Test Organism	Medium		Sterile buffer solution pH	Concentration Unit/ml	Incubate Condition	
		No.	pH			temp. /°C	time/h
Tobramycin		I	7.8-8.0	7.8	1-4	35-37	14-16
Roxithromycin		II	7.8-8.0	7.8	5-10	35-37	16-18
Kitasamycin		II ^②	8.0-8.2	7.8	20-40	35-37	16-18
Meleumycin		nutrient agar medium	8.0-8.2	7.8	5-40	35-37	16-18
Micronomycin		I	7.8-8.0	7.8	0.5-2.0	35-37	14-16
Gentamycin	<i>Bacillus pumilus</i>	I	7.8-8.0	7.8	2.0-12.0	35-37	14-16
Erythromycin	[CMCC(B)63202]	I	7.8-8.0	7.8	5.0-20.0	35-37	14-16
Netilmicin		I	7.8-8.0	7.8	5-20	35-37	14-16
Sisomicin		I	7.8-8.0	7.8	5-20	35-37	14-16
Azithromycin		I	7.8-8.0	7.8	0.5-20	35-37	16-18
Clarithromycin		I	7.8-8.0	7.8	2.0-8.0	35-37	14-16
Neomycin	<i>Staphylococcus aureus</i> [CMCC(B)26003]	II	7.8-8.0	7.8 ^③	4.0-25.0	35-37	14-16
Tetracycline	<i>Micrococcus lutea</i>	II	6.5-6.6	6.0	10.0-40.0	35-37	14-16
Oxytetracycline	[CMCC(B)28001]	II	6.5-6.6	6.0	10.0-40.0	35-37	16-18
Chlortetracycline		II	6.5-6.6	6.0	4.0-25.0	35-37	16-18
Chloramphenicol		II	6.5-6.6	6.0	30.0-80.0	35-37	16-18
Bacitracin		II	6.5-6.6	6.0	2.0-12.0	35-37	16-18
Fosfomycin		II	7.8-8.0	7.8	5-20	35-37	18-24
Colistin	<i>Escherichia coli</i> [CMCC(B)44103]	VI	7.2-7.4	6.0	614-2344	35-37	16-18
Amphotericin B ^④	<i>Saccharomyces cerevisiae</i> (ATCC 9763)	IV	6.0-6.2	10.5	0.5-2.0	35-37	24-36
Spectinomycin	<i>Klebsiella Pneumoniae</i> [CMCC(B)46117]	II	7.8-8.0	7.0	50-200	35-37	16-18
Polymyxin B	<i>Bordetella Bronchiseptica</i> [CMCC(B)58403]	medium for Polymyxin B	6.5-6.7	6.0	4-25	35-37	16-18

① Adjust the pH of medium I after it is sterilized to 8.0-8.2.

② Add 0.3% glucose to medium II.

③ Containing 3% sodium chloride.

④ Use 15 ml *Saccharomyces cerevisiae* inoculated seed layer instead of base and seed layers for the preparation of inoculated plate.

Table 2 The Antibiotic Reference Standards and Theoretical Potency

Antibiotic Reference Standards	Molecular Formula or Name	Calculated Theoretical Potency Unit/mg	Antibiotic Reference Standards	Molecular Formula or Name	Calculated Theoretical Potency Unit/mg
Streptomycin	(C ₂₁ H ₃₉ N ₇ O ₁₂) ₂ • 3H ₂ SO ₄	798.3	Chlortetracycline	C ₂₂ H ₂₃ ClN ₂ O ₈ • HCl	1000
Kanamycin	C ₁₈ H ₃₆ N ₄ O ₁₁ • H ₂ SO ₄	831.6	Erythromycin	C ₃₇ H ₆₇ NO ₁₃	1000
Amikacin	C ₂₂ H ₄₃ N ₅ O ₁₃ • nH ₂ SO ₄ (n=1.8 or 2)		Chloramphenicol	C ₁₁ H ₁₂ C ₁₂ N ₂ O ₅	1000
Ribostamycin	C ₁₇ H ₃₄ N ₄ O ₁₀ • nH ₂ SO ₄ (n<2)		Bacitracin	Bacitracin	
Neomycin	Neomycin Sulfate		Colistin	Colistin Sulfate	
Gentamycin	Gentamycin Sulfate		Norvancomycin	C ₆₅ H ₇₃ C ₁₂ N ₃ O ₂₄ • HCl	975.2
Sulbenicillin	C ₁₆ H ₁₆ N ₂ Na ₂ O ₇ S	904.0	Capreomycin	Capreomycin Sulfate	
Tetracycline	C ₂₂ H ₂₄ N ₂ O ₈ • HCl	1000	Amphotericin B	C ₄₇ H ₇₃ NO ₁₇	1000
Oxytetracycline	C ₂₂ H ₂₄ N ₂ O ₉ • 2H ₂ O	927	Paromomycin	C ₂₃ H ₄₅ N ₅ O ₁₄ • nH ₂ SO ₄	
Sisomicin	(C ₁₉ H ₃₇ N ₅ O ₇) ₂ • 5H ₂ SO ₄	646.3	Netilmicin	(C ₂₁ H ₄₁ N ₅ O ₇) ₂ • 5H ₂ SO ₄	660.1
Fosfomycin	C ₃ H ₅ CaO ₄ P • H ₂ O	711.5	Azithromycin	C ₃₈ H ₇₂ N ₂ O ₁₂	1000
Acetylspiramycin	Acetylspiramycin		Tobramycin	C ₁₈ H ₃₇ N ₅ O ₉	1000
Clarithromycin	C ₂₈ H ₄₀ NO ₁₁	1000	Roxithromycin	C ₄₁ H ₇₆ N ₂ O ₁₅	1000

continue

Antibiotic Reference Standards	Molecular Formula or Name	Calculated Theoretical Potency Unit/mg	Antibiotic Reference Standards	Molecular Formula or Name	Calculated Theoretical Potency Unit/mg
Spectinomycin	$C_{14}H_{24}N_2O_7 \cdot 2HCl \cdot 5H_2O$	670.9	Kitasamycin	Kitasamycin	
Micronomycin	$C_{20}H_{41}N_5O_7 \cdot 5/2H_2SO_4$	654.3	Meleumycin	Meleumycin	
Polymyxin B	Polymyxin B Sulfate				

Preparation of Inoculated Plates Fill Petri dishes with flat bottom, 90 mm diameter, 16-17 mm high with 20 ml of molten medium listed in the table 1. Place the dishes on a horizontal platform to produce layers of hardened culture medium in uniform thickness.

Then add to each plate 5 ml of the same medium which has previously been inoculated at 48-50°C (or 60°C for spores) with an inoculum of the test organism listed in the table 1. The concentration of the inoculum should be so selected that the sharpest zones of inhibition are obtained. The diameters of the inhibition zones produced by the high dose of the reference preparation are 18-22 mm for 2-dose assay, and 15-18 mm by middle dose for 3-dose assay respectively. Spread the medium evenly over the entire surface and allow to cool on a horizontal platform. Place 4 (2-dose assay) or 6 (3-dose assay) stainless steel cylinders (6.0 mm \pm 0.1 mm in internal diameter, 7.8 mm \pm 0.1 mm in external diameter and 10.0 mm \pm 0.1 mm in height) on the surface of each plate at equal distance, then cover them with circular clay lids.

Assay Procedures

2-dose assay Use not less than 4 inoculated plates prepared as above, fill two of the diagonal cylinders on each plate with the high and low doses of the reference preparation, fill the remaining cylinders with the high and low doses of the test preparation. The dose levels should be in the ratio of 2 : 1 or 4 : 1. Incubate the plate under the conditions prescribed in the table 1 measure the diameter (or area) of the inhibition zones. Carry out the statistical analysis of variance (Appendix XIV, method 2.2) and calculate the potency of the substance being examined.

3-dose assay Use not less than 6 inoculated plates prepared as above, fill three of the alternate cylinders on each plate with the high, middle and low doses of the reference preparation, fill the remaining cylinders with the high, middle and low doses of the test preparation. The dose levels should be in the ratio of 1 : 0.8. Incubate the plates under the conditions prescribed in the table 1 measure the diameter (or area) of the inhibition zones. Carry out the statistical analysis of variance (Appendix XIV, method 3.3) and calculate

the potency of the substance being examined.

Method 2 Turbidimetric method

The turbidimetric method is a method to determine the potency of an antibiotic, depends upon the preparation being examined that inhibits the growth of a microbial culture in a fluid medium and that of the standard preparation of that antibiotic are in the same degree of inhibition expressed by the turbidity of the microbial culture which can be measured photometrically.

Preparation of Inoculum

Staphylococcus aureus suspension Transfer the growth of *Staphylococcus aureus* [CMCC(B)26003] from the nutrient agar slant onto a fresh slant surface, incubate at 35-37°C for 20-22 hours. Wash off the growth with sterile water or sterile solution of 0.9% sodium chloride immediately before use.

Escherichia coli suspension Transfer the growth of *Escherichia coli* [CMCC(B)44103] from the nutrient agar slant onto a fresh slant surface, incubate at 35-37°C for 20-22 hours. Wash off the growth with sterile water immediately before use.

Candida albicans suspension Transfer the growth of *Candida albicans* [CMCC(F)98001] from the Martin agar modified medium slant onto 10 ml of medium IX, incubate at 35-37°C for 8 hours. Dilute to a suitable concentration with medium IX.

Reference preparation The reference substances should be handled as directed in the package inserts. Solutions of the reference substance are prepared using sterile buffers described in Table 3 and diluted immediately before use. The reference substances, molecular formula and theoretical potency are shown in Table 2.

Test preparation Dissolve an accurately weighed quantity of the substance being examined in the solvent prescribed under individual monographs and dilute to approximately the same concentration as that of the reference preparation.

Preparation of Inoculated Fluid Medium Add suitable quantity

Table 3 The Experimental Design of the Turbidimetric Assay of Antibiotics

Antibiotics	Test Organism	Medium		Sterile buffer solution pH	Concentration Unit/ml	Incubate Condition Temp. /°C
		No.	pH			
Gentamycin	<i>Staphylococcus aureus</i> [CMCC(B)26003]	III	7.0-7.2	7.8	0.15-1.0	35-37

of inoculum of the test organism listed in the table 3 to the fluid medium immediately before use, and swirling to attain a homogeneous suspension. The quantity of the inoculum should be so selected that the microbial culture should have absorbances between 0.3 to 0.7 absorbance unit after an incubation period of 3-4 hours at 35-37°C. The difference of absorbances of the microbial culture inhibited between adjacent doses of the reference preparation is at least 0.1 absorbance unit for the dose levels is in the ratio of 2 : 1. It is preferable to obtain the optimum dose-response relationship and measurable opacity occurs in the conditions

Use the inoculated medium immediately after its preparations.

Assay Procedures

Standard curve method (1-dose assay) Use glass or plastic test tubes that are relatively uniform in length, diameter, and thickness, sterilized before use. Unless otherwise specified, it may be necessary to select the median concentration from defined dose-response linearity as the median test level. Prepare dilutions representing 5 test levels which include one corresponding to the median concentration, of the Standard. The dose levels should be in the ratio of 1 : 2 : 4 : 8 : 16. Prepare a solution of a single

median test level of the antibiotic to be examined according to its estimated potency or labelled concentration. Add each dose to 3 replicate tubes at least. Distribute 1.0 ml of each solutions of Standard or the antibiotic to be examined into identical test tube and add to each tube 9.0 ml of inoculated medium, mix immediately. The tubes randomized block arrangement, place them under the appropriate incubation temperature and identical incubation time (incubate usually for 4 hours) in order to obtain a readily measurable opacity occurs in the conditions of the test. Measure the opacity online using suitable apparatus, or after incubation, stop the growth of the microorganisms by adding 0.5 ml of formaldehyde (1→3) to each tube and read its absorbance in a suitable spectrophotometer fitted with a 530 nm or 580 nm filter. Prepare at the same time 2 control tubes both containing 1.0 ml of the test diluent and 9.0 ml of the inoculated medium but no antibiotic. One incubates at the same condition as the test tube to observe the growth of microorganisms, the other adds immediately 0.5 ml of dilute formaldehyde (1→3) to be the blank of absorbance. Carry out the statistical analysis (Calculation and Statistical Analysis of Standard Curve Method) and calculate the potency of the substance being examined.

Calculation and Statistical Analysis of Standard Curve Method

1. Calculation of Standard Curve

Logarithm (lg) of each dose of Standard and corresponding absorbance are shown in table 4.

Table 4 Logarithm of each dose of Standard and corresponding absorbance

Group of Units	lg-dose of Standard	absorbance
1	x_1	y_1
2	x_2	y_2
3	x_3	y_3
4	x_4	y_4
...
n	x_n	y_n
Mean	\bar{x}	\bar{y}

Regression coefficient (i.e. Slope) b , intercept a and linear regression equation of Standard curve are calculated as follows:

$$\text{Regression coefficient } b = \frac{\sum (x_i - \bar{x})(y_i - \bar{y})}{\sum (x_i - \bar{x})^2} = \frac{\sum x_i y_i - \bar{x} \sum y_i}{\sum x_i^2 - \bar{x} \sum x_i} \quad (1)$$

$$\text{Intercept } a = \bar{y} - b\bar{x} \quad (2)$$

$$\text{Linear regression equation } Y = bX + a \quad (3)$$

2. Significance tests of regression coefficient

It used t -test to judge if the linear regression equation is established, i.e. if the relation between X and Y can be represented by a straight line. Calculate the value of t with the following equations:

$$\text{Estimated standard deviation: } S_{y,x} = \sqrt{\frac{\sum (y_i - Y)^2}{n - 2}} \quad (4)$$

$$\text{Standard error of regression coefficient: } S_b = \frac{S_{y,x}}{\sqrt{\sum (x_i - \bar{x})^2}} \quad (5)$$

$$t = \frac{b - 0}{S_b} \quad (6)$$

Where y_i is the true absorbance of Standard;
 Y is the estimated absorbance may be obtained from Linear regression equation;
 \bar{y} is the mean true absorbance of Standard;
 x_i is the logarithm of dose of Standard;
 \bar{x} is the mean logarithm of dose of Standard.

If the calculated value of t is larger than the tabulated value of $t_{0.05/(2n-4)}$ corresponding to $p = 0.05$ and $2n-4$ degrees of freedom, the regression is highly significant, i.e. the relation between X and Y can be represented by a straight line.

3. Estimation of potency and fiducial limits

(1) **Estimation of logarithm of dose of antibiotic** When the regression is highly significant, lg-dose of antibiotic may be estimated by the following equations:

$$\text{Logarithm of dose of antibiotic } X_0 = \frac{Y_0 - a}{b} \quad (7)$$

(2) **Estimation of fiducial limits of logarithm of dose of antibiotic** Fiducial limits of lg-dose of antibiotic for $p = 0.05$ are calculated as follows:

$$\text{Fiducial limits of } X_0 : FL = X_0 \pm t_{0.05(n-2)} \cdot \frac{S_{y,x}}{|b|} \cdot \sqrt{\frac{1}{m} + \frac{1}{n} + \frac{(X_0 - \bar{x})^2}{\sum x_i^2 - \bar{x} \sum x_i}} \quad (8)$$

Where n is the number of responses to S ;
 m is the number of responses to T ;
 X_0 is the logarithm of dose of T which is obtained from Linear regression equation;
 Y_0 is the mean absorbance of antibiotic.

(3) **Estimation of percentage of fiducial limits** Percentage of fiducial limits of lg-dose of antibiotic are calculated as follows:

$$\text{Percentage of fiducial limits } FL\% = \frac{\text{upper limit of } X_0 - \text{lower limit of } X_0}{2X_0} \times 100\% \quad (9)$$

Where X_0 is the dose of antibiotic.

Unless otherwise specified, the percentage of fiducial limits is not more than 5%.

(4) **Estimation of potency** The potency of antibiotic are obtained by multiplying the concentration (lg-dose transformed to concentration) and dilution multiple of antibiotic.

2-dose assay or 3-dose assay Use glass or plastic test tubes that are relatively uniform in length, diameter, and thickness, sterilized before use. Unless otherwise specified, it may be necessary to select the optimum high, (middle,) low doses of the reference preparation. Distribute 1.0 ml of each solutions of Standard or the antibiotic to be examined into identical test tube. For 2-dose assay the dose levels should be in the ration of 2 : 1 or 4 : 1, and for 3-dose assay the dose levels should be in the ration of 1 : 0.8. With the same operation as standard curve method (1-dos assay) test, add each dose to 4 replicate tubes at least. The tubes randomized block arrangement, place them under the appropriate incubation conditions. Carry out the statistical analysis of variance (Appendix XIV, method 2.2 and 3.3) and calculate the potency of the substance being examined.

Culture Media

Medium I : Peptone	5 g
Beef extract	3 g
Dipotassium hydrogen phosphate	3 g
Agar	15-20 g
Water	1000 ml

Mix the above ingredients with the exception of agar, adjust the pH value to 0.2-0.4 higher than the final pH of the

the pH of the solution so that it is 7.8-8.0 or 6.5-6.6 after sterilization. Sterilize the medium at 115 °C for 30 minutes.

Medium I:	Peptone	6 g
	Beef extract	1.5 g
	Yeast extract	6 g
	Glucose	1 g
	Agar	15-20 g
	Water	1000 ml

Mix the above ingredients with the exception of agar and glucose, adjust the pH value to 0.2-0.4 higher than the final pH of the solution. Add agar, heat to dissolution and filter, then mix thoroughly with glucose and adjust the pH of the solution so that it is 7.8-8.0 or 6.5-6.6 after sterilization. Sterilize the medium at 115°C for 30 minutes.

Medium III:	Peptone	5 g
	Beef extract	1.5 g
	Yeast extract	3 g
	Sodium chloride	3.5 g
	Dipotassium hydrogen phosphate	3.68 g
	Potassium dihydrogen phosphate	1.32 g
	Glucose	1 g
	Water	1000 ml

Mix the above ingredients with the exception of glucose, heat to dissolution and filter, then mix well with glucose and adjust the pH of the solution so that it is 7.0-7.2 after sterilization. Sterilize the medium at 115°C for 30 minutes.

Medium IV:	Peptone	10 g
	Sodium chloride	10 g
	Sodium citrate	10 g
	Glucose	10 g
	Agar	20-30 g
	Water	1000 ml

Mix the above ingredients with the exception of agar and glucose, adjust the pH value to 0.2-0.4 higher than the final pH of the solution. Heat it with agar at 109°C for 15 minutes and allow to stand at above 70°C for one hour, filter. Mix thoroughly with glucose and adjust the pH of the solution so that it is 6.0-6.2 after sterilization. Sterilize the medium at 115°C for 30 minutes.

Medium V:	Peptone	10 g
	Maltose	40 g
	Agar	15-20 g
	Water	1000 ml

Mix peptone with water, adjust the pH value to 0.2-0.4 higher than the final pH of the solution. Add agar, heat to dissolution and filter, then mix well with maltose and adjust the pH of the solution so that it is 7.2-7.4 after sterilization. Dispense the solution into suitable vessels and sterilize the medium at 115°C for 30 minutes. Allow it to set in a sloped form with butt on cooling.

Medium VI:	Peptone	8 g
	Beef extract	3 g
	Yeast extract	5 g
	Sodium chloride	45 g
	Dipotassium hydrogen phosphate	3.3 g
	Potassium dihydrogen phosphate	1 g
	Glucose	2.5 g
	Agar	15-20 g
	Water	1000 ml

Mix the above ingredients with the exception of agar and glucose, adjust the pH value to 0.2-0.4 higher than the final pH of the solution. Add agar, heat to dissolution and filter, then mix thoroughly with glucose and adjust the pH of the solution so that it is 7.2-7.4 after sterilization. Sterilize the medium at 115°C for 30 minutes.

Medium VII:	Peptone	5 g
	Beef extract	3 g

Dipotassium hydrogen phosphate	7 g
Potassium dihydrogen phosphate	3 g
Sodium citrate	2.5 g
Agar	15-20 g
Water	1000 ml

Mix the above ingredients with the exception of agar, adjust the pH value to 0.2-0.4 higher than the final pH of the solution. Add agar, heat to dissolution and filter, then mix thoroughly with glucose and adjust the pH of the solution so that it is 6.5-6.6 after sterilization. Sterilize the medium at 115°C for 30 minutes.

Medium VIII:	Yeast extract	1 g
	Ammonium sulfate	1 g
	Glucose	5 g
	Agar	15-20 g
	Phosphate BS (pH 6.0)	1000 ml

Mix the above ingredients heat to dissolution and filter. Sterilize the medium at 115°C for 30 minutes.

Medium IX:	Peptone	7.5 g
	Beef extract	1.0 g
	Yeast extract	2.0 g
	Sodium chloride	5.0 g
	Glucose	10.0 g
	Water	1000 ml

Mix the above ingredients with the exception of glucose, heat to dissolution and filter, then mix thoroughly with glucose and adjust the pH of the solution so that it is 6.5 after sterilization. Sterilize the medium at 115°C for 30 minutes.

Nutrient broth medium:	Peptone	10 g
	Sodium chloride	5 g
	Beef infusion*	1000 ml

Dissolve peptone and sodium chloride in the beef infusion, warming slightly until the substances are dissolved, adjust the pH value to slightly alkaline, heat to boil, filter if necessary, adjust the pH of the solution so that it is 7.2 ± 0.2 after sterilization. Sterilize the medium at 115°C for 30 minutes.

Nutrient agar medium:	Peptone	10 g
	Sodium chloride	5 g
	Agar	15-20 g
	Beef infusion*	1000 ml

Mix the above ingredients with the exception of agar, adjust the pH value to 0.2-0.4 higher than the final pH of the solution. Add agar, heat to dissolution and filter, adjust the pH of the solution so that it is 7.2-7.4 after sterilization. Dispense the solution into suitable vessels and sterilize the medium at 115°C for 30 minutes. Allow it to set in a sloped form with butt on cooling.

* Beef infusion can also be prepared by dissolving 3 g of beef extract powder in 1000 ml of water.

Modified Martin medium:	Peptone	5.0 g
	Yeast extract	2.0 g
	Glucose	20.0 g
	Dipotassium hydrogen phosphate	1.0 g
	Magnesium sulfate	0.5 g
	Agar	15-20 g
	Water	1000 ml

Mix the above ingredients in water except agar and glucose, warming slightly until the substances are dissolved, adjust pH value to about 6.8. Add agar, heat to boil and filter, then mix thoroughly with glucose and adjust the pH of the solution so that it is 6.4 ± 0.2 after sterilization. Dispense the solution into suitable vessels and sterilize the medium at 115°C for 30 minutes. Allow it to set in a sloped form with butt on cooling.

medium for Polymyxin B:	Peptone	6.0 g
	Beef extract	1.5 g
	Yeast extract	3.0 g
	Glucose	1.0 g
	Papaic digest of soybean	4.0 g
	Agar	15-20 g
	Water	1000 ml

Mix the above ingredients with the exception of agar, adjust the pH value to 0.2-0.4 higher than the final pH of the solution. Add agar, heat to dissolution and filter, adjust the pH of the solution so that it is 6.5-6.7 after sterilization. Sterilize the medium at 115°C for 30 minutes.

The culture medium can be replaced by the dry culture medium containing the same ingredients, preparation and sterilization are in accordance with the manufacture's instruction.

Sterile Buffer Solutions

Phosphate BS (pH 6.0) Dissolve 2 g of dipotassium hydrogen phosphate and 8 g of potassium dihydrogen phosphate in water to produce 1000 ml, filter, sterilize at 115°C for 30 minutes.

Phosphate BS (pH 7.0) Dissolve 9.39 g of disodium hydrogen phosphate and 3.5 g of potassium dihydrogen phosphate in water to produce 1000 ml, filter, sterilize at 115°C for 30 minutes.

Phosphate BS (pH 7.8) Dissolve 5.59 g of dipotassium hydrogen phosphate and 0.41 g of potassium dihydrogen phosphate in water to produce 1000 ml, filter, sterilize at 115°C for 30 minutes.

Phosphate BS (pH 10.5) Dissolve 35 g of dipotassium hydrogen phosphate in water, add 2 ml of 10 mol/L potassium hydroxide solution and sufficient water to produce 1000 ml, filter, sterilize at 115°C for 30 minutes.

XI B Preparation of Penicillinase and Determination of Its Activity

1. Culture medium

Peptone	15 g
Sodium chloride	4 g
Sodium citrate	5.88 g
Dipotassium hydrogen phosphate	4 g
Glycerine	50 g
0.1% Ferrous sulfate ($\text{FeSO}_4 \cdot 7\text{H}_2\text{O}$) solution	0.5 ml
2% Magnesium sulfate ($\text{MgSO}_4 \cdot 7\text{H}_2\text{O}$) solution	1 ml
Beef infusion	1000 ml

Mix the above ingredients, adjust to pH 7.0-7.2, dispense in 500 ml conical flasks, 80 ml for each flask, sterilize at 115°C for 30 minutes.

2. Preparation of penicillinase solution

Inoculate one slant culture of *Bacillus cereus* [CMCC(B)63301] to one of the culture media flasks, incubate on a rotatory shaker at 25°C for 18 hours. Inoculate 10 ml of this culture to each of the remaining culture media flasks and add 4500 Units of sterile penicillin solution, incubate at 25°C for 24 hours, again add 20000 Units of sterile penicillin solution and incubate for 24 hours, and once more add 20000 Units of sterile penicillin solution and further incubate for another 24 hours. Centrifuge, sterilize the supernatant liquid by filtration through a suitable filter medium after adjusting pH to about 8.5. Adjust the pH of the filtrate to 7.0 using aseptic technique, dispense the sterile filtrate to suitable containers and stored below 10°C.

3. Determination of the activity of penicillinase

Preparation of penicillin solution Dissolve an accurately weighed quantity of benzylpenicillin sodium (or potassium) in phosphate BS (pH 7.0) to produce a solution containing 10000 penicillin units per ml.

Preparation of dilute penicillinase solution Dilute the penicillinase solution with phosphate BS (pH 7.0) to produce a solution of about 8000 to 12000 penicillinase units per ml, warm to 37°C before use.

Procedure Measure accurately 50 ml of penicillin solution to a 100 ml volumetric flask, warm to 37°C, add accurately 25 ml of dilute penicillinase solution, previously warmed to 37°C, mix promptly and allow to stand at 37°C for exactly 1 hour. Add 3 ml, accurately measured, to 25 ml, accurately measured, of iodine (0.005 mol/L) VS immediately [measure accurately 10 ml of iodine (0.05 mol/L) VS to 100 ml volumetric flask, dilute to volume with sodium acetate BS (pH 4.5)], allow to stand in a dark place at room temperature for 15 minutes, titrate with sodium thiosulfate (0.01 mol/L) VS, using starch IS added towards the end of the titration and continue the titration to the disappearance of the blue colour.

Blank titration Allow 2 ml, measured accurately, of prewarmed penicillin solution to stand at 37°C for 1 hour, add accurately 25 ml of iodine (0.005 mol/L) VS, and then 1 ml of dilute penicillinase solution. Allow to stand in dark place at room temperature for 15 minutes, titrate with sodium thiosulfate (0.01 mol/L) VS, calculate the enzyme activity as follows:

$$E = (B - A) \times M \times F \times D \times 100$$

Where E is enzyme activity of penicillinase, (Units/ml)/hour;

B is volume of sodium thiosulfate VS consumed in blank titration, ml;

A is volume of sodium thiosulfate VS consumed in the titration of penicillinase, ml;

M is concentration of sodium thiosulfate VS, mol/L;

F is the penicillin units, equivalent to each ml of iodine (0.005 mol/L) VS, under the experimental condition described above;

D is dilution factor of penicillinase solution.

Annotation **Phosphate BS (pH 7.0)** To dipotassium hydrogen phosphate 7.36 g and potassium dihydrogen phosphate 3.14 g, add sufficient water to produce 1000 ml.

Sodium acetate BS (pH 4.5) To glacial acetic acid 13.86 ml, add sufficient water to produce 250 ml; to crystalline sodium acetate 27.30 g add sufficient water to produce 200 ml. Mix the two solutions.

XI C Test for Undue Toxicity

The undue toxicity of a substance being examined is determined by observing the death and survival of mice within a period of 48 hours after having received by injection (or other route of administration) a dose of the substance being examined.

Animal Healthy mice from normal breeding each weighing 17-20 g are used and can only be used once for the test.

Preparation of test solution Unless otherwise specified, dissolve the substance being examined in sodium chloride injection to produce a solution of the concentration specified

in individual monographs.

Procedure Administer to each of 5 mice 0.5 ml of the test solution by one of the following routes specified in the individual monograph.

Intravenous injection Inject the test solution into a tail vein of each mouse. Usually the injection should be completed within 4-5 seconds at a uniform rate, but for those preparations specified to inject slowly in the monographs, the injection time may be prolonged to 30 seconds.

Intraperitoneal injection Inject the test solution from the abdominal surface into the peritoneal cavity.

Subcutaneous injection Inject the test solution subcutaneously at one side of the dorsal surface or under the abdominal surface.

Oral administration Administer the test solution orally by means of a suitable cannula.

Evaluation of the results Unless otherwise specified, none of the mice received the test solution dies within 48 hours. If one or more mice die within 48 hours, repeat the test using another 10 mice each weighing 18-19 g; none of the second group of mice dies within 48 hours.

XI D Test for Pyrogens

The test for pyrogens is carried out in rabbits by measuring the rise of body temperature following the intravenous injection of a specified dose of the preparation being examined.

Test animal Use healthy, matured rabbits weighing 1.7-3.0 kg, male or non-pregnant female. Keep the rabbits under observation for 7 days before the selection test, loss of weight, loss of appetite or other abnormal signs should not appear. Within 3-7 days prior to pyrogen test, rabbits which have not previously been used in a pyrogen test should be subject to a selection test as prescribed under the *procedure* except injection. Record the body temperature of each rabbit 8 times successively at 30 min intervals, if the recorded body temperatures of a rabbit are all in the range of 38.0-39.6°C, and the difference between the highest and lowest temperature is not greater than 0.4°C, it is fit for the pyrogen test. Do not use a rabbit more than 10 times and more frequently than once every 48 hours. The selection test should be repeated if a rabbit is to be used again after a break of 3 weeks, or if it has a maximum temperature rise of 0.6°C or more in a previous pyrogen test. All rabbits which have been used in a pyrogen test in which the preparation being examined was adjudged to be pyrogenic should not be used again.

Test conditions House the rabbits in a living area of uniform temperature (a temperature which does not differ by more than 5°C from that of the laboratory where the test is to be conducted) 1-2 days before the test. Conduct the pyrogen test in a laboratory of 17-25°C and free from disturbances. During the test, the variation of room temperature should not be more than 3°C. Withhold food from the rabbits and place the animals in suitable boxes at least 1 hour before the test, until the test is completed. Measure the body temperature with a suitable temperature-sensing device with a precision of $\pm 0.1^\circ\text{C}$. Insert the thermometer or temperature sensing probe into the rectum of the rabbit to an uniform depth (about 6 cm) for not less than 1.5 minutes. Record the body temperature of each rabbit once at an interval of 30 minutes, usually measure twice. The difference between the

greater than 0.2°C, use the mean value of these two readings as the normal body temperature of each rabbit. In any one test, the normal body temperature of each rabbit must be within 38.0-39.6°C and must not differ from one another by more than 1°C.

Render the syringes, needles and glassware free from pyrogens by heating at 250°C for 30 minutes or by any other suitable method.

Procedure Warm the preparation being examined to about 38.0°C. Within 15 minutes after the determination of normal body temperature, inject a dose as specified in the monograph into the ear vein of each of 3 rabbits slowly. Record the temperature of each rabbit once at an interval of 30 minutes, measure 6 times after the injection. The temperature rise of each rabbit is calculated by subtracting its normal temperature from the highest temperature recorded. If one of the 3 rabbits shows a temperature rise of 0.6°C or more; or none of the 3 rabbits shows a temperature rise of 0.6°C or more, but the sum of the 3 temperature rises exceeds 1.4°C, repeat the test with 5 other rabbits using the same procedure.

Evaluation of the results If none of the 3 rabbits in the first test shows a temperature rise of 0.6°C or more, and the sum of the 3 temperature rises does not exceed 1.4°C; or if only one of the 3 rabbits in the second test shows a temperature rise of 0.6°C or more, and the sum of the 8 temperature rises does not exceed 3.5°C, the preparation being examined passes the test. If more than one rabbits in either test show a temperature rise of 0.6°C or more; or the sum of the 8 temperature rises exceed 3.5°C, the preparation being examined is considered to be pyrogenic.

When the temperature rise is negative, the result is counted as a zero response.

XI E Test for Bacterial Endotoxin

The test for bacterial endotoxins is used to detect or quantify endotoxins of gram-negative bacterial origin using TAL reagent. It is used to determine the limit concentration of bacterial endotoxin in a preparation being examined.

Two methods are used for this test; the gel-clot method and the photometric method. The latter includes a turbidimetric method and a chromogenic method. Proceed by any one of these two methods. In the event of doubt or dispute, the final decision is made based on the gel-clot method, unless otherwise indicated in the monograph.

The quantities of endotoxin are expressed in Endotoxin Units (EU).

The National Standard for Endotoxin (NSE) is prepared and purified from *Escherichia coli*. It is used only for calibration of the working standard for endotoxin (WSE) and for calibration and verifying the sensitivity of TAL reagents.

The working standard for endotoxin (WSE) of which the potency has been standardized against NSE in collaboration assay, is used for bacterial endotoxin test as positive control, for interference test and for sensitivity test of TAL reagent.

The water used in the gel-clot test for bacterial endotoxins is a sterile water for injection, of which quantities of bacterial endotoxins are less than 0.015 EU per ml. The quantities of bacterial endotoxins of water used in the photometric test are less than 0.005 EU per ml.

Depyrogenate all glassware and other heat-stable apparatus used in the test by heating in a hot-air oven at 250°C for at least 60 minutes (or by any other validated suitable method).

employing plastic apparatus, such as microtitre plates and pipette tips for automatic pipettors, use apparatus shown to be free of detectable endotoxin and of interfering effects for the test. Avoid microbial contamination during the test.

Preparation of the test solutions Prepare the test solutions by dissolving or diluting active substances or medicinal products using water for bacterial endotoxins test (water for BET). Some substances or preparations may be more appropriately dissolved or diluted in other aqueous solutions. If necessary, adjust the pH of the test solution (or dilution thereof) so that the pH of the mixture of the TAL reagents and test solution falls within the pH range specified by the TAL reagents manufacturer. This usually applies to a product with a pH in the range of 6.0 to 8.0. The pH may be adjusted by the use of acid, base or a suitable buffer, as recommended by the TAL reagents manufacturer. Acids and bases may be prepared from concentrates or solids with water for BET in containers free of detectable endotoxin. Buffers must be validated to be free of detectable endotoxin and interfering factors.

Establishment of endotoxin limits The endotoxin limit (L) for drugs or biological products is usually defined as follows:

$$L = K/M$$

Where L is the endotoxin limit for active substances administered parenterally, which is specified in units such as EU/ml, EU/mg, or EU/Unit of biological activity;

K is the threshold human pyrogenic dose of endotoxin per kg of body weight in a single hour period, which is expressed as EU/(kg · h). For injections, $K = 5$ EU/(kg · h); for injections of radio-pharmaceuticals, $K = 2.5$ EU/(kg · h); and for intrathecal injections, $K = 0.2$ EU/(kg · h);

M is equal to the maximum recommended human dose of product per kg of body weight in a single hour period, which is specified in units such as ml/(kg · h), mg/(kg · h), or U/(kg · h). Here the human average body weight is 60 kg; the injection period is calculated as 1 hour when the injection is completed within 1 hour.

The endotoxin limit calculated by human dose may be adjusted according to the situation of manufacture and clinical use if necessary. In that case, appropriate reasons for adjustment have to be submitted.

Determination of the Maximum Valid Dilution (MVD) The Maximum Valid Dilution (MVD) is the maximum allowable dilution of the substance being examined at which the endotoxin limit can be determined. Determine the MVD using the following formulae:

$$MVD = cL/\lambda$$

Where L is the endotoxin limit of the substance being examined

c is the concentration of the substance being examined, when L is expressed as EU/ml, c is 1.0 ml/ml; when L is expressed as EU/mg or EU/U, the unit of C is mg/ml or U/ml. Minimum valid dilution concentration, $c = \lambda/L$, may be calculated for drug substance or sterilized powders for injection when MVD is 1.

λ is the labelled sensitivity of TAL reagent in the gel-clot method (EU/ml) or the lowest point used in the standard curve of the turbidimetric or chromogenic method.

Gel-clot method (Method 1)

The gel-clot method detects or qualifies endotoxins based on

Test for confirmation of labelled TAL reagent sensitivity The labelled sensitivity of TAL reagent (EU/ml) is defined as the lowest concentration of endotoxin that is required to cause the TAL reagent to clot under the conditions specified in the following procedure. The test for confirmation of the labelled TAL reagent sensitivity is to be carried out when each new batch of TAL reagent is used or when there is any change in the experimental conditions which may affect the outcome of the test.

Dissolve NSE or CSE in water for BET according to the labelled sensitivity of TAL reagent (λ), mix for 15 minutes using a vortex mixer. Prepare four replicate series of two-fold dilutions of NSE or CSE using water for BET to produce 4 dilutions with concentration of 2.0 λ , 1.0 λ , 0.5 λ , 0.25 λ , mix each dilution for 30 seconds using a mixer. Use 18 tubes of 10 mm × 75 mm in size containing of 0.1 ml of TAL reagent or use 18 original ampoules of 0.1 ml of TAL reagent. Add 0.1 ml of each of 16 endotoxin standard solutions (four standard concentrations in quadruplicate) to each of 16 tubes, and 0.1 ml of water for BET to each of 2 tubes as negative control. Mix gently after each addition, cover the tubes tightly and incubate the tubes vertically at $37 \pm 1^\circ\text{C}$ for 60 ± 2 minutes.

Take each tube in turn directly from the incubator and invert it through about 180° in one smooth motion to test the integrity of the gel. If a firm gel has formed that remains in place upon inversion, record the result as positive. A result is negative if an intact gel is not formed. Handle the tubes with care to avoid vibration, or false negative may result.

The test is not valid unless all the four tubes of highest concentration (2.0 λ) give positive results, all the four tubes of lowest concentration (0.25 λ) give negative results and the two tubes of negative control give negative results. Calculate the geometric mean endpoint concentration, i.e. the measured sensitivity of the TAL reagent (λ_c), using the following expression:

$$\lambda_c = \lg^{-1} (\sum X/4)$$

Where X is the log endpoint concentration which is the last positive result in a series of decreasing concentrations of endotoxin.

If this λ_c is not less than 0.5 λ and not more than 2 λ , the labelled sensitivity (λ) is confirmed and is used in tests performed with this TAL reagent.

Test for interfering factors Prepare solutions A, B, C and D as shown in Table 1, and use the test solutions at a dilution less than the MVD, not containing any detectable endotoxins, operating as described under the *Test for confirmation of labelled TAL reagent sensitivity*.

The test is not valid unless all replicates of solutions A and D show no reaction and the result of solution C confirms the labelled TAL reagent sensitivity. The geometric mean endpoint concentrations of solutions B (E_s) and C (E_t) are determined using the following formulas.

$$E_s = \lg^{-1} (\sum X_s/4)$$

$$E_t = \lg^{-1} (\sum X_t/4)$$

Where X_s is the log endpoint concentration of the solution C. X_t is log endpoint concentration of the solution B.

If both E_s and E_t are not less than 0.5 λ and not more than 2 λ , the test solution does not contain interfering factors under the experimental conditions used. Otherwise, the solution interferes with the test. If the preparation being examined interferes with the test at a dilution less than the MVD, repeat the test for interfering factors using a greater dilution, not exceeding the MVD. The use of a more sensitive TAL reagent permits a greater dilution of the preparation being examined and this may contribute to the elimination of interference.

Table 1 Preparation of solutions in the test for interfering factors by using gel-clot method

Solution	Endotoxin Concentration/Solution to which endotoxin is added	Diluent	Dilution factor	Initial endotoxin concentration	Number of replicates
A	None/Test solution	—	—	—	2
B	2 λ /Test solution	Test solution	1	2 λ	4
			2	1 λ	4
			4	0.5 λ	4
			8	0.25 λ	4
C	2 λ /Water for BET	Water for BET	1	2 λ	4
			2	1 λ	4
			4	0.5 λ	4
			8	0.25 λ	4
D	None/Water for BET	—	—	—	2

Solution A: solution of the preparation being examined that is free of detectable endotoxins.

Solution B: test for interference.

Solution C: control of the labelled TAL reagent sensitivity.

Solution D: negative control (water for BET).

Interference may be overcome by suitable treatment, such as filtration, neutralization, dialysis or heat treatment. To establish that the treatment chosen effectively eliminates interference without loss of endotoxins, repeat the test for interfering factors using the preparation being examined to which the standard endotoxin has been added and which has then been submitted to the chosen treatment.

When establish a method of bacterial endotoxin test for a new drug, the test for interfering factors should be carried out.

When the source of the TAL reagent, or the formula or the

manufacture process of the substance being examined are changed, or there is any change in the experimental conditions which may affect the outcome of the test, the test for interfering factors should be performed again.

Procedure

(1) Gel-clot limit test

Prepare solutions A, B, C and D as shown in Table 2, and perform the test following the procedure in the *Test for confirmation of labelled TAL reagent sensitivity*.

Table 2 Preparation of solutions in gel-clot limit test

Solution	Endotoxin Concentration/Solution to which endotoxin is added	Number of replicates
A	None/Diluted test solution	2
B	2 λ /Diluted test solution	2
C	2 λ /Water for BET	2
D	None/Water for BET	2

Solution A: solution of the preparation being examined

Solution B: positive product control

Solution C: positive control

Solution D: negative control

Prepare solution A and solution B (positive product control) using a test solution at the dilution of the MVD, with which the *Test for interfering factors* was completed.

Invaluation of results The test is not valid unless both replicates of the two positive control solutions B and C are positive and those of negative control solution D are negative. The preparation being examined complies with the test when a negative result is found for both replicates of solution A. The preparation being examined does not comply with the test when a positive result is found for both replicates of solution A. Repeat the test by 4 replicates of solution A

when a positive result is found for one replicate of solution A and a negative result is found for the other. The preparation being examined complies with the test if a negative result is found for all replicates of solution A in the repeat test.

(2) Gel-clot semi-quantitative test

The test quantifies bacterial endotoxins in the test solution by titration to an endpoint. Prepare solutions A, B, C and D as shown in Table 3, and perform the test following the procedure in the *Test for confirmation of labelled TAL reagent sensitivity*.

Table 3 Preparation of solutions in the gel-clot semi-quantitative test

Solution	Endotoxin Concentration/Solution to which endotoxin is added	Diluent	Dilution factor	Initial endotoxin concentration	Number of replicates
A	None/Test solution	Water for BET	1	—	2
			2	—	2
			4	—	2
			8	—	2
B	2 λ /Test solution	Water for BET	1	2 λ	2
C	2 λ /Water for BET		2	1 λ	2

continue					
Solution	Endotoxin Concentration/Solution to which endotoxin is added	Diluent	Dilution factor	Initial endotoxin concentration	Number of replicates
D	None/Water for BET	—	4	0.5 λ	2
			8	0.25 λ	2
			—	—	2
			—	—	2
Solution A: test solution at the dilution, not exceeding the MVD, with which the test for interference factors was carried out. Subsequent dilution of the test solution must not exceed the MVD. Use water for BET to make two dilution series of 1, 1/2, 1/4, and 1/8, relative to the dilution with which the test for interfering factors was carried out.					respectively.
Solution B: solution A containing standard endotoxin at a concentration of 2 λ (positive product control).					
Solution C: two series of water for BET containing the standard endotoxin at concentrations of 2 λ, λ, 0.5 λ, and 0.25 λ,					
Solution D: negative control (water for BET).					

Invaluation of results The test is not valid unless the following 3 conditions are met: (1) both replicates of solution D (negative control) are negative; (2) both replicates of solution B (positive product control) are positive; and (3) the geometric mean endpoint concentration of solution C is in the range of 0.5 λ to 2 λ .

To determine the endotoxin concentration of solution A, calculate the endpoint concentration for each replicate series of dilutions by multiplying each endpoint dilution factor by λ . The endotoxin concentration in the test solution is the geometric mean endpoint concentration of the replicates ($E = \lg^{-1}(\sum X/2)$). If the test is conducted with a diluted test solution, calculate the concentration of endotoxin in the original solution by multiplying the result by the dilution factor. If none of the dilutions of the test solution is positive in a valid test, record the endotoxin concentration as less than λ (or, if a diluted sample was tested, as less than λ times the lowest dilution factor of the sample). If all dilutions are positive, the endotoxin concentration is recorded as equal to or greater than the greatest dilution factor multiplied by λ . The preparation being examined meets the requirements of the test if the concentration of endotoxin is less than that specified in the individual monograph. Otherwise, the preparation being examined does not meet the requirements of the test.

Photometric method (Method 2)

The photometric method includes a turbidimetric method and a chromogenic method.

The turbidimetric method measures the endotoxin concentrations of test solutions based on the measurement of the increase in turbidity during the gel formation of the TAL reagent. Depending on the test principle used, this method is classified as being the endpoint-turbidimetric test or the kinetic-turbidimetric test. The endpoint-turbidimetric test is based on the quantitative relationship between the concentration of endotoxins and the turbidity (absorbance or transmission) of the reaction mixture at the end of an incubation period. The kinetic-turbidimetric test is a method to measure either the onset time needed for the reaction mixture to reach a predetermined absorbance, or the rate of turbidity development.

The chromogenic method measures the chromophore released from a suitable chromogenic peptide by the reaction of

endotoxins with the TAL reagent. Depending on the test principle employed, this method is classified as being the endpoint-chromogenic test or the kinetic-chromogenic test. The endpoint-chromogenic test is based on the quantitative relationship between the concentration of endotoxins and the quantity of chromophore released at the end of an incubation period. The kinetic-chromogenic test is a method to measure either the onset time needed for the reaction mixture to reach a predetermined absorbance, or the rate of colour development. All photometric tests are usually carried out by special instrumentation at the incubation temperature of $37 \pm 1^\circ\text{C}$. The quantities and volume ratios of the substance being examined and the TAL reagent, incubation time etc. employed in the test are decided according to the related instructions of instruments and the TAL reagents.

To assure the precision or validity of the turbidimetric and chromogenic tests, preparatory tests are conducted to assure that the criteria for the standard curve are satisfied and that the test solution does not interfere with the test.

Assurance of criteria for the standard curve The test for assurance of criteria for the standard curve must be carried out when each new batch of TAL reagent is used or any changes are made to the experimental conditions that are likely to influence the result of the test.

Using the standard endotoxin solution, prepare at least three endotoxin concentrations (the dilution factor of adjacent concentrations is not greater than 10) to generate the standard curve within the range of endotoxin concentrations indicated by the TAL reagent manufacturer. The mixing time for every dilution is the same as that of gel-clot method. Perform the test using at least three replicates of each standard endotoxin solution, and duplicate of negative control solution at the same time. When both reaction times of the duplicate of negative control solution are greater than that of the lowest concentration, perform statistic analysis of linear regression for all the data.

The test is not valid unless the absolute value of the correlation coefficient, $|r|$, is greater than or equal to 0.980, otherwise repeat the test.

Test for interfering factors Select an endotoxin concentration (λ_m) at or near the middle of the endotoxin standard curve. Prepare solutions A, B, C and D as shown in Table 4.

Table 4 Preparation of solutions in the test for interfering factors by using photometric method

Solution	Endotoxin Concentration	Solution to which Endotoxin is Added	Number of Replicates
A	None	Test solution	not less than 2
B	Middle concentration (λ_m) of the standard curve	Test solution	not less than 2
C	At least 3 concentrations (lowest concentration, λ , is designated)	Water for BET	each not less than 2

continue

Solution	Endotoxin Concentration	Solution to which Endotoxin is Added	Number of Replicates
D	None	Water for BET	not less than 2
Solution A: test solution, that may be diluted not to exceed the MVD.			
Solution B: preparation to be examined at the same dilution as Solution A, containing added endotoxin at a concentration equal to or near the middle of the standard curve.			
Solution C: standard endotoxin solution at the concentrations used in the validation of the method described in <i>Assurance of criteria for the standard curve</i> .			
Solution D: water for (negative control) BET.			

Calculate the content of endotoxin contained in the solution A (C_1) and solution B (C_2) respectively, and calculate the recovery of the endotoxin added to solution B as follows:

$$R = [(C_2 - C_1) / \lambda_m] \times 100\%$$

If under the conditions of the test, the recovery of the endotoxin added to solution B is within 50% to 200%, the test solution is considered to be free of interfering factors. When the endotoxin recovery is out of the specified ranges, the interfering factors must be removed as described in the *Test for interfering factors under Gel-Clot Techniques*. The efficiency of the treatment is verified by repeating the test for interfering factors.

When the source of the TAL reagent, or the origin, formula and the manufacture process of the substance being examined are changed, or there is any change in the experimental conditions which may affect the outcome of the test, the *Test for interfering factors* should be performed again.

Procedure

Follow the procedure described in the *Test for interfering factors under Photometric method*.

Calculate the endotoxin concentration of each replicate of solution A using the standard curve generated by the series of positive controls, solution C.

The test is not valid unless the following 3 requirements are met:

- (1) the results obtained with the series of positive controls, solution C, comply with the requirements for validation defined in the *Assurance of criteria for the standard curve under Photometric method*;
- (2) the endotoxin recovery, calculated from the concentration found in solution B after subtracting the endotoxin concentration found in solution A, is within the range of 50% to 200%;
- (3) both reaction times of the solution D (negative control) are greater than that of the lowest concentration of the endotoxin standard curve.

Invaluation of results The preparation being examined complies with the test if the mean endotoxin concentration of the replicates of solution A, after correction for dilution and concentration, is less than the endotoxin limit for the product. Otherwise, the preparation being examined does not meet the requirements of the test.

Note In this chapter, the term "tube" includes all types of receptacles such as micro-titer plate wells.

XI F Test for Vasopressor Substance

The vasopressor substance of the preparation being examined (T) is determined by comparing its vasopressor activity on anesthetized rat with that of standard preparation of posterior pituitary (S) under the condition of the following method.

the same way as that described under the Preparation of Standard Solution for the Biological Assay of Oxytocin (Appendix XII F) to produce a solution containing 1.0 Unit of vasopressor activity in 1 ml, calculated on the basis of the stated potency for vasopressin. Store the solution at a temperature of 4-8°C. The solution may be used over a period of not exceeding three months if it is still remained clear. Dilute the solution with sodium chloride injection to produce a standard dilution of 0.1 Unit per ml immediately before the test.

Preparation of test solution Dissolve the preparation being examined in water (or sodium chloride injection) to produce a solution of suitable concentration specified in the monograph. Adjust the concentration of the solution so that of the volume of the solution being injected will be equal to that of the standard dilution.

Procedure A healthy male rat weighting over 300 g is anaesthetized with suitable anaesthetics (such as i.p. 1 g urethane per kg body weight). Tie the rat on back to a operating table and maintain the body temperature of the rat during the test. Dissect the trachea for cannulation when necessary. Insert the femoral (or carotid) vein a cannula filled with sodium chloride injection for intravenous injection. Inject through the venous cannula 50-100 Units of heparin per 100 g body weight. Insert a artery cannula (filled with suitable units of heparin solution) into one of the dissected carotid artery and connect the other end of the cannula with a suitable pressure measuring device by a column of saline solution for making continuous record of blood pressure.

At this stage, adjust the pressure of the device to a level corresponding to the normal blood pressure of the rat, and remove the artery clamp. Inject slowly a α -adrenoceptor blocking agent (such as phentolamine mesylate 0.1 mg for 100 g body weight) and repeat the same dose of injection after 5-10 minutes. Start the test only when the blood pressure of the rat remains stable. Injections should be made at a uniform rate and at a regular interval of 5-10 minutes depending on the time at which the blood pressure returns to its original level. Each injection is followed by a fixed volume of sodium chloride injection.

Inject intravenously in turn two doses of standard dilution (ml) with the dose ratio of about 1 : 0.6, and repeat the injection for 2-3 times. If the elevation response of blood pressure to the lower doses is corresponding to 1.33-3.33 kPa, and the mean response caused by higher doses is clearly greater than that of the mean response caused by lower doses, the sensitivity of the rat is suitable for the test. Let d_s represent a dose of standard dilution (ml) which lies between the range of lower and higher doses used in the sensitivity test, and d_T the dose of test preparation specified in the monograph, inject a series of four dose in the order of d_s , d_T , d_s , d_T , compare the elevation response of blood pressure caused by the third dose (d_T) to that caused by the first dose (d_s), and the response caused the second dose (d_T) to that caused by the fourth dose (d_s). The preparation complies with the test if the two responses caused by d_T are

another series of four doses of d_s and d_T and compare the responses in the same way. The preparation complies with the test if, in the two series of doses, none of the response of d_T is greater than that of d_s . The preparation fails the test if all the responses caused by d_T are greater than that of d_s . If it is not the case, repeat the test with another cat. The test preparation fails the test if in the repeated test one depressor response caused by d_T is greater than that caused by d_s .

XI G Test for Depressor Substances

The depressor substance of a preparation being examined (T) is determined by comparing its depressor effect on anesthetized cat (or dog) with that of the histamine reference standard (RS) under the condition of the following method.

Preparation of standard solution Dissolve an accurately weighed quantity of the histamine phosphate RS in water to produce a solution of 1 mg histamine base per ml. Immediately before the test, dilute the histamine solution with sodium chloride injection to produce a solution of 0.5 μ g of histamine base per ml.

Preparation of test solution Prepare a solution of preparation being tested to produce a solution with suitable concentration specified in the monograph so that the volume of the solution being injected will be equal to that of the standard solution.

Procedure A healthy cat weighing over 2 kg (or a dog weighing over 5 kg), male or non-pregnant female, is anesthetized with a suitable anesthetic such as one of the barbiturates. Care should be taken to maintain the body temperature of the animal during the test. Fix the cat on an operating table, introduce a short glass cannula into the trachea so as to be ready for artificial respiration when necessary. Insert a cannula filled with suitable anticoagulant solution into one of the carotid artery and connect the cannula to a suitable pressure measuring device for making a continuous record of blood pressure. Cannulate the femoral vein for intravenous injection. Adjust the pressure of the pressure measuring device to a level corresponding to the normal blood pressure of the animal (usually 13.3-16.0 kPa) and remove the artery clamp. The doses can be given only when the blood pressure of the animal is constant. Injections should be made at a uniform rate and at regular intervals of 3-5 minutes depending on the speed at which the blood pressure returns to a constant level. Each injection is followed by a fixed volume of normal saline solution.

Inject intravenously in turn 3 doses of standard solution corresponding to 0.05 μ g, 0.1 μ g and 0.15 μ g of histamine base per kg of the cat's weight. Repeat the injections for 2-3 times, if the depressor responses to the injections of 0.1 μ g/kg are approximately the same and correspond to a fall of blood pressure not less than 2.67 kPa and the responses to the graded doses are clearly discriminated, the sensitivity of the animal is suitable for the test.

Let d_s represents the dose of 0.1 μ g of the histamine base per kg of the cat's weight and d_T the dose of test preparation specified in individual monographs, inject a series of doses in the order of d_s , d_T , d_T , d_s , compare the depressor response caused by the third dose with that caused by the first dose, and the response caused by the second dose with that caused by the fourth dose. The preparation complies with the test if none of the depressor responses caused by d_T is greater than 1/2 of that caused by d_s . If one response

another series of d_s , d_T , d_T , d_s and compare their responses in the same way. The test preparation complies with the test if none of the depressor responses caused by d_T is greater than that caused by d_s . The test preparation fails the test if all responses caused by d_T are greater than that caused by d_s . If it is not the case, repeat the test with another cat. The test preparation fails the test if in the repeated test one depressor response caused by d_T is greater than that caused by d_s .

The animal can further be used for test of depressor substances if the sensitivity of the animal is still suitable for the test.

XI H Test for Sterility

Test for sterility is a method to detect whether raw materials, preparations, medical devices or other articles, which are required to be sterile according to the Pharmacopoeia, are aseptic. However, a result conforming with the requirements only indicates that no contaminating micro-organism has been found in the sample examined under the conditions of the test.

Test for sterility should be carried out in a class 100 laminar-air-flow cabinet located within a 10000-class clean-room, or an isolator. The whole process should be performed under strictly aseptic conditions to avoid any microbial contamination. The cleanliness of working areas including laminar flow cabinet, working bench, background room should be monitored regularly according to the current national standard such as the detecting method for airborne particles, airborne microbe and settling microbe in the clean room (area) of the pharmaceutical industry. The isolator should be validated according to the relevant requirements, the cleanliness of inner isolator space should also comply with aseptic requirements.

1. Culture media

(1) Media preparation

Media for the test may be prepared as described below, dehydrated media may be used provided that they have same ingredients and comply with the requirements. Media should be sterilized using a validated process. Store at a temperature between 2°C and 25°C and protect from light. If the prepared media are stored in unsealed containers, they can be used in 3 weeks. If stored in suitable sealed containers, the media can be used in 1 year.

1) Fluid thioglycollate medium (for culturing aerobic bacteria and anaerobic bacteria)

Pancreatic digest of casein	15.0 g
Glucose	5.0 g
L-Cystine	0.5 g
Sodium thioglycollate or (Thioglycollic acid)	0.5 g 0.3 ml
Yeast extract	5.0 g
Sodium chloride	2.5 g
0.1% Resazurin solution (freshly prepared)	1.0 ml
Agar	0.75 g
Water	1000 ml

Mix the above ingredients in water except glucose and resazurin solution, heat until dissolved, adjust pH to slightly alkaline, boil and filter, add glucose and resazurin solution, mix, adjust the pH so that after sterilization the solution will have a pH of 7.1 ± 0.2 . Dispense the medium in suitable containers which provide a ratio of surface to depth of medium such that no more than the upper half of the medium has undergone a colour change (pink colour) indicative of oxygen uptake at the end of the incubation

use, not more than the upper one-fifth of the medium has acquired a pink colour, otherwise, the medium can be restored only once by heating the containers in a water-bath until the pink colour disappears (no more than 20 minutes), cooled quickly, taken care to prevent the introduction of non-sterile air into the container.

Fluid Thioglycollate Medium is to be incubated at 30-35°C.

2) Modified Martin medium (for culturing fungi)

Peptone	5.0 g
Yeast extract	2.0 g
Glucose	20.0 g
Dipotassium hydrogen phosphate (K_2HPO_4)	1.0 g
Magnesium sulfate ($MgSO_4$)	0.5 g
Water	1000 ml

Mix the above ingredients in water except glucose, heat until dissolved, adjust pH to about 6.8, boil, add glucose, mix, filter, adjust the pH so that after sterilization the solution will have a pH of 6.4 ± 0.2 , dispense the media into containers and sterilize using a validated process.

Improved Martin medium is to be incubated at 23-28°C.

3) Selective medium

Before sterilization or inoculation, add proper quantity of suitable neutralizer or surface-active substance, such as p-aminobenzoic acid (used in test for sterility of sulfonamides), polysorbate 80 (used in test for sterility for water insoluble substances) or β -lactamase (used in test for sterility of β -lactam preparations) etc. to each of the media described above. The quantity of neutralizer or surface-active substance should be validated.

4) Nutrient broth medium

Peptone	10.0 g
Beef powder	3.0 g
Sodium chloride	5.0 g
Water	1000 ml

Mix the above ingredients in water, heat until dissolved, adjust pH to slightly alkaline, boil, filter, adjust the pH so that after sterilization the solution will have a pH of 7.2 ± 0.2 , dispense the media into containers and sterilize using a validated process.

5) Nutrient broth agar medium

Add 14.0 g agar to nutrient broth medium as described above, adjust the pH so that after sterilization, the solution will have a pH of 7.2 ± 0.2 , dispense the media into containers and sterilize using a validated process.

6) 0.5% glucose broth medium (used in test for sterility of antibiotic such as Streptomycin sulfate)

Peptone	10.0 g
Beef powder	3.0 g
Glucose	5.0 g
Sodium chloride	5.0 g
Water	1000 ml

Mix the above ingredients in water except glucose, heat until dissolved, adjust the pH to slightly alkaline, boil, add glucose, mix, filter, adjust the pH so that after sterilization, the solution will have a pH of 7.2 ± 0.2 , dispense the media into containers and sterilize using a validated process.

7) Modified Martin agar medium

Add 14.0 g agar to Improved Martin medium as described above, adjust the pH so that after sterilization the solution will have a pH of 6.4 ± 0.2 . Dispense the media into containers and sterilize using a validated process.

(2) Suitability Tests of Medium

The media used in the test for sterility, as described above, should comply with the following sterility and sensitivity tests, carried out before or in parallel with the test on the

(3) **Sterility** Incubate no less than 5 vessels of each batch of sterilized medium at the specified incubation temperature for 14 days. Growth of microorganisms should not occur.

(4) Test for sensitivity of medium

1) Test strains	<i>Staphylococcus aureus</i>	[CMCC (B) 26003]
	<i>Pseudomonas aeruginosa</i>	[CMCC (B) 10104]
	<i>Bacillus subtilis</i>	[CMCC (B) 63501]
	<i>Clostridium sporogenes</i>	[CMCC (B) 64941]
	<i>Candida albicans</i>	[CMCC (F) 98001]
	<i>Aspergillus niger</i>	[CMCC (F) 98003]

The viable microorganisms used in the test must not be more than five passages removed from the original master seed lot. The suitable seed-stock technique should be used so that the microorganism characters can be maintained.

2) **Preparation of inoculum** Inoculate freshly cultured *Staphylococcus aureus* or *Pseudomonas aeruginosa* or *Bacillus subtilis* into nutrient agar medium or nutrient broth medium and freshly cultured *Clostridium sporogenes* into fluid thioglycollate medium, incubate at 30-35°C for 18-24 hours. Inoculate freshly cultured *Candida albicans* into Modified Martin medium or Modified Martin agar medium, incubate at 23-28°C for 24-48 hours, prepare suspension, with the above cultures, containing less than 100 cfu microorganisms per ml with sterile 0.9% w/v sodium chloride solution. Inoculate freshly cultured *Aspergillus niger* into Modified Martin agar medium, incubate at 23-28°C for 5-7 days until good sporulation is obtained. Wash the *Aspergillus niger* spore culture and transfer it to sterile tube, prepare spore suspension containing less than 100 cfu per ml with sterile 0.9% w/v sodium chloride solution.

3) **Inoculation of medium** Take 9 containers of fluid thioglycollate medium (containing 12 ml medium per container), inoculate 2 containers of the medium with less than 100 cfu test microorganisms of *Staphylococcus aureus*, *Pseudomonas aeruginosa*, *Bacillus subtilis* and *Clostridium sporogenes* respectively, and the remaining uninoculated culture medium (one container) is used as blank control, then incubate for not more than 3 days. Take 5 containers of Modified Martin medium (containing 9 ml medium per container), inoculate 2 containers of the medium with less than 100 cfu test microorganisms of *Candida albicans* and *Aspergillus niger* respectively, and use the remaining uninoculated culture medium (one container) as blank control, incubate for not more than 5 days. Observe the test containers for growth of the microorganisms every day during the incubation.

4) **Evaluation of results** The blank control must be no growth of microorganisms. If a clearly visible growth of the microorganisms occurs in an inoculated culture medium, the medium meets the requirement of the test for sensitivity of medium.

2. Diluents and rinsing fluids

(1) 0.1% Peptone solution

Dissolve 1.0 g of peptone in 1000 ml of water, heat until dissolved, adjust the pH to 7.1 ± 0.2 , filter and dispense into containers. Sterilize using a validated process.

(2) pH 7.0 sodium chloride-peptone buffer

Mix 3.6 g KH_2PO_4 , 7.2 g Na_2HPO_4 , 4.3 g sodium chloride and 1.0 g peptone in 1000 ml of water. heat until dissolved, filter and dispense into containers. Sterilize using a validated process.

If necessary, Add suitable neutralizer or surface-active substance to each of the diluents or rinsing fluids described above before or after sterilization

In the course of establishing sterility testing method for product to be examined, the method must be verified to ensure that the adopted method is suitable for sterility test of the product. Whenever there is a change of drug composition or experimental conditions of the test, the testing method must be revalidated.

Validation test is to be conducted as described below under Test for sterility of the product being examined using exactly the same methods and the following instructions. The tests should be performed separately for each of the microorganism tested.

(1) **Tested strains and preparation of inoculum** Same as the test for sensitivity of medium described above.

(2) **Membrane filtration** Filter the specified quantity of the test specimen with Membrane filtration apparatus, rinse the membrane, add test microorganism with less than 100 cfu to the final portion of rinsing fluids, filter again. Transfer the membrane filter into fluid thioglycollate medium or Modified Martin medium, or add the medium to the filtration apparatus containing the membrane. Use another container containing the same volume of the medium, then add the same amount of test microorganisms as control. Incubate the containers at specified temperature for 3-5 days. Repeat the procedure for each of the test microorganism tested.

(3) **Direct Inoculation** Take 8 containers containing certain required volume of fluid thioglycollate medium for direct Inoculation, inoculate into 2 containers of each of medium with less than 100 cfu test microorganisms of *Staphylococcus aureus*, *Pseudomonas aeruginosa*, *Bacillus subtilis* and *Clostridium sporogenes* separately. Take 4 containers containing Modified Martin medium complying with the required volume for direct Inoculation, inoculate into 2 containers of each of the medium with less than 100 cfu test microorganisms of *Candida albicans* and *Aspergillus niger* separately. Add specified quantity of the product being tested to one of the inoculated containers of each test microorganism, the other inoculated container is for control. Incubate the containers at specified temperature for 3-5 days.

(4) **Invaluation of results** Compare with the control container, if clearly visible growth of each test microorganisms is obtained in the test containers containing the product to be tested, visually either the product possesses no antimicrobial activity under the conditions of the test or such activity has been satisfactorily eliminated. The test for sterility of the product being examined may then be carried out using the same method and conditions of the test. If the growth of test microorganisms is not obtained, or poor, or slow in any tested container, visually comparable to that in the control container without product, then the product with the specified quantity possesses antimicrobial activity under the conditions of the test.

In such a case, modify the conditions in order to eliminate the antimicrobial activity by using a large amount of rinsing fluid, or increase the volume of medium, or using suitable neutralizer or inactivator such as β -lactamase or p-aminobenzoic acid, or replacing the type of the membrane filter used etc. and repeat the validation test. The validation may also be performed simultaneously with the Test for sterility of the product being examined.

4. Test for sterility of the product being examined

(1) **Number of products to be tested** It is the number of the minimum package of the product to be examined for test for sterility once. Unless otherwise specified, test the number of products is specified in Table 1. The number of the products for positive control test is not included in table 1.

(2) **Quantity of product to be tested** It is the minimum

Unless otherwise specified, the minimum quantity of the product for each medium are defined in table 2 and table 3. When using the technique of direct inoculation, if the contents in a single container are sufficient to inoculate two containers of medium, they should be transferred to fluid thioglycollate medium and Modified Martin medium respectively. When using the technique of membrane filtration, the quantity of the products to be tested should not be less than the whole quantity used in direct inoculation, whenever permitted, the whole contents of each container should be filtered for testing.

(3) **Positive control** The microorganisms for positive control should be selected according to the nature of the product being examined. *Staphylococcus aureus* is used for the product possessing no antimicrobial activity or mainly anti-gram-positive-bacteria activity. *Encherichia coli* is used for the product mainly possessing anti-gram-negative-bacteria activity. *Clostridium sporogenes* is used for the product possessing anti-anaerobic bacteria activity. *Candida albicans* is used for the product possessing fungistatic activity. Preparation of the inoculums for positive control is the same as described under the Test for sensitivity of medium (*E. Coli* inoculums preparation is same as *Staphylococcus aureus* inoculums), number of test microorganism added should be less than 100 cfu, the quantity of the product used is the same as described under the Test for sterility of the product being examined for each container of medium. Incubate the positive control container for 48-72 hours, the growth of the test microorganisms should be well.

(4) **Negative control** In the course of the sterility test for examined product, a negative control should be performed with the same solvent and diluents as the test used. There must be no growth of microorganisms. If surface-active substances, neutralizers or inactivators etc. are used during the test, their efficacy and their absence of inhibition for growth and survival of microorganisms must be demonstrated.

The test for sterility is carried out by the membrane filtration method or direct Inoculation method. The membrane filtration method is used whenever the nature of the product permits. The same method and experimental conditions should be adopted in sterility test as that used in validation test. Before opening the product containers to be tested, the exterior surfaces of containers must be thoroughly cleansed with a suitable disinfectant. If the containers are packaged under vacuum, sterile air should be transmitted into the container aseptically with suitable equipments (eg. Needles with sterilizing filter) before the container is opened to release the contents.

(5) Sample preparation and medium inoculation

Unless otherwise specified, Carry out the test as described below.

1) Membrane filtration method

Sealed sterility testing system may be preferred used in the technique of membrane filtration. Other general membrane filter may also be adopted. The membrane used in the test for sterility has a nominal pore size which is not greater than $0.45 \mu\text{m}$ and a diameter about 50 mm. Selection of filtration membrane type should be performed according to the characters of product to be tested and solvent used. The filtration apparatus and membrane should be sterilized by appropriate means before use. Integrity of the membrane in the apparatus should be kept during the process filtration. When filtering aqueous solution, the membrane in the filter should be pre-wetted with a small quantity of rinsing fluids. When the samples tested are oily preparations, the filtration apparatus and membrane must be thoroughly dried before

always cover the whole surface of the membrane throughout the operation for maximal filtration efficiency. If necessary, wash the membrane by filtering through it with 100 ml of rinsing fluid for one single membrane each time, and the total volume used should not be too much to avoid any damage to the microorganisms held by the membrane, after filtering the sample solution.

① Aqueous solutions Transfer the specified quantity of samples tested directly into the membrane or membranes, or mix the samples into an aseptic vessels containing suitable quantity of the sterile diluent and transfer the mixture to the the membrane or membranes. Filter immediately. If the product being examined contain preservatives or have inherent antimicrobial activity, the membrane should be washed not less than three times by filtering through it with suitable quantity of the rinsing fluid. If sealed sterility testing system is used, transfer 100 ml of fluid thioglycollate medium and Modified Martin medium into the correspondence filter apparatus respectively after washing. If other general membrane filters are used, aseptically remove the membrane from the apparatus and cut it into three equal parts, and transfer each part to each of container containing 50 ml of suitable media, set one of the container as a positive control.

② Solid soluble in aqueous vehicle Transfer the specified quantity of specimens tested, dissolve with suitable sterile diluent or as directed in the label. Proceed with the test as directed above for Aqueous solutions.

③ β -lactam antibiotics Transfer the specified quantity of specimens and prepare samples as directed above for aqueous solutions or Solid soluble in aqueous vehicle, filter immediately, wash the membrane with suitable rinsing fluid. Then rinse the filter with rinsing fluids containing suitable quantity of sterile β -lactamase to inactivate any residual antibiotic activity on the membranes, if necessary, add a few sterile β -lactamase into the medium. Alternatively, the membranes can be inoculated directly to medium containing suitable quantity of sterile β -lactamase. Inoculate medium as directed above for Aqueous solutions.

④ Water insoluble substances Transfer the specified quantity of specimens and filter directly, or mix in a sterile diluent containing polysorbate 80 or other suitable emulsifying agent, and transfer it into the membrane or membranes. Filter immediately. Wash the membrane at least three times with rinsing fluid containing 0.1%-1% polysorbate 80. The membranes are inoculated to medium with or without containing polysorbate 80. Inoculate medium as directed above for Aqueous solutions.

⑤ Ointments and Viscous oils soluble in isopropyl myristate Mix specified quantity of specimens tested in suitable quantity of sterile isopropyl myristate, shake vigorously to completely dissolve the sample. If necessary, heat the mixture to not more than 44°C, Filter as rapidly as possible before the mixture cools down. In exceptional case when the mixture is unable to be filtered, more than 100 ml diluents should be added to the above mixture, shake sufficiently and extract the solution, then transfer the aqueous phase in underlayer into the membrane or membranes and filter immediately. Proceed washing membrane and inoculating medium as described above for water insoluble substances.

⑥ Sterile aerosol (or nebulization) products Transfer the specified quantity of product containers tested to a refrigeratory, and freeze for about 1 hour. Aseptically drill quickly a hole in the top end of each container and release the propellant, then open the container aseptically. Proceed as directed above for aqueous solutions or water insoluble substances, whichever applicable.

specimens tested, fit a sterile needle on the syringe (not included in the product package). If necessary, dissolve with suitable sterile diluent or with solvent specified by product label. Proceed with the test as directed above for Aqueous solutions or water insoluble substances, whichever applies. Needles included in the product package should also be tested for sterility using direct inoculation method.

⑧ Devices with pathways Take the specified quantity of devices tested, pass 50-100 ml rinsing fluids through each one to wash the inner surface of device. Collect the fluids in a sterile vessel. Proceed as directed above for Aqueous solutions. At the same time, Needles attached with package should be tested for sterility using direct inoculation method.

2) Direct Inoculation method

Direct Inoculation method is to directly transfer the specified quantity of product tested into fluid thioglycollate medium and Modified Martin medium respectively. In each container Incubated, the volume of samples tested is not more than 10% of the volume of the medium, and the volume of fluid thioglycollate medium should not be less than 15 ml, the volume of Modified Martin medium should not be less than 10 ml, unless otherwise specified. Use the same medium volume and height in the container as in Validation test. Inoculate the same number of containers for each medium as the number of products to be tested.

① Turbid aqueous solution Transfer the specified quantity of specimens tested into each culture medium.

② Solid articles Directly transfer specified quantity of specimens tested into each culture medium, or prepare a suspension of the product with suitable sterile diluent or as directed in the label, then transfer the specified quantity of specimens into each culture medium.

③ β -lactam antibiotics or sulfonamides Mix the specified quantity of specimens tested to the sterile dilution containing suitable quantity of sterile β -lactamase or p-aminobenzoic acid for neutralizing the antimicrobial activity. Inoculate the prepared suspension into each culture medium. Alternatively, Transfer directly the specified quantity of specimens into each culture medium containing sterile β -lactamase or p-aminobenzoic acid.

④ Water insoluble substances Transfer the specified quantity of specimens tested to a sterile container, add the dilution containing suitable quantity of polysorbate 80 or other emulsifying agent to the container and mix to emulsify the specimens. Inoculate the suspension prepared above into each culture medium. Alternatively, Transfer directly the specified quantity of specimens into each culture medium containing polysorbate 80 or other emulsifying agent.

⑤ Surgical dressing Take the specified quantity of packages. Aseptically open the package, and remove about 100 mg or 1 cm×3 cm dressings from different parts of each package into each culture medium containing sufficient volume to completely immerse the sample tested.

⑥ Catgut or sutures or other single-use material Take the specified quantity of the minimal package. Aseptically open the package and remove the entire material of each package into each culture medium containing sufficient volume to completely immerse the sample tested.

⑦ Sterile medical devices Take the specified quantity of packages, inoculate the whole device to each culture medium containing sufficient volume to immerse the device completely, if necessary, the devices tested should be disassembled or cut into pieces.

⑧ Radiopharmaceutical Open one container of product

medium and 7.5 ml Modified Martin medium separately.

(6) Incubation and observation

Incubate all medium containers above for 14 days at required temperature. Observe and record each medium container for evidence of microbial growth every day during incubation period. If the product being tested renders medium turbid so that the presence or absence of microbial growth can not be readily determined by visual examination, 14 days after the beginning of incubation, transfer suitable portions of the medium to fresh containers with the same kind of medium or slants, and incubate the fresh containers 2 days for bacteria and 3 days for fungi, then examine the fresh containers for evidence of microbial growth; or smear a small amount of the medium on a slide, stain and examine with microscope for the suspected microbial growth.

5. Evaluation of results

Except the positive control container, if no evidence of microbial growth is found in all of the test containers described above, the product to be examined complies with the test for sterility; if evidence of microbial growth is found in any one of the test containers, the product to be examined

does not comply with the test for sterility, unless it can be clearly demonstrated that the test was invalid for causes unrelated to the product to be examined. The test may be considered invalid only when one or more of the following conditions are fulfilled;

(1) The result of the microbiological monitoring of the sterility testing facility shows that it does not meet the requirements of the test for sterility.

(2) A review of the testing procedure used during the test in question reveals a fault.

(3) Microbial growth is found in the negative control container.

(4) After determination of the identification of the microorganisms isolated from the test, the growth of this species (or these species) may be ascribed unequivocally to faults in respect with the material or the technique used in conducting the sterility test procedure.

If the test is validated to be invalid, it should be repeated with the same number of the samples and procedure as in the original test. If no evidence of microbial growth is found in the test repeated, the product examined complies with the test for sterility; if microbial growth is found, the product examined does not comply with the test for sterility.

Table 1 Minimum number of product to be tested from each batch

Product to be tested	Number of items in the batch	Minimum number of items to be tested for each medium*
Parenteral preparations	Not more than 100	10% or 4 containers, whichever is the greater
	More than 100 and not more than 500	10 containers
	More than 500	2% or 20 containers, whichever is less
For large-volume parenteral preparations (more than 100 ml)		2% or 10 containers, whichever is less
Ophthalmic and other noninjectable preparations	Not more than 200 containers	5% or 2 containers, whichever is the greater
	More than 200	10 containers
	Up to 4	Each container
Bulk solid products	More than 4 containers, and not more than 50 containers	20% or 4 containers, whichever is greater
	More than 50 containers	2% or 10 containers, whichever is greater
Pharmacy bulk packages of Antibiotics (greater than 5 g)		6 containers
Medical Devices	Not more than 100 articles	10% or 4 articles, whichever is greater
	More than 100, and not more than 500 articles	10 articles
	More than 500 articles	2% or 20 articles, whichever is less

* If the content of one container are not sufficient to inoculate the two media, this number may be doubled.

Table 2 Minimum quantity of liquid product to be used for each medium

Quantity per container	Minimum quantity per container to be used for each medium
Not more than 1 ml	The whole contents of each container
more than 1 ml, and less than 5 ml	Half the contents of each container
Not less than 5 ml, and less than 20 ml	2 ml
Not less than 20 ml, and less than 50 ml	5 ml
Not less than 50 ml, and less than 100 ml	10 ml
Not less than 50 ml, and less than 100 ml (Intravenous)	Half the contents of each container
Not less than 100 ml, and not more than 500 ml	Half the contents of each container
More than 500 ml	500 ml

Table 3 Minimum Quantity of solid product to be tested for each medium

Quantity per container	Minimum quantity per container to be used for each medium
Less than 50 mg	The whole contents of each container
Not less than 50 mg and less than 300 mg	Half the contents of each container
Not less than 300 mg and less than 5 g	150 mg
Not less than 5 g	500 mg
Surgical dressing/cotton/gauze	100 mg or 1 cm×3 cm
Sutures and other single-use material	the whole device*
Devices with pathways for single-use	the whole device
Other medical devices	the whole device (cut into pieces or disassembled if necessary)*

* : If the device is bulky, the device may be submerged in more than 2000 ml of the medium.

XI J Microbial Limit Tests

Microbial limit tests provide tests for the estimation of the number of viable micro-organisms present in non-sterile pharmaceutical products of all kinds, including preparations, raw materials, excipients. The bacteria, fungi or yeasts count, as well as the specified bacteria, are tested.

Microbial limit tests should be carried out in a class 100 laminar-air-flow cabinet located within a 10000-class clean-room. The whole process should be performed under strictly aseptic conditions to avoid any microbial contamination. The cleanliness of working areas including laminar flow cabinet, working bench, background room should be monitored regularly according to the current national standard such as **The detecting method for airborne particles, airborne microbe and settling microbe in the clean room (area) of the pharmaceutical industry.**

Surfactants, neutralizing agents, or inactivators do not affect the growth of micro-organisms if they are used in the products to be examined.

Unless otherwise specified, incubate bacteria at 30-35°C, at 23-28°C for fungi or yeasts, and at 35-37°C for specified bacteria.

The test result is reported in the unit of 1 g, 1 ml, 10 g, 10 ml or 10 cm².

Quantity of products to be tested

It refers to the quantity of the product to be examined for one single test (in g, ml, or cm²).

Unless otherwise specified, use samples of 10 g or 10 ml of the product to be examined for testing. Use 100 cm² for pellicles. The quantity may be appropriately decreased for expensive drugs and small-package drugs. Increase the quantity by 10 g or 10 ml when *Salmonella* is tested.

Select the samples at random from at least 2 minimum containers, and at least 4 pieces for pellicles.

The quantity of sampling (from at least 2 minimum containers) is 3 times the quantity for testing.

Preparation of the sample

Samples are prepared appropriately depending on their physico-chemical properties and biological characteristics. If necessary, samples are warmed in a water bath not more than 45°C. The samples are inoculated to the culture media within one hour of preparation.

Unless specified otherwise, follow the methods below to prepare the samples.

1. Liquids

Take 10 ml of the product, dilute to 100 ml with sterile

this 1 : 10 solution as the test solution. Add an appropriate amount of sterile polysorbate 80 to an oil to make it dispense evenly. For aqueous preparations, the products may be mixed as the test solution.

2. Solids, semi-solids, and viscous products

Take 10 ml of the product, dilute to 100 ml with sterile sodium chloride-peptone buffer (pH 7.0), mix well with a homogenizer or other devices. Use this 1 : 10 solution as the test solution. If necessary, add an appropriate amount of polysorbate 80 and warm the sample in a water bath so that it dispense evenly.

3. Sample specified preparation

(1) Non-aqueous products

Method 1 Transfer 5 g (or 5 ml) of the product into a sterile beaker containing 5 g melt (not exceeding 45°C) Span 80, 3 g glyceryl monostearate, 10 g polysorbate 80, mix, slowly add sterile sodium chloride-peptone buffer (pH 7.0, 45°C) to 100 ml with agitating to make an emulsion. Use this 1 : 20 emulsion as the test solution.

Method 2 Transfer 10 g of the product to a suitable container with 20 ml sterile isopropyl myristate (prepared as described under Sterility test, the amount may be increased if necessary) and sterile glass beads, agitate thoroughly to dissolve the product. Then add 100 ml sterile sodium chloride-peptone buffer (pH 7.0, 45°C), agitate for 5-10 min for extraction. Allow it to stand until the two layers separate. Use the 1 : 10 aqueous layer as the test solution.

(2) Pellicles

Take 100 cm² of the pellicles, cut into pieces. Immerse into 100 ml of sterile sodium chloride-peptone buffer (pH 7.0), and agitate. Use the 1 : 10 diluent as the test solution.

(3) Enteric-coated and colonic-coated products

Transfer 10 g of the product, dilute to 100 ml with sterile phosphate buffer solution (pH 6.8 for enteric-coated and pH 7.6 for colonic-coated), warm in a 45°C water bath, and shake to dissolve. Use this 1 : 10 solution as the test solution.

(4) Aerosols and sprays

Chill a prescribed amount of the product in a refrigerator for approximately 1 hour. Take it out, dig a small hole rapidly and aseptically. Put it at room temperature and allow the propellant to escape. Transfer all the residue with a sterile syringe, add an appropriate amount of sterile sodium chloride-peptone buffer (pH 7.0, add an appropriate amount of sterile polysorbate 80 for water-insoluble ingredients), and mix well. Take a sample equivalent to 10 g or 10 ml, and dilute by 10 folds. Use this 1 : 10 solution as the test solution.

(5) Products containing antimicrobial agents

When the products to be examined possess antimicrobial

methods described below.

① Culture media dilution Transfer the prescribed amount of the product to an adequate volume of culture media. Thus the concentration of the product decreases until it possesses no antimicrobial activity. For the limit test of bacteria, fungi, and yeasts, distribute 2 ml of the diluted solution over Petri dishes. Add agar media, mix well, and allow it to solidify. Incubate the dishes under appropriate conditions. Count the average number of colonies obtained with 1 ml of the solution. Report the counts by the plate-count method. The amount of diluting culture media may increase when specified bacteria are tested.

② Enrichment of micro-organisms by centrifugation Centrifuge a specified quantity of the product at 3000 rpm for 20 minutes. If the product contains precipitates, centrifuge at 500 rpm for 5 minutes at first, and then collect the supernatant and centrifuge again as described above. Discard the supernatant and dilute the residue at the bottom (about 2 ml) to original specified quantity with diluting solution.

③ Membrane filtration See the membrane filtration method under Bacteria, fungi, and yeasts count.

④ Neutralization If the product to be examined contains antimicrobial agents like mercury, arsenic, or antiseptics, use suitable neutralizing agents or inactivators to eliminate its antimicrobial activity. The neutralizing agents or inactivators may be added in the diluting solutions or culture media.

Bacteria, fungi or yeasts count

Method validation

The bacteria, fungi or yeasts count method for microbial limit tests is validated before it is used for drugs. The count method is revalidated if changes in composition of the product or testing conditions may affect the result. Validation test is to be conducted as described under Bacteria, fungi or yeasts count using exactly the same methods and the following instructions. The tests should be performed separately for each of the micro-organism tested.

Test strains

The viable micro-organisms used in the test must not be more than five passages removed from the original master seed lot. The suitable seed-stock technique should be used so that the micro-organism characters can be maintained.

<i>Escherichia coli</i>	[CMCC (B) 44102]
<i>Staphylococcus aureus</i>	[CMCC (B) 26003]
<i>Bacillus subtilis</i>	[CMCC (B) 63501]
<i>Candida albicans</i>	[CMCC (F) 98001]
<i>Aspergillus niger</i>	[CMCC (F) 98003]

Preparation of Inoculum Inoculate freshly cultured of *Escherichia coli*, *Staphylococcus aureus*, or *Bacillus subtilis* to nutrient broth medium or nutrient agar medium, incubate for 18-24 hours; Inoculate freshly cultured of *Candida albicans* to modified Martin medium or modified Martin agar medium, and incubate for 24-48 hours; The above cultures are diluted to 50-100 colony-forming units (cfu) per ml with sterile solution of 0.9% sodium chloride. Inoculate freshly cultured of *Aspergillus niger* to modified Martin agar medium, and incubate for 5-7 days. Wash out the spores with 3-5 ml sterile solution of 0.9% sodium chloride. Transfer the spore suspension to a sterile test tube. Dilute the suspension to 50-100 cfu per ml with sterile solution of 0.9% sodium chloride.

Validation test Carry out at least 3 parallel tests, and calculate the recovery of micro-organisms for each test.

(1) Testing group When the plate count method is used, transfer 1 ml of the lowest possible serial dilution of the sample and 50-100 cfu testing micro-organisms to a Petri

dish, and pour the agar medium immediately. Use 2 Petri dishes for each microbial strain, and record the colony number by the plate count method. When the membrane filtration method is used, transfer specified quantity of the sample solution through a membrane, rinse appropriately, add 50-100 cfu testing micro-organisms in the last portion of rinsing solution. Record the colony number by membrane filtration method.

(2) Microbial group Determine the number of micro-organisms added in the test.

(3) Product control Transfer a prescribed quantity of the product, determine the number of bacteria, fungi or yeasts in sample.

(4) Diluting solution control Diluting solution control should be carry out when the sample of preparation used dispersant, emulsification, neutralization, centrifugation and filtration etc. Use diluting solution instead of sample and add the testing micro-organisms to 50-100 cfu per ml, preparation test solution and determine the number of micro-organisms as described above for testing group.

Evaluation of results

In each of the 3 parallel tests, the microbial recovery is not less than 70% (average colony number of the diluting solution control/average colony number of the testing group $\times 100\%$). If the microbial recovery of the testing group is not less than 70% [(average colony number of the testing group-average colony number of the product control)/average colony number of the microbial group $\times 100\%$], proceed the bacteria, fungi or yeasts count of the product to be examined as described above. If the microbial recovery in any of the tests is below 70%, eliminate the antimicrobial activities of the product by appropriate methods like culture media dilution, centrifugation, membrane filtration, or neutralization. The method needs re-validation.

The validation test is carried out in parallel with the bacteria, fungi, or yeasts count of the product to be examined.

Examination method

Examination method include plate count and membrane filtration method. Use validated plate count method or membrane filtration method to carry out the bacteria, fungi, or yeasts count of the product to be examined.

Dilute the homogenized solution to be test with pH 7.0 sterile solution of sodium chloride-peptone buffer solution to make serial dilutions of 1:10, 1:100, 1:1000, etc.

1. Plate count method

Use two to three successive serial dilutions as the testing solution. Transfer 1 ml of the sample to a sterile Petri dish (90 mm in diameter), add 15-20 ml Nutrient agar medium, or Sodium rose bengal agar medium, or Yeast extracts peptone glucose agar medium (melted at not exceeding 45°C), mix well, and allow the contents to solidify at room temperature. Invert the Petri dish and incubate under appropriate conditions. For each dilution, use at least 2 Petri dishes for each culture medium.

Negative control Transfer 1 ml of the dilution to a sterile Petri dish, promptly add the culture medium, and allow the contents to solidify at room temperature. Invert the Petri dish and incubate under appropriate conditions. Use at least 2 Petri dishes for each culture medium. No evident growth of micro-organisms occurs in either of the Petri dish.

Incubation and counting Unless otherwise prescribed, incubate the bacteria for 48 hours, count the number of colonies every day, report the number on the 48 hour; incubate the fungi and yeasts for 72 hours, count the number of colonies every day, report the number on the 72 hour; extend the incubation time to 5-7 days if necessary. Do not

count the number of colonies assemble. Following counting, calculate the number of colonies of each dilution of the product, report the result following the Microbial number report rule described below.

For liquid preparations containing honey and royal jelly, use Sodium rose bengal agar medium for fungi count and Yeast extracts peptone glucose agar medium for yeasts count. Sum the counts as the final result.

Microbial number report rule Select the dilution in which the average number of colonies of bacteria and yeasts is 30-300 cfu and of the fungi is 30-100 cfu.

If average microbial number of any dilution is less than 30, select the number of the lowest dilution. Calculate the number of cfu per g or per ml product to be tested.

When no microbial growth occurs in any of the dilutions, or it only occurs for the lowest dilution where the average microbial number of the cfu is less than 1, report the result with 1 multiplying by the lowest dilution folds.

2. Membrane filtration

Use membranes having a nominal pore size not greater than 0.45 μm , and a diameter of appropriately 50 mm. The type of filter material is chosen in such a way that the bacteria retaining efficiency is not affected by the component or solvent of the sample to be investigated. The filter unit and membrane are sterilized prior to use by appropriate means. Maintain the performance characteristic of the filter during the testing process. Moist the membrane with a minimum amount of rinsing solution before the test of aqueous products. Where the product to be examined is an oil, the membrane and filter unit are thoroughly dried before use. Let the product solution and rinsing solution cover the whole membrane to obtain its maximal performance. Rinse the membrane with 100 ml of rinsing solution each time if necessary. Do not use a large amount of rinsing solutions to avoid disturbance of the micro-organisms on the membrane. Take representing 1 g or 1 ml of the product, or 1 ml suitable dilution solution of the sample if product include large numbers of micro-organism, and dilute to 100 ml with diluting solution, mix well and filter. Rinse the membrane with pH 7.0 sterile sodium chloride-peptone buffer solution or other suitable rinsing solution, as described above for validation test. Transfer the membrane onto a Nutrient agar medium or Sodium rose bengal agar medium, or Yeast extracts peptone glucose agar medium plate, and incubate. Use at least one membrane for each medium.

Negative control Use 1 ml of the dilution, and carry out the test as described above. No evident growth of micro-organisms occurs in the negative control.

Incubation and counting Carry out the test as described above for plate count method. The number of micro-organisms on each membrane is not more than 100 cfu.

Microbial number report rule Multiply the average microbial number by dilution folds as the number of cfu per g or per ml product to be test. If no microbial growth occurs, report the result with less than 1 or 1 multiplying by the lowest dilution folds.

Test for specified micro-organisms

Method validation

The method for specified micro-organisms test is validated before it is used for microbial limit tests for drugs. The method is re-validated if changes in composition of the product or testing conditions may affect the result.

Validation micro-organisms used should be complied with requirements of the microbial limits of the product. Validation the method of coliform should be used *Escherichia coli*. Carry out the test as described under the Test for

specified micro-organisms exactly the same methods and the following instructions.

Test strains he strains comply with the requirements as described above for bacteria, fungi, or yeasts count.

Escherichia coli [CMCC (B) 44102]

Staphylococcus aureus [CMCC (B) 26003]

Salmonella paratyphi B [CMCC (B) 50094]

Pseudomonas aeruginosa [CMCC (B) 10104]

Clostridium sporogenes [CMCC (B) 64941]

Preparation of Inoculum Inoculate freshly cultured of *Escherichia coli*, *Staphylococcus aureus*, *Salmonella paratyphi B*, or *Pseudomonas aeruginosa* to nutrient broth medium or nutrient agar medium; inoculate freshly cultured of *Clostridium sporogenes* to fluid thioglycollate medium; incubate for 18-24 hours. Dilute the suspension to 10-100 cfu per ml with sterile solution of 0.9% sodium chloride.

Validation test

(1) **Testing group** Add a specified quantity of the product to be examined and 10-100 cfu testing micro-organisms to the culture medium, carry out the test by prescribed methods described below. When the membrane filtration method is used, filter an appropriate quantity of the product through a membrane, rinse appropriately, add the testing micro-organisms in the last portion of rinsing solution. Transfer the membrane to the culture medium for incubation.

(2) **Negative control** Negative control is set to verify the specificity of the testing method. The procedure is the same as described above for testing group. Use *Staphylococcus aureus* as the negative control microorganism for the test of *Escherichia coli*, coliform, or *Salmonella* species. Use *Escherichia coli* as the negative control microorganism for the test of *Pseudomonas aeruginosa*, *Staphylococcus aureus*, and *Clostridium* species. No control micro-organism is detected.

Evaluation of results

No control micro-organism is detected in the negative control. If the tested micro-organism is detected in the testing group, proceed the test with the product to be examined. If the tested micro-organism is not detected in the testing group, eliminate the antimicrobial activities of the product by appropriate methods like culture media dilution, centrifugation, membrane filtration, or neutralization. The method needs re-validation.

The validation test is carried out in parallel with the test for specified micro-organisms of the product to be examined.

Examination method

Carry out the test of the product to be examined as described above for validation test.

Positive control Add 10-100 cfu of the tested micro-organism to the positive control, carry out the test as the Test for specified micro-organisms. The tested micro-organism can be detected in the positive control.

Negative control Transfer 10 ml of diluting solution to a prescribed amount of culture media, and incubate as the Test for specified micro-organisms. No micro-organism growth occurs in the negative control.

(1) ***Escherichia coli*** Inoculate 10 ml of the test solution (equivalent to 1 g, 1 ml or 10 cm^2) to be examined to an appropriate amount of Bile salt lactose culture medium (not less than 100 ml) directly or after appropriate treatment, incubate for 18-24 hours (48 hours if necessary).

Inoculate 0.2 ml of the above culture to a tube containing 5 ml MUG medium, and incubate. Observe under 366 nm UV light at the time of 5 hours and 24 hours, respectively. Use blank MUG medium as the negative control. The result is MUG-positive if the cultures give fluorescent light, or MUG

negative if no fluorescent light is observed. Following observation, add several drops of indole test solution. The result is indole-positive if the liquid surface presents a rosy colour, or indole-negative if no colour change takes place. The negative control is MUG-negative and indole-negative. A MUG-positive and indole-positive result indicates the presence of *E. coli* in the product. A MUG-Negative and indole-Negative result indicates the absence of *E. coli* in the product. If the product is MUG-positive and indole-negative, or MUG-negative and indole-positive, inoculate the cultures on eosin methylene blue agar medium plate or MacConkey agar medium plate, and incubate for 18-24 hours.

If no growth of micro-organism occurs on the plate, or the appearance of the microbial colonies does not match the descriptions in Table 1, the product passes the test. Otherwise, confirm the result by suitable biochemical tests.

Table 1 Morphologic characteristics of *Escherichia coli* colonies

Culture medium	Characteristic colonial morphology
Eosin methylene blue agar medium	Purple black, light purple, bluish purple or pink, deep purple at the center of colony or no obvious dark center, circular, slight convex, regular margin, smooth surface, moist, metal gloss often appeared.
MacConkey agar medium	Brilliant pink or pale red, deep pink at center of the colony, circular, flat, regular margin, smooth surface, moist.

(2) **Coliform** Use 3 tubes each containing an appropriate amount of Bile salt lactose fermentation culture medium (not less than 10 ml), respectively add 1 ml of 1 : 10 (containing 0.1 g or 0.1 ml of the product), 1 : 100 (containing 0.01 g or 0.01 ml of the product), 1 : 1000 (containing 0.001 g or 0.001 ml of the product) dilutions. Add 1 ml of diluting solution to another tube as the negative control. Incubate for 18-24 hours.

The product passes the test if no microbial growth occurs, or no gas bubbles or acid forms. If the formation of acid and gas bubbles is observed, inoculate the cultures on Eosin methylene blue agar medium plate or MacConkey agar medium plate, and incubate for 18-24 hours.

If no growth of micro-organisms occurs on the plate, or the appearance of the microbial colonies does not match the descriptions in Table 2, or the colonies are not gram-negative bacilli, the product passes the test. If the morphology of the colonies matches the descriptions in Table 2, and they are gram-negative bacilli without spores, confirm the result by suitable biochemical tests.

Table 2 Morphologic characteristics of coliform colonies

Culture medium	Characteristic colonial morphology
Eosin methylene blue agar medium	Purple black, or purple red, circular, slight convex, regular margin, smooth surface, moist.
MacConkey agar medium	Brilliant pink or pale red, circular, flat, regular margin, smooth surface, moist.

Validation test Choose 4-5 suspect colonies from the plate, individually inoculate in tubes containing bile salt lactose culture medium, and incubate for 24-48 hours. The formation of acid and gas bubbles indicates the presence of coliform. Otherwise, absence coliform in the product.

According to the number of coliform-positive tubes, and Table 3, record the probable number of coliform 1 g or 1 ml

Table 3 Probable number of coliform

Result of each quantity of product			Probable number of coliform N(per g or ml)
0.1 g or 0.1 ml	0.01 g or 0.01 ml	0.001 g or 0.001 ml	
+	+	+	$N > 10^3$
+	+	-	$10^2 < N < 10^3$
+	-	-	$10 < N < 10^2$
-	-	-	$N < 10$

Note: + represents coliform is detected, and - not detected.

(3) ***Salmonella species*** Inoculate 10 g or 10 ml of the product to be examined to an appropriate amount (not less than 200 ml) of Nutrient broth culture medium directly or after appropriate treatment, mix well with a homogenizer or other devices, and incubate for 18-24 hours.

Inoculate 1 ml of the culture above to 10 ml Sodium tetrathionate brilliant green culture medium, incubate for 18-24 hours. Then streak the cultures on the surface of Bile salt sulfur milk agar culture medium (or *Salmonella* and *Shigella* agar medium) and MacConkey agar medium (or Eosin methylene blue agar) plates separately, incubate for 18-24 hours (or 40-48 hours if necessary). If no bacterial growth occurs on the plate, or the morphology of the colonies does not conform to the descriptions in Table 4, *Salmonella* is absence in the product to be tested.

If the morphology of the colonies conforms to or is similar to the description in Table 4, choose 2-3 colonies and transfer to Triple sugar iron agar culture medium slant with a inoculating needle, using surface and deep inoculation. Incubate for 18-24 hours. If red colour on the surface and yellow colour at the bottom, or yellow on the surface and black at the bottom is not observed, *Salmonella* is absence in the product to be tested. Otherwise, confirm the presence of *Salmonella* by carrying out suitable biochemical and Serum agglutination tests with the cultures on triple sugar iron agar culture medium slant.

Table 4 Morphologic characteristics of *Salmonella* colonies

Culture medium	Characteristic colonial morphology
Bile salt sulfur lactose agar	Colourless to pale orange, semitransparent, black at the center or whole black or no black
<i>Salmonella</i> and <i>Shigella</i> agar medium	Colourless to pale red, semitransparent or opaque, black brown in the center of the colonies occasionally
Eosin methylene blue agar medium	Colourless to pale orange colour, transparent or semitransparent, smooth moist circular colonies
MacConkey agar medium	Colourless to pale orange colour, transparent or semitransparent, dark in the center occasionally

(4) ***Pseudomonas aeruginosa*** Inoculate 10 ml of the test solution (equivalent to 1 g, 1 ml or 10 cm² of the product) to an appropriate amount (not less than 100 ml) of Bile salt lactose culture medium, incubate for 18-24 hours. Then streak the cultures on the surface of Cetyl trimethylammonium bromide agar culture plate, and incubate for 18-24 hours.

Pseudomonas aeruginosa colonies are typically flat, irregular, diffusing margin, moist surface, greyish white, occasionally surrounded by bluish green zone. If no bacterial growth occurs on the plate, or the morphology of the colonies does not conform to the above descriptions, *Pseudomonas aeruginosa* is absence in the product to be tested. If the growth colonies reveal the above characters,

culture slant, incubate for 18-24 hours. Use the slant cultures for Gram's staining, microscopical examination, and oxidase test.

Oxidase test Place a piece of clean filter paper in a Petri dish, spread the slant cultures on the filter paper with a sterile glass bar, add dropwise freshly prepared 1% *N*, *N*-dimethyl-*p*-phenylenediamine dihydrochloride test solution. The oxidase test is positive if the cultures appear pink and then turn into purplish red within 30 seconds. Otherwise, the test is negative.

If the slant cultures are not Gram-negative bacilli, or the oxidase test is negative, *Pseudomonas aeruginosa* is absence in the product to be tested. Otherwise, carry out the pyocyanin test.

Pyocyanin test Inoculate the slant cultures onto PDP agar culture slant, and incubate for 24 hours. Then add 3-5 ml of chloroform to the test tube, agitate the medium and shake thoroughly. Allow to stand for a while, then transfer the chloroform layer to a new tube, add about 1 ml of 1 mol/L hydrochloric acid solution, allow to stand for a moment following shaking, observe the phenomenon. If the solution appears pink, the pyocyanin test is positive; or otherwise, negative. Use un-inoculated PDP agar culture slant as the negative control. The negative control is pyocyanin-negative. If the bacteria in question are Gram-negative bacilli, and are oxidase test positive and pyocyanin test positive, *Pseudomonas aeruginosa* is presence in the product to be examined. If the bacteria in question are Gram-negative bacilli, and are oxidase test positive and pyocyanin test negative, proceed the test by carrying out suitable biochemical tests to confirm whether they are *Pseudomonas aeruginosa*.

(5) *Staphylococcus aureus* Inoculate 10 ml of the test solution (equivalent to 1 g, 1 ml or 10 cm² of the product) to an appropriate amount (not less than 100 ml) of Sodium tellurite broth culture medium (or Nutrient broth culture medium) directly or after appropriate treatment, incubate for 18-24 hours (48 hours if necessary). Then streak the cultures on the surface of Egg yolk high salt agar culture medium plate or Mannitol high salt agar culture medium plate, incubate for 24-72 hours. If no bacterial growth occurs on the plate, or the morphology of the colonies does not conform to the descriptions in Table 5, *Staphylococcus aureus* is absence in the product in question.

Table 5 Morphologic characteristics of *Staphylococcus aureus* colonies

Culture medium	Characteristic colonial morphology
Mannitol high salt agar culture medium	Golden yellow, circular convex, regular margin, yellow outer circle, colony diameter 0.7-1 mm.
Egg yolk high salt agar culture medium	Golden yellow, circular convex, regular margin, opaque outer circle due to lecithin degradation, colony diameter 1-2 mm.

If the morphology of the colonies conforms to or is similar to the description in Table 5, choose 2-3 colonies and inoculate onto Nutrient agar culture medium slant, and incubate for 18-24 hours. Take the obtained cultures for Gram's staining. And inoculate the cultures in Nutrient broth culture medium, and incubate for 18-24 hours, then carry out the coagulase test.

Coagulase test Use 3 sterile tubes, add 0.5 ml of (1 : 1) mixture of plasma and sterile water in each tube, then respectively add 0.5 ml of nutrient broth cultures of the suspect bacteria (or concentrated bacterial suspension prepared from the nutrient agar slant cultures), 0.5 ml of

concentrated bacterial suspension prepared from the nutrient agar slant cultures), and 0.5 ml of Nutrient broth culture medium or 0.9% sterile sodium chloride solution, which are testing tube, positive tube, and negative tube, respectively. Incubate the 3 tubes together. Examine the tubes at 3 hours and subsequently at suitable intervals up to 24 hours. The plasma in the negative tube maintains fluidity, and the plasma coagulates in the positive tube. If the plasma in the testing tube coagulates, the coagulase test is positive, or otherwise, negative. If the result of positive or negative tube does not conform to the above description, repeat the test.

If the suspect bacteria are not Gram-positive cocci, and the coagulase test is negative, *Staphylococcus aureus* is absence in the product to be tested.

(6) *Clostridium* Take two equal portions (10 ml, equivalent to 1 g or 1 ml of the product) of the sample solution. Heat one portion at 80°C for 10 minutes and cool rapidly. Do not heat the other portion. Inoculate the test solutions above to 100 ml of Chopped meat culture medium directly or after appropriate treatment separately. Incubate under anaerobic conditions for 72-96 hours. If no turbidity, gas bubbles, beef digestion, or bad smells form in the testing tube, *Clostridium* is absent in the product being examined. Otherwise, spread 0.2 ml of the cultures onto the surface of columbia agar culture medium plate to which gentamicin has been added, and incubate under anaerobic conditions for 48-72 hours. If no microbial growth occurs on the plate, *Clostridium* is absent in the product to be tested. If colonies are observed on the plate, select 2-3 colonies and carry out Gram's staining test and catalase test.

Catalase test Put the colonies from the plate above onto clean glass slices, add dropwise 3% hydrogen peroxide solution. If gas bubbles appear on the colony surface, the catalase test is positive, or otherwise, negative.

If the suspect colonies are Gram-positive *Clostridium*, with or without oval or round spores, and catalase test is negative, *Clostridium* is presence in the product being examined. Or otherwise, *Clostridium* is absence.

Evaluation of results.

If specified micro-organisms or other pathogenic micro-organisms are detected in one single test, the product does not pass the test. The test needs not repetition.

If any count of bacteria, of fungi, or of yeasts does not comply with the requirements, take samples at random from the same batch, and carry out two more independent repetitive tests. Report the average value from three determinations as the final result.

If fungi and yeasts are detected in eye preparations, the product being examined passes the test for fungi and yeasts count only if micro-organisms are not detected in two more repetitive tests.

If results of bacteria, fungi and yeasts count, as well as the test for specified micro-organisms meet the specified requirements for the product being examined, the product passes the test. If the result of bacteria, fungi and yeasts count, or the result for the test for specified micro-organisms does not comply with the specified requirements for the product being examined, the product does not pass the test.

Diluting solutions

The diluting solutions are sterilized by validated sterilization methods after preparation.

1. pH 7.0 sterile sodium chloride-peptone buffer solution
Prepare the solution as described under the Test for Sterility

2. pH 6.8 sterile phosphate buffer solution, pH 7.6 sterile phosphate buffer solution

Prepare the solution as described under Appendix XV D, filter, dispense in containers, and sterilize.

If necessary, add surfactants or neutralizing solutions before or after the sterilization.

3. 0.9% sterile sodium chloride solution

Transfer 9.0 g sodium chloride, dissolve in 1000 ml water, filter, dispense in containers, and sterilize.

Culture media

The media may be prepared as described below, or their dehydrated formulations may be used. The media should be Sterilized using a validated process.

1. Nutrient agar culture medium, nutrient broth culture medium, fluid thioglycollate medium, modified Martin medium, and modified Martin agar medium

Prepare the media as described under the Test for Sterility (Appendix XI H).

2. Sodium rose bengal agar medium

Peptone	5.0 g
Glucose	10.0 g
Potassium dihydrogen phosphate (KH_2PO_4)	1.0 g
Magnesium sulfate ($\text{MgSO}_4 \cdot 7\text{H}_2\text{O}$)	0.5 g
Sodium tetrachloro-tetraiodo-fluorescein	0.0133 g
Agar	14.0 g
water	1000 ml

Mix the above ingredients in water except glucose and sodium tetrachloro-tetraiodo-fluorescein, heat until dissolved, filter, and then add glucose and sodium tetrachloro-tetraiodo-fluorescein. Dispense in containers and sterilize.

3. Yeast extracts peptone glucose agar medium (YPD)

peptone	10.0 g
Yeast extracts	5.0 g
Glucose	20.0 g
agar	14.0 g
water	1000 ml

Mix the above ingredients in water except glucose, heat until dissolved, filter, and then add glucose. Dispense in containers and sterilize.

4. Bile salts lactose medium (BL)

peptone	20.0 g
lactose	5.0 g
Sodium chloride	5.0 g
Dipotassium hydrogen phosphate (K_2HPO_4)	4.0 g
Potassium dihydrogen phosphate (KH_2PO_4)	1.3 g
Ox bile salts (or sodium desoxycholate 0.5 g)	2.0 g
water	1000 ml

Mix the above ingredients in water except lactose and ox bile salts (or sodium desoxycholate), heat until dissolved, adjust the pH so that after sterilization it is 7.4 ± 0.2 , boiling. Filter, add lactose and ox bile salts (or sodium desoxycholate), dispense in containers and sterilize.

5. Bile salts lactose fermentation medium

Add 0.04% bromocresol purple indicator to the un-sterilized bile salts lactose medium, dispense in suitable tubes containing inverted tubule, and sterilize.

6. Eosin methylene blue agar medium (EMB)

Nutrient agar medium	100 ml
2% eosin solution	2 ml
20% lactose solution	5 ml
0.5% methylene blue solution	1.3-1.6 ml

Melt the nutrient agar medium by heating, cool to 60°C , add aseptically the other three solutions, shake thoroughly, and pour into Petri dishes.

7. MacConkey agar medium (MacA)

Peptone	20.0 g
Sodium chloride	5.0 g
lactose	10.0 g
1% neutral red solution	3.0 ml
Ox bile salts	5.0 g
Agar	14.0 g
water	1000 ml

Mix peptone and sodium chloride in water, heat until dissolved, adjust the pH so that after sterilization it is 7.2 ± 0.2 . Add agar, heat to melt, then add the other ingredients. Shake thoroughly, dispense in containers, and sterilize. Cool to 60°C , and pour into the Petri dishes.

8. 4-methylumbelliferyl- β -D-glucuronide (MUG) culture medium

peptone	10.0 g
Manganese sulfate	0.5 mg
Zinc sulfate	0.5 mg
Magnesium sulfate	0.1 g
Sodium chloride	5.0 g
Calcium chloride	50 mg
Potassium dihydrogen phosphate (anhydrous)	0.9 g
Disodium hydrogen phosphate (anhydrous)	6.2 g
Sodium sulfite	40 mg
Sodium desoxycholate	1.0 g
MUG	75 mg
water	1000 ml

Mix the above ingredients in water except MUG, heat until dissolved, adjust the pH so that after sterilization it is 7.3 ± 0.1 , add MUG, dissolve, dispense 5 ml of the medium to each tube and sterilize.

9. Triple sugar iron agar medium (TSI)

Peptone	20.0 g
glucose	1.0 g
Beef extract powder	5.0 g
Sodium chloride	5.0 g
lactose	10.0 g
sucrose	10.0 g
Ferrous sulfate	0.2 g
Sodium thiosulfate	0.2 g
0.2% phenosulfonphthalein solution	12.5 ml
agar	12.0 g
water	1000 ml

Mix peptone, beef extracts powder, sodium chloride, ferrous sulfate and sodium thiosulfate, dissolve in water heat until dissolved, adjust the pH so that after sterilization it is 7.3 ± 0.1 . Add agar, heat to melt, then add the other ingredients. Shake thoroughly, dispense in containers, and sterilize. Make short slants (2-3 cm) after the media cool.

10. Sodium tetrathionate brilliant green medium (TTB)

Peptone	5.0 g
Calcium carbonate	10.0 g
Ox bile salts	1.0 g
Sodium thiosulfate	30.0 g
water	1000 ml

Dissolve the above ingredients in water heat until dissolved, and sterilize.

Just prior to use, add 0.2 ml iodine test solution and 0.1 ml brilliant green test solution to 10 ml of the medium, and shake thoroughly.

11. Salmonella and Shigella agar culture medium (SS)

peptone	5.0 g
Sodium citrate	8.5 g
0.1% Brilliant green solution	0.33 ml
Beef extract powder	5.0 g
Ammonium ferrous citrate	1.0 g
lactose	10.0 g
Sodium thiosulfate	8.5 g
Ox bile salts	8.5 g
1% neutral red solution	2.5 ml

agar	16.0 g
water	1000 ml

Mix the above ingredients in water except lactose, neutral red solution and agar, heat until dissolved, adjust the pH so that after sterilization it is 7.2 ± 0.1 . Filter, add agar and heat to melt. Then add the other ingredients, shake thoroughly, sterilize, cool to 60°C , and pour into Petri dishes.

12. Bile salts sulfur lactose agar culture medium (DHL)

peptone	20.0 g
Beef extracts	3.0 g
lactose	10.0 g
sucrose	10.0 g
Sodium desoxycholate	1.0 g
Sodium thiosulfate	2.3 g
Sodium citrate	1.0 g
Ammonium ferrous citrate	1.0 g
1% neutral red solution	3 ml
agar	16.0 g
water	1000 ml

Mix the above ingredients in water except sugars, indicators and agar, heat until dissolved, adjust the pH so that after sterilization it is 7.2 ± 0.1 . Add agar and heat to melt. Then add the other ingredients, shake thoroughly, sterilize, cool to 60°C , and pour into Petri dishes.

13. Cetrinide agar medium

peptone	10.0 g
Beef extracts powder	3.0 g
Sodium chloride	5.0 g
Cetyl trimethyl ammonium bromide	0.3 g
agar	14.0 g
water	1000 ml

Mix the above ingredients in water except agar, heat until dissolved, adjust the pH so that after sterilization it is 7.2 ± 0.1 . Add agar and heat it to melt, shake thoroughly. Dispense in containers, sterilize, cool to 60°C , and pour into Petri dishes.

14. Tellurite broth medium

Just prior to use, add 0.2 ml of freshly prepared 1% sodium (or potassium) tellurite solution, mix well.

15. Egg yolk high salts agar medium

peptone	6.0 g
Beef extracts	1.8 g
Sodium chloride	30.0 g
10% sodium chloride egg yolk solution	100 ml
agar	16.0-18.0 g
water	650 ml

Mix the above ingredients in water except 10% sodium chloride egg yolk solution, heat until dissolved, adjust the pH so that after sterilization it is 7.6 ± 0.1 . Sterilize and cool to 60°C . Add aseptically 10% sodium chloride egg yolk solution, shake thoroughly, and pour into Petri dishes.

16. Mannitol high salts agar medium

peptone	10.0 g
Beef extracts	1.0 g
mannitol	10.0 g
Sodium chloride	75.0 g
1% phenolsulfonphthalein solution	2.5 ml
agar	14.0 g
water	1000 ml

Mix the above ingredients in water except mannitol, phenolsulfonphthalein solution and agar, heat until dissolved, adjust the pH so that after sterilization it is 7.6 ± 0.1 , add agar and heat to melt. Filter and dispense in containers, sterilize and cool to 60°C , then pour into Petri dishes.

17. Lactose fermentation culture medium

peptone	20.0 g
Lactose	10.0 g
0.04% bromocresol purple indicator	25 ml
water	1000 ml

Mix the above ingredients in water except 0.04% bromocresol purple indicator, heat until dissolved, adjust the pH so that after sterilization it is 7.2 ± 0.2 , add the indicator, dispense in suitable tubes (3 ml per tube). Sterilize.

18. Pyocyanin culture medium

peptone	20.0 g
Magnesium chloride (anhydrous)	1.4 g
Potassium sulfate (anhydrous)	10.0 g
glycerol	10 ml
agar	14.0 g
water	1000 ml

Mix peptone, magnesium chloride and potassium sulfate, heat until dissolved, adjust the pH so that after sterilization it is 7.3 ± 0.1 , add glycerol and agar, heat to melt, shake thoroughly, dispense in suitable tubes and sterilize. Cool at room temperature to make slants.

19. Chopped meat culture medium

Preparation of the Beef bits. Use fresh beef, remove the fats and muscles, and boil for 10 minutes. Cut into pieces of 5 mm^3 , add three folds (w/w) of distilled water, immerse in $4\text{-}10^\circ\text{C}$ water for 18-20 hours, then boil for 1 hour, filter through gauze. The residue is washed twice with water. Then put the beef bits into an appropriate amount of sodium hydroxide solution so that the pH is around 8:4, agitate thoroughly. Immerse the beef overnight, and discard the upper water the next day, and wash 2-3 times with water. Spread the beef on a tray, sterilize, and dry at $80\text{-}100^\circ\text{C}$, remove the powders, put into bottles, and keep away from moisture.

Preparation of chopped meat culture medium. Put the beef bits in suitable containers, add an appropriate amount of Nutrient broth medium so that the beef bits constitute 1.5% of the volume, adjust the pH so that after sterilization it is 7.3 ± 0.1 , sterilize.

20. Columbia agar culture medium

Pancreatic digest of casein	10.0 g
Pepsin digest of beef	5.0 g
Pancreatic digest of heart	3.0 g
Yeast extracts powder	5.0 g
Corn flour	1.0 g
Sodium chloride	5.0 g
agar	15.0 g
water	1000 ml

Mix the above ingredients in water except agar, heat until dissolved, adjust the pH so that after sterilization it is 7.3 ± 0.2 , add agar and heat to melt. Filter, dispense in containers and sterilize. Cool to $45\text{-}50^\circ\text{C}$, add sterile gentamicin sulfate (equivalent to 20 mg gentamicin), mix well, and pour into Petri dishes.

Microbial contamination limits of Pharmaceutical Preparations

The microbial contamination limits of non-sterile preparations is drawn by fully considering the drug administration routes and potential harm to the patients. Unless otherwise prescribed, Microbial limit test follows the criterion below in the manufacturing, storage and distribution of preparations, as well as in the establishment of new preparations standards, evaluation of imported preparations, and the quality control of preparations, raw materials, and excipients.

1. Sterile preparations specified in General Notice or monographs, and other preparations labelled sterile

Comply with the test for Sterility.

2. Preparations for oral administration

Bacteria count Not more than 1000 per g, or 100 per ml.
 Fungi and yeasts count Not more than 100 per g or per ml.
E. coli. Absence in 1 g or 1 ml.

3. Preparations for local administration

(1) Local administration preparations for surgery, burn or serious injury
 Comply with the test for sterility.

(2) Preparations for eye administration

Bacteria count Not more than 10 per g or per ml.
 Fungi and yeasts count Absence in 1 g or 1 ml.

Staphylococcus aureus, *Pseudomonas aeruginosa* and *Escherichia coli* Absence in 1 g or 1 ml.

(3) Preparations administered via ear, nose or respiratory tract

Bacteria count Not more than 100 per g, per ml or per 10 cm².
 Fungi and yeasts count Not more than 10 per g, per ml or per 10 cm².

Staphylococcus aureus and *Pseudomonas aeruginosa*
 Absence in 1 g, 1 ml or 10 cm².

Escherichia coli. Absence in 1 g, 1 ml or 10 cm² for preparations for nose and respiratory tract administration.

(4) Preparations for vagina and urethra administration

Bacteria count Not more than 100 per g or per ml.
 Fungi and yeasts count Less than 10 per g or per ml.

Staphylococcus aureus and *Pseudomonas aeruginosa*
 Absence in 1 g or 1 ml.

(5) Preparations for rectal administration

Bacteria count Not more than 1000 per g, and not more than 100 per ml.
 Fungi and yeasts count Not more than 100 per g or per ml.

Staphylococcus aureus, *Pseudomonas aeruginosa* and *Escherichia coli* Absence in 1 g or 1 ml.

(6) Other preparations for local administration

Bacteria count Not more than 100 per g, per ml or per 10 cm².
 Fungi and yeasts count Not more than 100 per g, per ml or per 10 cm².

Staphylococcus aureus and *Pseudomonas aeruginosa*
 Absence in 1 g, 1 ml or 10 cm².

4. Oral preparations containing animal tissues (including

extracts)

Salmonella species are absence per 10 g or per 10 ml.

5. Preparations for more than one administration routes

Comply with the requirements for each administration route.

6. Raw materials and excipients

Refer to the limit for corresponding preparation.

XI K Test for Allergen

The general allergic reactions of a substance being examined are determined by injecting a dose of test solution into guinea pigs, after a fixed interval challenging intravenously into each sensitized animal a solution of the substance being examined and observing allergic reactions of each challenged animal.

Use healthy guinea pigs weighing 250-350 g, male or non-pregnant female. Breed in normal condition before and during test. Guinea pigs can only be used once for the test.

Preparation of test solution Unless otherwise prescribed, prepare a solution of a substance being examined with suitable concentration specified in the monograph.

Procedure Unless otherwise prescribed, inject intraperitoneally 0.5 ml of the test solution into each of 6 guinea pigs for 3 times successively, once every other day, then distribute sensitized animals into two groups with 3 guinea pigs in each group. Challenge intravenously into each guinea pig of one group 1 ml of the test solution on the fourteenth day and each of the other group on the twenty-first day after the first injection. Examine the Guinea pigs everyday and measure the weight of each animal before sensitization and challenge. Observe if allergic reactions such as hair pricking, short of breathing, twitching happen within 30 minutes after challenge.

Evaluation of the results None of the guinea pigs shows two or more types of allergic reactions within 30 minutes after challenge, such as hair pricking, sneezing, retching or continuous cough for three times and short of breathing; or one of the following allergic reactions: twitching, shock or dying. Otherwise, the substance being examined does not meet the requirements of the test.

Appendix XII

XII A Biological Assay of Vasopressin

The potency of the preparation of vasopressin being examined (T) is estimated by comparing its blood pressor activity on the rat with that of the Posterior Pituitary Standard (S) under the condition of following assay method.

Preparation of standard solution Transfer a suitable quantity of the Posterior Pituitary Standard, accurately and rapidly weighed to avoid the absorption of moisture, to a small glass vessel. Add accurately a small volume of 0.25% acetic acid and mix thoroughly. Place the total content of the vessel into a large test tube and add accurately 0.25% acetic acid to the test tube to produce a solution of 1 Unit of vasopressin per ml. Stopper the test tube lightly with a glass stopper and heat the tube, with continuous and gentle shaking, in a boiling water bath for 5 minutes. Cool the tube rapidly and filter. Distribute the filtrate into a suitable glass container and store it at 4-8°C. The solution may be used within 3 months if it remains clear.

On the day of the assay, dilute an accurately measured portion of the standard solution with sodium chloride injection to produce two dilutions of (S). The ratio (r) of the concentration between two dilutions should not be greater than 1 : 0.6. Adjust 2 dose levels such that the smaller dose produces a response of rise in blood pressure significantly and the larger dose does not produce a maximum response.

Preparation of test solution Prepared in the same way as described under Preparation of Standard Solution. The concentration of the test solution is calculated on the basis of the labelled or assumed potency (A_T) of the vasopressin being examined. The ratio (r) of the concentration between two dilutions of (T) should be the same as that of (S). The mean value of the responses given by each dose level of the test solution should be approximately the same as that of the standard solution.

Assay A healthy male rat weighing over 300 g is anaesthetized with suitable anaesthetics (such as i. p. 1 g of urethane per kg body weight). Tie the rat on back to an operating table and maintain the body temperature of the rat during the test. Dissect the trachea for cannulation when necessary. Insert the femoral (or jugular) vein a cannula filled with sodium chloride injection for intravenous injection. Inject through the venous cannula 50-100 Units of heparin per 100 g body weight. Insert a artery cannula (filled with 200-400 Units of heparin solution) into one of the dissected carotid artery and connect the other end of the cannula with a suitable pressure measuring device via a tube containing saline solution for making continuous record of blood pressure.

At this stage, adjust the pressure of the device to a level corresponding to the normal blood pressure of the rat, and remove artery clamp. Inject slowly a α -adrenoceptor blocking

body weight) and repeat the same dose of injection after 5-10 minutes. Start the test only when the blood pressure of the rat remains stable. Injections should be made at a uniform rate and at a regular interval of 10-15 minutes depending on the time at which the blood pressure returns to its original level. Each injection is followed by a fixed volume of sodium chloride injection (about 0.3-0.5 ml). Repeat 4-6 replicate of four doses (d_{S_1} , d_{S_2} , d_{T_1} , d_{T_2}), following random or random block design.

Measure all the responses and calculate the result of the assay by Statistical Method in Biological Assays; parallel line assay, random or randomized block design (Appendix XIV). The percentage of fiducial limits of error (FL%) should not be greater than 20%.

XII B Determination of Cytochrome C Activity

Reagents (1) *Phosphate BS* (0.2 mol/L) Dissolve 71.64 g of disodium hydrogen phosphate in water to produce 1000 ml as solution A; dissolve 27.60 g of sodium dihydrogen phosphate in water to produce 1000 ml as solution B. Mix 81 ml of solution A with 19 ml of solution B, adjust pH to 7.3.

(2) *Phosphate BS* (0.1 mol/L) Dilute 500 ml of phosphate BS (0.2 mol/L) with water to produce 1000 ml, adjust pH to 7.3.

(3) *Phosphate BS* (0.02 mol/L) Dilute 100 ml of phosphate BS (0.2 mol/L) with water to produce 1000 ml, adjust pH to 7.3.

(4) *Succinate solution* Dissolve 4.72 g each of succinic acid and potassium hydroxide in water to produce 100 ml, adjust the pH to 7.3.

(5) *Potassium cyanide solution* Dissolve 0.65 g of potassium cyanide in water to produce 100 ml, adjust pH with dilute sulfuric acid to 7.3.

(6) *Cytochrome C-free heart suspension* Remove the fat and connective tissue of two fresh pig or bovine hearts, strip and mince with a mincing machine. Transfer to a gauze bag, rinse with tap water for about two hours, stir frequently and squeeze to remove the haemochrome, squeeze dry, wash with water in portions, squeeze dry. Soak it in phosphate BS (0.1 mol/L) for about 1 hour, squeeze dry. Repeat the soaking process. Wash, with water in portions, squeeze dry. Transfer to a homogenizer, immerse in a quantity of phosphate BS (0.02 mol/L) and homogenize to a uniform paste. Centrifuge for 10 minutes. To the supernatant suspension add some ice, adjust pH to about 5.5 with dilute acetic acid rapidly and centrifuge for 15 minutes immediately. To the precipitate add an equal volume of phosphate BS (0.1 mol/L), triturate with a glass homogenizer to form a homogenate, store in a refrigerator. Dilute 1.0 ml with

Preparation of test solution Prepare a solution containing about 3 mg of cytochrome C per ml in water.

Procedure Transfer 5 ml of phosphate BS (0.2 mol/L), 1.0 ml of succinate solution and 0.5 ml of test solution (if the test solution is a reducing type, add 0.05 ml of 0.01 mol/L potassium ferricyanide solution) to a 25 ml Nessler cylinder with stopper, add 0.5 ml of cytochrome C-free heart suspension and 1.0 ml of potassium cyanide solution, dilute with water to produce 10 ml, mix well. Measure the absorbance using reagent as a blank until the absorbance value ceases to increase at the maximum wavelength found at intervals of 0.5 nm in the vicinity of 550 nm (Appendix IV A), this is the absorbance due to enzymatic reduction. Add about 5 mg of sodium hydrosulfite to each tube, mix well, allow the solutions to stand for about 10 minutes, measure the absorbance until the value ceases to increase at the same wavelength. This is the absorbance due to chemical reduction. Calculate according to the following expression.

$$\text{Cytochrome C Activity} = \frac{\text{Absorbance due to Enzymatic Reduction}}{\text{Absorbance due to Chemical Reduction}} \times 100\%$$

XII C Assay of Hyaluronidase

Reagents (1) *Acetic acid-potassium acetate BS* Dissolve 14 g of potassium acetate and 20.5 ml of glacial acetic acid in water to produce 1000 ml.

(2) *Phosphate BS* Dissolve 2.5 g of sodium dihydrogen phosphate, 1.0 g of anhydrous disodium hydrogen phosphate and 8.2 g of sodium chloride in water to produce 1000 ml.

(3) *Hydrolysed gelatin* Dissolve 50 g of gelatin in 1000 ml of water, heat at 121°C for 90 minutes and freeze dry.

(4) *Hydrolysed gelatin solution* To a mixture of 250 ml of phosphate BS and 250 ml of water add 330 mg of hydrolysed gelatin, mix well and store at 0-4°C. It is usable if no turbidity appears in the solution.

(5) *Serum stock solution* Dilute 1 volume of fresh bovine serum with 9 volumes of acetic acid-potassium acetate BS, adjust the pH to 3.1 with 4 mol/L hydrochloric acid solution and allow to stand for 18-24 hours before use. Store at 0-4°C and use within 30 days.

(6) *Dilute serum solution* Determine the content of total serum solids in serum stock solution as follows: Place an accurately weighed quantity of fresh bovine serum in a crucible containing clean sand, previously dried to constant weight at 105°C, evaporate to dryness on a water bath and dry to constant weight at 105°C. Calculate the content of total solids in the serum stock solution. On the day of the assay, dilute 1 volume of the serum stock solution containing about 8% of total solids with 3 volumes of acetic acid-potassium acetate BS; or dilute with 2 volumes of acetic acid-potassium acetate BS for that containing about 5% of total solids.

(7) *Potassium hyaluronate stock solution* Prepare a stock solution by dissolving potassium hyaluronate, previously dried over phosphorous pentoxide under reduced pressure for 48 hours, in water to produce a solution of 0.5 mg per ml. Store at a temperature below 0°C and use within 30 days.

volume of potassium hyaluronate stock solution with one volume of phosphate BS. Prepare on the day of the assay.

Preparation of standard solution To a quantity of hyaluronidase RS, accurately weighed, add cold hydrolysed gelatin solution to produce a solution of 1.5 Units per ml. Prepare on the day of the assay.

Preparation of test solution To a quantity of the substance being examined, accurately weighed, add cold hydrolysed gelatin solution to produce a solution of 1.5 Units per ml calculated on the basis of assumed potency. Prepare on the day of the assay.

Preparation of standard curve To 6 pairs of the same size test-tubes in turn add 0.00 ml, 0.10 ml, 0.20 ml, 0.30 ml, 0.40 ml and 0.50 ml of standard solution per pair, and then in turn add 0.50 ml, 0.40 ml, 0.30 ml, 0.20 ml, 0.10 ml and 0.00 ml of hydrolysed gelatin solution per pair respectively. At intervals of 30 seconds add to each tube successively 0.50 ml of dilute potassium hyaluronate solution, making the final volume in each tube 1.00 ml, mix well and place each tube in a water-bath maintained at 37°C ± 0.5°C. After exactly 30 minutes, remove each tube successively from the water-bath at intervals of 30 seconds and immediately add 4.0 ml of dilute serum solution. Shake and allow them to stand at room temperature for 30 minutes. Mix well and determine the absorbance of the resulting solutions at 640 nm (Appendix IV A). Repeat the operation described above, using a mixture of 0.50 ml of phosphate BS and 0.50 ml of hydrolysed gelatin solution, beginning at the words "place each tube in a water bath maintained at 37°C ± 0.5°C...". Plot a standard curve with absorbance as the ordinate and Units of standard solution as the abscissa.

Procedure To 3 pairs of the same size test-tubes in turn add 0.20, 0.30 and 0.40 ml of test solution per pair, and then in turn add 0.30 ml, 0.20 ml and 0.10 ml of hydrolysed gelatin solution per pair respectively. Carry out the operation described under the preparation of standard curve beginning at the words "At intervals of 30 seconds add to each tube successively 0.50 ml of dilute potassium hyaluronate solution", read the units from the standard curve, divide by the corresponding weights (mg) of substance being examined. The mean of the six values is the potency of the sample being examined.

XII D Biological Assay of Heparin

The potency of a preparation of heparin being examined (T) is estimated by comparing its clot delaying effect on fresh rabbit blood (or plasma) with that of Heparin Standard (S) under the condition of the following assay method.

Preparation of standard solution Dissolve an accurately weighed quantity of the Heparin Standard in sterile water to produce a solution of 100 Units per ml. Store the solution at a temperature of 4-8°C. The solution may be used within 3 months if it remains clear.

On the day of the assay, dilute an accurately measured portion of the above solution with 0.9% sodium chloride solution to produce 3 dose levels of standard solution in geometric progression (d_{s_3} , d_{s_2} , d_{s_1}), the ratio (r) of adjacent dose level should be equal. For an assay using fresh blood, the ratio (r) is about 1 : 0.7 and the highest dose may contain 2-5 Units of heparin per ml. The mean clotting time for the highest dose should not be more than 60

normal clotting time. For an assay using plasma, the ratio (r) is about $1 : 0.85$ and the highest dose (may contain $0.5-1.5$ Units of heparin per ml) should give a clotting time of not more than 30 minutes.

Preparation of test solution Prepare 3 dose levels of test solution (d_{T_3} , d_{T_2} , d_{T_1}), in the same way as described under Preparation of Standard Solution. The concentration of the test solution is calculated on the basis of the labelled or assumed potency (A_T) of the heparin being examined. The ratio (r) of adjacent dose levels should be the same as that of standard solution. The clotting time observed with each dose should be nearly the same as that observed with the corresponding doses of the standard solution.

Preparation of plasma Collect fresh blood from rabbit or pig in a vessel containing 8% sodium citrate solution. For 1 volume of sodium citrate solution 19 volumes of blood may be collected, shake gently while the blood is being collected. When the necessary amount of blood is collected, centrifuge promptly for 20 minutes, the centrifuging force is preferably not greater than 1500 folds of the gravity constant. Transfer portions of the pooled plasma into flasks and allow to freeze. On the day of the assay, thaw the plasma by putting the flasks in a constant temperature water bath at $37^\circ\text{C} \pm 0.5^\circ\text{C}$, filter the thawed plasma through a porous filter paper or two layers of gauze. Store the plasma in refrigerator. During the assay, keep the plasma at a temperature of $4-8^\circ\text{C}$.

Assay

Method 1 Use clean, dry test tubes of uniform size ($0.8\text{ cm} \times 3.8\text{ cm}$ or $1.0\text{ cm} \times 7.5\text{ cm}$). Add 0.1 ml of one of the 3 doses of standard solution, or one of the 3 doses of test solution to each tube, for each dose at least 3 tubes are used, followed by 0.9 ml of fresh rabbit blood and mix well, taking care to avoid the formation of air bubbles. The time elapsed between the addition of blood to the first and the last tube should be not more than 3 minutes. Place the tubes in a constant temperature water bath maintained at $37^\circ\text{C} \pm 0.5^\circ\text{C}$ and record the time of blood clotting for each tube.

Method 2 Add to each tube 0.5 ml (or 0.8 ml) of plasma, place the tubes in a constant temperature water bath at $37^\circ\text{C} \pm 0.5^\circ\text{C}$ for 5-10 minutes. Add to each tube 0.4 ml (or 0.1 ml) of one of the 3 doses of standard solution or one of the 3 doses of test solution, for each dose at least 3 tubes are used, followed by 0.1 ml of 1% calcium chloride solution, mix well, taking care to avoid the formation of air bubbles. Record the time of blood clotting for each tube. Carry out the statistical calculation for quantitative response based on the linear relationship of the logarithm of clotting time to the logarithm of heparin concentration (Appendix IV). The percentage of fiducial limits of error (FL%) should not be greater than 10% for method 1, and 5% for method 2.

III E Biological Assay of Chorionic Gonadotrophin

The potency of a preparation of chorionic gonadotrophin being examined (T) is estimated by comparing the uteri weight increasing effect produced on immature female mice with that produced by Chorionic Gonadotrophin Standard (S) under the condition of the following assay method.

Preparation of standard solution On the day of the assay dissolve the contents of the sealed container of Chorionic Gonadotrophin Standard in 0.9% sodium chloride

accurately measured portion of this solution with 0.5% carboxymethylcellulose sodium solution to produce 3 dose levels of (S) (d_{S_3} , d_{S_2} , d_{S_1}) in geometric progression, the ratio (r) of adjacent dose levels should be equal and not be greater than $1 : 0.5$ and the highest dose (may contain $0.3-0.8$ Units of chorionic gonadotrophin per ml) should not produce a maximum response of uteri weight gain, the lowest dose should produce a significant weight gain than the normal uterus. Store the dilute solution at $4-8^\circ\text{C}$ and use it within three days.

Preparation of test solution Prepare three dose levels of (T) (d_{T_3} , d_{T_2} , d_{T_1}) in the same way as described under Preparation of standard solution. The concentration of the test solution is calculated on the basis of the labelled or assumed potency (A_T) of the chorionic gonadotrophin being examined. The ratio (r) of adjacent dose levels should be the same as that of standard and the mean value of the responses produced by each dose level of (T) should be approximately the same as that of (S).

Assay Use healthy female mice of 17-23 days old, weighing 9-13 g, but in one assay the age difference between individual mouse should not be greater than 3 days and the weight difference not be greater than 3 g. Distribute the mice into 6 groups at random with at least 15 mice in each group. Inject subcutaneously into each of the six groups one of the three dose level of (S) or of (T) with equal volume (0.2 ml) for each mouse on three successive day at approximately the same time each day. Kill the mice about 24 hours after the third injection, remove the uterus of each mouse by cutting through the cervix. Free the uterus from extraneous tissue, gently squeeze out the uterine fluid on an absorbent paper and weigh immediately (precision 0.5 mg), express the weight of uterus in mg per 10 g of body weight. Carry out the statistical calculation for quantitative response assay (Appendix XIV), the percentage of fiducial limits of error (FL%) should not be greater than 25%.

III F Biological Assay of Oxytocin

The potency of a preparation of oxytocin being examined (T) is estimated by comparing the contraction effect produced on isolated rat uterus with that produced by Posterior Pituitary Standard or synthetic Oxytocin Standard (S) under the condition of the following assay method.

Preparation of standard solution Transfer a suitable quantity of the Posterior Pituitary Standard, weighed accurately and rapidly to avoid the absorption of moisture, to a small glass vessel. Add accurately a small volume of 0.25% acetic acid and mix thoroughly. Place the total content of the vessel into a large test tube and add accurately 0.25% acetic acid to the test tube to produce a solution of one of oxytocic unit per ml calculated on the basis of stated potency. Stopper the test tube lightly with a glass stopper and heat the tube with continuous and gentle shaking, in a boiling water bath for 5 minutes. Cool the tube rapidly and filter through a dry filter paper. Distribute the filtrate into a suitable glass container and store it at $4-8^\circ\text{C}$. The solution may be used within 3 months if it remains clear.

On the day of the assay, take an accurately measured portion of the standard solution or a quantity of synthetic Oxytocin Standard, add 0.9% sodium chloride solution to produce two dilutions of (S). The ratio (r) of the concentration between two dilutions should not be greater than $1 : 0.7$ and

ml. The concentration of two dilutions should be chosen as such that the higher dose should not produce maximum contraction (generally about 50-85 mm), the lower dose produces a response of contraction (generally about 20-50mm) and the contractions produced by higher and lower doses should be clearly discriminated.

Preparation of test solution On the day of the assay, prepare the solution and dilutions of oxytocin injection being examined by diluting the injection with 0.9% sodium chloride solution to produce two dilutions of (T). The concentration of the dilution of (T) is calculated on the basis of the labelled or assumed potency of the preparation being examined. The ratio (r) of the concentration between two dilutions of (T) should be the same as that of (S). The mean value of contractions produced by each dose level of (T) should be approximately the same as that of (S).

Preparation of lock solution for isolated rat uterus Prepare the solution by adding slowly 200 ml of 0.25% sodium bicarbonate to 800 ml of aqueous solution containing the following ingredients: sodium chloride 9 g, potassium chloride 0.42 g, calcium chloride (anhydrous) 0.06 g, glucose 0.5 g, mix well.

Assay Use healthy female rat of 3 months old weighing 160-240 g. On the day of the assay, confirm by vaginal smear that the rat is in proestrus. The proestrus stage of the rat can be produced by injecting intramuscularly some oestrogen hormone about 24 hours before the assay.

Kill the rat and remove the uterus freeing from extraneous tissue. Suspend one horn of the uterus in an isolated organ bath by fixing the lower end of the uterus horn to the bottom of the bath and connecting the upper end of the uterus horn to a recording lever for making a record of the contraction of the uterus. Fill the organ bath with equal volume of lock solution (about 30-50 ml) and maintain the bath at a constant temperature ($\pm 0.5^\circ\text{C}$) of about $32-35^\circ\text{C}$. Oxygenate the solution in the bath with small air bubbles or bubbles of a mixture of 95% oxygen and 5% carbon dioxide, 15 minutes later, add in turn into the bath the two standard dilutions and two test dilutions (d_{s_2} , d_{s_1} , d_{t_2} , d_{t_1}) in equal volume (0.3-0.8 ml). After each addition, when the contraction of uterus reaches its maximum and begin to relax, change and replace twice the bath solution with fresh lock solution. The second addition can be given only when the uterus is restored to its normal condition. The time interval between two additions should be equal (about 3-5 minutes). Repeat 4-6 replicate of four doses (d_{s_2} , d_{s_1} , d_{t_2} , d_{t_1}), following random or random block design.

Measure all the responses and calculate the result of the assay by the Statistical Method for Biological Assay; parallel line assay, random or randomized block design. The percentage of fiducial limits of error ($FL\%$) should not be greater than 10%.

XII G Biological Assay of Insulin

The potency of a preparation of insulin being examined (T) is estimated by comparing the hypoglycaemic effect it produces on mice with that produced by Insulin Standard (S) under the condition of the following assay method.

Preparation of standard solution Dissolve an accurately weighed quantity of Insulin Standard in 0.9% sodium chloride solution (acidified with hydrochloric acid to pH 2.5 and containing 0.2 g phenol in 100 ml) to produce a

temperature of $4-8^\circ\text{C}$. The solution may be used within 5 days.

On the day of the assay, dilute an accurately measured portion of this solution with 0.9% sodium chloride solution (pH 2.5) to produce two dilutions. The ratio (r) of the concentration of two dilutions is not greater than $1:0.5$. In general, the higher concentration may contain 0.06-0.12 Units of insulin per ml. Adjust the concentration of two dilutions to such that the smaller dose produces a positive depletion of blood sugar and the larger dose does not produce maximum depletion of blood sugar.

Preparation of test solution Prepare the solution and dilutions of (T) in the same way as that described under the preparation of standard solution. The concentration of the solution of (T) is calculated on the basis of the labelled or assumed potency (A_T) of preparation being examined. The ratio (r) of the concentration between two dilutions should be the same as that of two standard dilutions and the mean value of the blood sugar depletion produced by each concentration of (T) should be approximately the same as that of (S).

Assay Use healthy mice of same strain, same sex and approximately the same in age. In one assay, the difference of weight should not be greater than 3 g. Distribute the mice at random into four equal groups with at least 10 mice in each group. Mark the mice in each group for identification. Inject subcutaneously each of the four prepared dilutions of (S) (d_{s_2} , d_{s_1}) and (T) (d_{t_2} , d_{t_1}) into one group of mice, using the equal volume of 0.2-0.3 ml for each mouse. Exactly 40 minutes after each injection, take a suitable amount of blood sample from the orbital venous sinus of each mouse. Determine the glucose concentration of each blood sample by a suitable method such as that of Glucose Oxidase-Peroxidase method. Not less than 3 hours later, inject each of the dilution into the above four groups of mice following the twin cross-over design, and at the same time interval after injection, determine the blood glucose concentration of each mouse. Calculate the result of the assay by the Statistical Method for Biological Assay; parallel line assay, twin cross-over design (Appendix XIV). The percentage of fiducial limits of error ($FL\%$) should not be greater than 25%.

XII H Test for the Prolongation of Insulin Effect

The prolongation of the hypoglycaemia effect of protamine zinc insulin being examined (T) is tested by comparing the hypoglycaemia it produces on rabbits with that produced by Insulin Standard (S) under the condition of the following method.

Preparation of standard solution Dissolve an accurately weighed quantity of Insulin Standard in 0.9% sodium chloride solution (pH 2.5, acidified with hydrochloric acid) containing 0.2% of phenol to produce a solution of the same concentration Units per ml as that of the protamine zinc insulin injection being tested.

Preparation of test solution The protamine zinc insulin injection is used directly without further dilution.

Procedure Use healthy rabbits weighing 2.0-3.0 kg, male or nonpregnant female, and house the rabbits singly, 18-20 hours before the test, deprive the rabbits of food and feed

provide no food or water to the rabbits and handle them with care to avoid any excitement. Distribute the rabbits at random into two equal groups of approximately the same weight and sex in each group. Take a blood sample of not more than 1.5 ml from the marginal ear vein and determine the normal blood sugar level for every rabbit using a suitable blood sugar determination method.

Inject subcutaneously the rabbits in one group an accurate dose of about 1.2 Units of the standard solution of insulin (S) and the rabbit in other group the same volume of solution being examined (T) at the same site as that of the standard group. At 2 and 6 hours after injection of standard solution and at 6 and 9 hours after injection of test solution, take blood samples and determine the blood sugar level (mg of glucose per 100 ml of blood) for every rabbit at each bleeding time. Calculate the blood sugar levels as the percentage of its normal blood sugar level and expressed it as Percentage of Blood Sugar. If none of the blood sugar percentage for a rabbit was lowered below 90%, or if the rabbit died or convulsed in the course of the test, the data of that rabbit should be rejected. There should be at least six rabbits available in each group. Calculate the mean percentage of blood sugar for (S) and (T) group at each bleeding time.

Evaluation of result In the standard group, if the number of rabbit died or convulsed is more than 1 in five, or if the mean percentage of blood sugar at 2 hours bleeding time has not lowered to 65% or at 6 hours bleeding time has not returned to 95%, adjust the dose of (S) and repeat the test. The protamine zinc insulin being examined complies with the test for prolongation if its mean percentage of blood sugar has lowered to or below 75% either at 6 hours or at 9 hours bleeding time.

XII J Biological Assay of Protamine Sulfate

The potency of a preparation of protamine sulfate being examined (T) is determined by testing its capacity to neutralize the anticoagulant effect of Heparin Standard (S) in test tubes containing fresh rabbit blood or plasma under the condition of the following assay method.

Preparation of heparin standard solution Dissolve an accurately weighed quantity of Heparin Standard in 0.9% sodium chloride solution to produce a series of solution different in concentration of not more than 5 Units per ml in succession, e.g. 85, 90, 95, 100, 105, 110, 115, 120, 125 Units per ml.

Preparation of test solution Dissolve an accurately weighed quantity of Protamine Sulfate being examined (T) in 0.9% sodium chloride solution to produce a solution of 1 mg per ml, calculated on the dried basis or, if it is an injection, dilute with 0.9% sodium chloride solution to 1 mg per ml, calculated with reference to the labelled amount.

Preparation of plasma Carry out the preparation of plasma as described under the Biological Assay of Heparin (Appendix XII D).

Assay Use 8 dry clean test tubes of uniform size (0.8 cm × 3.8 cm). To the first and eighth tube add 0.2 ml each of 0.9% sodium chloride solution as the control tube. To each of the six remaining tubes add 0.1 ml of the solution being examined followed by 0.1 ml of one of the heparin standard solution in succession, mix thoroughly. To each of the eight tubes add 0.8 ml of fresh rabbit blood, mix immediately

bubbles. Record the time of blood clotting for each tube. Place the tubes in a constant temperature water bath maintained at $37^{\circ}\text{C} \pm 0.5^{\circ}\text{C}$. The time elapsed between the blood collection and placing the tubes in the bath should not be more than 2 minutes.

If, instead of fresh rabbit blood, plasma is used in an assay, add 0.7 ml of plasma to each of 8 tubes, mix well and allow the tubes to stand in the water bath for 5-10 minutes. Then to each tube add 0.1 ml of 1% calcium chloride solution, mix immediately after each adding taking care to avoid the formation of air bubbles and record the clotting time for each tube.

Evaluation of result The assay is valid if the difference of clotting time between two control tubes is not more than 1:1.35. Take the mean clotting time of the two control tubes as the normal clotting time.

In the series of six test tubes in order of increasing concentration of heparin, the last tube which shows the clotting time of not more than 150% of the normal clotting time is the terminal tube of the test.

Perform 5 assays in series, if the heparin concentration of five terminal tubes does not differ by more than 10 Units, take the mean value of the 5 assay results as the potency of protamine sulfate in Units per mg.

XII K Biological Assay of Digitalis

The potency of a preparation of digitalis being examined (T) is determined by comparing the minimum lethal dose it produces on pigeons with that produced by Digitalis Standard (S) under the condition of the following assay method.

Preparation of standard solution Transfer a suitable quantity of the Digitalis Standard, weighed accurately and rapidly to avoid the absorption of moisture, to a glass stoppered vessel. To each unit of digitalis, calculated with reference to the stated potency of the Standard, add 1 ml of 76% ethanol. Stopper the vessel tightly and shake continuously for 1 hour, filter through a dry filter; the solution contains 1 Unit of digitalis per ml. Store the solution at a temperature of 4-8°C. The solution may be used within 1 month if it remains clear.

On the day of the assay, dilute an accurately measured portion of the standard solution with 0.9% sodium chloride solution so that the mean lethal dose of the diluted solution will be 25-34 ml per kg of pigeon's body weight (usually 1 ml of the standard solution is to be diluted to 30 ml with 0.9% sodium chloride solution).

Preparation of test solution Weigh accurately a quantity of the digitalis being examined (if it is in the form of tablets, accurately weigh more than 20 tablets to determine the average weight, powder the tablets rapidly, weigh a quantity of the powdered tablet equivalent to not less than 20 tablets) and prepare the test solution as described under Preparation of Standard Solution. The concentration of the test solution is calculated on the basis of labelled or assumed potency (A_T) of digitalis being examined and the lethal dose of test solution (ml/kg) should be approximately the same as that of the standard solution.

Assay Use healthy pigeons weighing 250-400 g, but in one assay the weight difference between individual pigeon should not be greater than 100 g; 16-24 hours before assay, deprive the pigeons of food and give drinking water only. On the day of the assay, distribute pigeons at random into two equal

standard group, another is the test group. Secure the pigeon on a board, pluck a few feathers covering the alar vein and insert a fine needle connected with a microburette into the exposed vein. Infuse 0.5 ml of the standard solution or test solution into the vein, followed by a continuous infusion of 0.2 ml per minute until cardiac arrest occurs. Pigeons may have tremor, emesis or evacuation of stool before it is dying, but only the dilation of pupil and cessation of breath can be considered as the critical point of death. Record the total volume of standard solution or test solution infused for each pigeon and calculate the minimum lethal dose as ml (or Units) per kg of body weight. Multiply the minimum lethal dose by 10 and convert it into logarithm. Carry out the statistical calculation for direct assays (Appendix XIV), the percentage of fiducial limits of error ($FL\%$) should not be greater than 15%.

XII L Toxicity Test of Sodium Stibogluconate

The toxicity of sodium stibogluconate is determined by comparing the number of mice killed by injection of the preparation being tested (T) with that by Sodium Stibogluconate Standard (S) under the condition of following method.

Preparation of standard solution Dissolve an accurately weighed quantity of the Standard in water by warming at about 70°C for 15 minutes. Cool to room temperature and add water to make a suitable concentration. Warm the solution at 50°C for 30 minutes (water evaporation should be avoided), cool to room temperature. The concentration of the solution, calculated on pentavalent antimony, should be such that after intravenous injection into a group of mice, using 0.02 ml/g body weight, will cause a mortality of approximately 50% (20%-80% is suitable).

Preparation of test solution If the sample being tested is a powdered material, prepare the test solution in the same manner as that of standard solution. If the sample is sodium stibogluconate injection, prepare the test solution by diluting it with water and warm the solution at 50°C for 30 minutes (water evaporation should be avoided), cool to room temperature. In either case, the concentration of the solution of test preparation should be 83% as that of standard solution.

Procedure Use 40 or 20 healthy mice weighing 17-25 g with the difference of not exceeding 3 g in one test. Distribute the mice into two groups at random with 20 or 10 mice in each group. Inject intravenously one group the standard solution and the other the test solution using a volume of 0.02 ml per g body weight. The injection for each mouse should be completed within 4-5 seconds. Record the number of mice died within 15 minutes after injection.

Evaluation of result When two groups of twenty mice are used in a test: The sample complies with the test if the number of mice killed by the injection of the test solution is not greater than the number killed by standard solution; the sample fails the test if the number of mice killed by test solution is greater than the number killed by standard solution.

When two groups of ten mice are used in a test: the sample complies with the test if the number of mice killed by the test solution is at least two less than the number killed by standard solution. The sample fails the test if the number of

killed by standard solution. If it is not the case, repeat the test with another two groups of ten mice and evaluate the test result in the same way as that described above by comparing the total number of mice killed in the two series of ten mice of (S) and (T) group.

XII M Biological Assay of Follicle Stimulating Hormone

The potency of menotrophin being examined (T) with respect to its follicle stimulating hormone activity is estimated by comparing its effect in enlarging the ovaries of immature female rats with that of Menotrophin Standard (S) under the condition of following method of assay.

Preparation of solvent On the day of the assay dissolve a quantity of bovine serum albumin in 0.9% sodium chloride solution to produce a solution of 1 mg per ml, adjust to pH 7.2 ± 0.2 with 1 mol/L sodium hydroxide solution. Dissolve chorionic gonadotrophin (raw material or preparation for injection), accurately weighed, in above solution to produce a solution of 20 Units per ml calculated on the basis of the labelled. Use this solution as the solvent.

Preparation of standard solution On the day of the assay dissolve the contents of Menotrophin Standard with respect to its follicle stimulating hormone potency in above solvent to produce 3 dose levels of (S) (d_3 , d_2 , d_1) in geometric progression, the ratio (r) of adjacent dose levels should be equal and not be greater than $1 : 0.5$ and the highest dose (may contain 2-5 Units of follicle stimulating hormone per ml) should not produce a maximum response of ovaries weight gain, the smallest dose should produce a response of ovaries weight gain significantly. Store the solutions at a temperature of 4-8°C and use them within three days.

Preparation of test solution Prepare three dose levels of (T) (d_3 , d_2 , d_1) in the same way as described under Preparation of Standard Solution. The concentration of the test solution is calculated on the basis of the labelled or assumed potency (A_T) of the follicle stimulating hormone being examined. The ratio (r) of adjacent dose levels should be the same as that of standard and the mean value of the responses given by each dose level of (T) should be approximately the same as that of (S).

Assay Select healthy female rats of the same strain, 19-23 days old, weighing 36-50 g, but in an assay the age difference between individual rat should not be greater than 3 days and the weight difference not be greater than 10 g. Assign the rats at random to six groups of at least eight animals. Inject subcutaneously into each of six groups one of the three dose levels of the standard solution or test solution with equal volume (0.5 ml) for each rat on three successive days at approximately the same time each day. About 24 hours after the last injection, kill the rats and remove the ovaries. Free the ovaries from extraneous tissue and oviduct, remove any extraneous fluid on an absorbent paper and immediately weigh the ovaries (precision 0.2 mg) from each animal.

Calculate the result of the assay by Statistical Method in Biological Assays; parallel line assay, random design (Appendix XIV). The percentage fiducial limits of error ($FL\%$) should not be greater than 45%.

XII N Biological Assay of Luteinising Hormone

The potency of menotrophin being examined (T) with respect to its luteinising hormone activity is estimated by comparing its effect in increasing the weight of the seminal vesicles of immature male rats with that of Menotrophin Standard (S) under the condition of following method of assay.

Preparation of solvent On the day of the assay dissolve a quantity of bovine serum albumin in 0.9% sodium chloride solution to produce a solution of 1 mg per ml, adjust to pH 7.2 ± 0.2 with 1 mol/L sodium hydroxide solution. Use this solution as the solvent.

Preparation of standard solution On the day of the assay dissolve the contents of Menotrophin Standard with respect to its luteinising hormone potency in above solvent to produce 3 dose levels of (S) (d_{s_3} , d_{s_2} , d_{s_1}) in geometric progression, the ratio (r) of adjacent dose levels should be equal and not be greater than $1 : 0.5$ and the highest dose (may contain 8-10 Units of luteinising hormone per ml) should not produce a maximum response of seminal vesicle weight gain, the smallest dose should produce a response of seminal vesicles weight gain significantly. Store the solutions at a temperature of $4-8^\circ\text{C}$ and use them within four days.

Preparation of test solution Prepare three dose levels of (T) (d_{T_3} , d_{T_2} , d_{T_1}) in the same way as described under Preparation of Standard Solution. The concentration of the test solution is calculated on the basis of the labelled or assumed potency (A_T) of the luteinising hormone being examined. The ratio (r) of adjacent dose levels should be the same as that of standard and the mean value of the responses given by each dose level of (T) should be approximately the same as that of (S).

Assay Select healthy male rats of the same strain, 19-23 days old, weighing 36-50 g, but in an assay the age difference between individual rat should not be greater than 3 days and the weight difference not be greater than 10 g. Assign the rats at random to six groups of at least six animals. Inject subcutaneously into each of six groups one of the three dose levels of the standard solution or test solution with equal volume (0.5 ml) for each rat on four successive days at approximately the same time each day. About 24 hours after the last injection, kill the rats and remove the prostate gland. Free the seminal vesicles from extraneous tissue and anterior lobe of prostate gland, remove any extraneous fluid on an absorbent paper and immediately weigh the seminal vesicles (precision 0.2 mg) from each animal.

Calculate the result of the assay by Statistical Method in Biological Assays; parallel line assay, random design (Appendix XIV). The percentage of fiducial limits of error (FL%) should not be greater than 35%.

XII O Biological Assay of Calcitonin

The potency of the preparation of calcitonin being examined (T) is estimated by comparing the hypocalcemic effect it

under the condition of following assay method.

Preparation of solvent Dissolve 0.2 g of bovine serum albumin in 20 ml of water, mix well, warm in a water bath at 56°C for 1 hour, cool to room temperature, freeze at -10 to -20°C . On the day of the assay thaw in a water bath at $36^\circ\text{C} \pm 0.5^\circ\text{C}$. Transfer to a 200 ml volumetric flask, a solution containing 2 g of sodium acetate previously added, add 3.5 ml of hydrochloric acid. Dilute to approximate total volume with water, adjust to pH 3.5-4.5 with a solution of hydrochloric acid or sodium hydroxide. Dilute to volume with water.

Preparation of standard solution On the day of the assay dissolve the contents of Calcitonin Standard with respect to its labelled potency in above solvent to produce 2 levels of (S) (d_{s_2} , d_{s_1}) in geometric progression, the ratio (r) of adjacent dose levels should not be greater than $3 : 1$ and the solution of higher dose may contain 50-100 mIU per ml.

Preparation of test solution Prepare two dose levels of (T) (d_{T_2} , d_{T_1}) in the same way as described under Preparation of Standard Solution. The concentration of the test solution is calculated on the basis of the labelled or assumed potency (A_T) of the calcitonin being examined. The ratio (r) of adjacent dose levels should be the same as that of standard and the mean value of the responses given by each dose level of (T) should be approximately the same as that of (S).

Assay Select healthy rats of the same sex and of the same strain, weighing 40 to 250 g, but in an assay the weight difference between individual rat should not be greater than 20 g. Deprive the rats of food 16 hours before the test but allow access to unlimited quantities of water prepared by distillation. On the day of test assign the rats at random to four groups of at least five animals, two groups being allocated to the higher and lower dose levels of Standard and two to those of the preparation being examined. Weigh and number the rats. Inject subcutaneously into the abdomen or intravenously into tail vein of each rat of four groups one of the two dose levels of the standard solution or test solution according to body weight of each animal with the dose volume 0.4 ml per 100 g of body weight. Exactly one hour after injection, bleed each animal from ophthalmic venous plexus in the order of injection. Determine the calcium content of the plasma by suitable method, such as *o*-cresolphthalein complexation method.

Calculate the result of the assay by Statistical Method in Biological Assays; parallel line assay, random design (Appendix XIV). The percentage of fiducial limits of error (FL%) should not be greater than 45%.

XII P Biological Assay of Growth Hormone

Method 1

The potency of the preparation of growth hormone being examined (T) is estimated by comparing its effect in increasing the body mass of immature hypophysectomised rat with that of Growth Hormone Standard (S) under the condition of following assay method.

Preparation of standard solution On the day of the assay dissolve the contents of Growth Hormone Standard in 0.9% sodium chloride solution containing 0.1% bovine serum albumin to produce two solutions (higher and lower dose levels) of (S). The ratio (r) of the concentration between

may contain 0.1-0.2 IU per ml and the solution of lower dose may contain 0.025-0.05 IU per ml. Store the daily doses in tightly closed ampoules at a temperature below -15°C . Thaw the daily doses before use.

Preparation of test solution Prepare and store two solutions of the preparation being examined in the same way as described under Preparation of standard solution. The concentration of the test solution is calculated on the basis of the labelled or assumed potency (A_T) of the preparation being examined.

Assay Select healthy rats of the same sex and of the same strain 26 days to 28 days old, weighing 60 to 80 g. From 2 to 3 weeks before the test, weigh the rats and carry out hypophysectomy. After operation, keep the rats at a clean animal lab and allow them to recovery.

On the first day of the test, weigh the rats again and discard those which have gained or lost more than 10 per cent of their body mass. Assign the remaining rats at random into four equal groups of not fewer than eight. Weigh and number the rats. Inject subcutaneously into the neck of each rat of four groups one of the two dose levels of the standard solution or test solution with equal volume (0.5 ml) for each rat on six successive days at approximately the same time each day. Kill the rats 24 hours after the last injection, weigh the rats, cleave the sellar region and inspect macroscopically for traces of pituitary gland if necessary. Exclude from the test rats showing remnants of the organ. The difference in mass of each rat between the day of the first injection and the last weighing is taken as the response. The mean value of the responses given by each dose level of (T) should be approximately the same as that of (S) and the lower dose should produce a response of body weight gain significantly, the higher dose should not produce a maximum response of

body weight gain.

Calculate the result of the assay by Statistical Method in Biological Assays; parallel line assay, random design (Appendix XIV). The percentage of fiducial limits of error (FL%) should not be greater than 50%.

Method 2

The potency of the preparation of growth hormone being examined (T) is estimated by comparing its effect in increasing the width of the proximal epiphysis of the tibia in immature hypophysectomised rat with that of Growth Hormone Standard (S) under the condition of following method of assay.

Preparation of standard solution and preparation of test solution As described under the method 1.

Assay Carry out the assay as described under the method 1. Cut out the two tibiae from each of the rats after killing them and store them in 10% formaldehyde solution. Cleave the proximal part of the bone in the middle sagittal plane. Rinse the bone parts with water for 10 minutes, with acetone for 10 minutes and again with water for 3 minutes. Transfer to 2% silver nitrate solution. Allow to stand for two minutes and flush with water. Place each of the bone parts in water and expose them to strong light until the calcified parts have become dark brown. Fixate them in 10% sodium thiosulfate solution for 30 seconds, and then put them in 80% ethanol solution and ready for measuring. The width of the epiphysis is measured as the response using 1 mm thickness of slice under a microscope.

Calculate the result of the assay by Statistical Method in Biological Assays; parallel line assay, random design (Appendix XIV). The percentage of fiducial limits of error (FL%) should not be greater than 50%.

Appendix XIII The Test of Radiopharmaceutical Preparations

Radiopharmaceutical Preparations are the preparations containing one or more radionuclides for diagnostic and clinical usage. The production, testing and use of radiopharmaceutical preparations should comply with the requirements in the Drug Administration Law of the People's Republic of China and "The Regulations for the Administration of Radiopharmaceutical preparations" promulgated by the State Council of the People's Republic of China.

1. Terminologies and Definitions

Nuclide Refers to a species of atom characterised by its mass number, the number of protons and the nuclear energy state and its average life is long enough to be observable.

Isotope Refers to nuclides of the same element with same atomic number but different mass number.

Radioactive and radioactive nuclide Refers to the property of certain nuclides emitting spontaneously radiation of one or more particles or γ -ray, emitting of γ -ray after the generation of tracked electron capture or spontaneous fission. Radionuclide is a nuclide that is radioactive.

Decay Refers to a transformation process of radionuclide emitting spontaneously one or more particles or γ -ray and transforming into another nuclide or nuclide in another energy state. Each individual radionuclide obeys the exponential decay rule described in the expression:

$$N_t = N_0 e^{-\lambda t}$$

Where N_t is the number of atoms of nuclide at elapsed time t ;

N_0 is the number of atoms of nuclide when $t=0$;

λ is the decay constant of radionuclide;

t is the time elapsed;

e is the base of natural logarithm.

Half-life Refers to the time in which the amount of radionuclide decays to half of its initial value in the process of individual radioactive decay. It is usually expressed as $T_{1/2}$. Each nuclide has its specific half-life which is related to the decay constant as follows:

$$T_{1/2} = 0.693/\lambda$$

Radioactivity Refers to the number of nuclear transformation of nuclide per second. The official unit of radioactivity is becquerel (Bq). Other units commonly used are megabecquerel (MBq), gigabecquerel (GBq), kilobecquerel (kBq).

Specific activity Refers to the radioactivity per unit mass of the element or of the compound concerned.

Radioactive concentration Refers to the radioactivity in a unit volume of radiopharmaceutical preparation.

Radionuclidic purity Refers to the percentage of total radioactivity that is present in the form of radionuclide concerned.

Radiochemical purity Refers to the ratio, expressed as a percentage, of the radioactivity of the stated radionuclide

of the radionuclide present in the radiopharmaceutical preparation.

Carrier Refers to the stable nuclide or its compound added or present in the radionuclide or its compound concerned.

2. Test for Identification

Tests for Identification of radiopharmaceutical preparation may be classified into the tests for identity and of the nature of the radionuclide. The later may be identified by the method described under Radiochemical purity.

Identification of radionuclide depends upon the characteristic transformation and its nature of the radionuclide. The basic method employed is the accurate measurement of the half-life, mass absorption coefficient or the γ -spectrum of the radionuclide.

(1) **Gamma-ray spectrum method** The gamma-ray energy spectrum of radionuclide should be identical with the energy of main photon complies with the requirement specified under the nuclide concerned. The energy of photoelectric peak should be identical with the γ -ray transition energy given in the decay scheme of the radionuclide.

The γ -ray spectrum of the nuclide in a radiopharmaceutical preparation is recorded by multiple channel γ -spectrometer with Sodium (Thallium) iodide scintillating crystal, Germanium (Lithium) or high purity Germanium semiconductor as detector through the use of the calibration curve of energy and channel by means of a series of γ -ray emission standard specimens or sources of known energy. The identification of the nuclide may be made with reference to a decay scheme or a curve of energy spectrum of the same radionuclide.

(2) **Measurement of half-life** A suitable detection apparatus is chosen based upon the nature of the radionuclide. The radioactive source is prepared by an appropriate amount of radiopharmaceutical preparation being examined with reference to the measuring range of the detection apparatus and the half-life of the radionuclide. Keep the source and the detector of the apparatus in a fixed geometrical condition and measure the count rate successively at a time interval for a period of 3 half-lives of the radionuclide concerned. Draw a curve with time as abscissa and count rate as ordinate on a semilog paper. The half-life calculated from the graph should not differ by more than 5% from the half-life stated for the individual radionuclide.

The following should be considered in the measurement.

① It is necessary to ensure that the efficiency of the detection apparatus remains constant;

② The geometrical conditions of the detection assembly are kept to be constant;

③ Make any necessary correction for the dead time on the basis of the radioactivity of the radionuclide.

Note *geometric condition* The validity of relative calibration and measurement of radionuclides is dependent

the detector and its surroundings. The geometric condition must be coincident in the measurement.

Correction for dead time The minimum time interval that is required for the counter to resolve two consecutive signal pulses is known as the dead time. If the counting rate is high when measuring, the correction for dead time must be made.

$$f_r = m/n = 1 - m\tau \quad (m\tau \ll 1)$$

where f_r is the correction factor, τ the dead time, m the counting rate, n the true counting rate.

(3) **Mass absorption coefficient method** Generally used for a purified β -ray radionuclide with a long half-life. Take an example of ^{32}P . Prepare a membrane source with ^{32}P solution, mount on a suitable counter. Carry out count rate determinations individually and successively using 6 aluminium foils, different in thickness, chosen from a range of 20-50 mg/cm² and one foil of 800 mg/cm² at least as the absorber. The sample and absorbers should be placed as close as possible to the detector in order to minimize the scattering effects. The net β -ray count rate is obtained by subtracting the count rate found with the thickest absorber of 800 mg/cm² or more from the count rates found with various absorbers. Plot the logarithm of the net β -ray count rate against the total absorbers thickness, which is the sum of the thickness of aluminium absorbers, the thickness of the counter window and the air equivalent thickness (the distance, expressed in cm, of the sample from the counter window multiplied by 1.205 under a pressure of 76 cm of Hg column and 20°C). An approximately straight line is obtained. Select two of the absorbers of different thickness that are 20 mg/cm² or more apart, their total absorber thickness should fall on the linear part of the absorption curve. The absorption coefficient is calculated from the equation:

$$\mu = \frac{1}{t_2 - t_1} \ln \frac{N_{t_1}}{N_{t_2}}$$

Where t_1 and t_2 are the thinner and the thicker absorber expressed in mg/cm²; N_t represent the net β count rate with t_1 and t_2 absorbers, respectively.

The calculation result should be not more than 10% in comparison with the mass absorption coefficient of the same pure nuclide measured under identical conditions.

3. Testing for Purity

(1) **Determination of radionuclidic purity** Radionuclidic impurities may be present in pharmaceutical preparation. The requirement for limit of specific radionuclidic impurities must be considered with regards to the nature of radiation and its effects to human. Usually, the nuclidic purity may be specified by the percentage of the radioactivity of radionuclidic impurities at the time when the measurements are made or that of total radioactivity present in the form of labelled radioactivity of the main nuclide.

The determination of nuclidic purity is carried out with multiple channel gamma spectrometer, using Germanium (Lithium) or high purity Germanium semiconductor as detector. Keep the form and size of the reference standard source and of the sources of samples being examined to be constant and maintain the geometric conditions of the sources and the detector to be identical conditions under a suitable environmental condition for performing of the spectrometric measurements. The radionuclidic purity may be obtained from the curve plot against the accurately measured energy and the efficiency of the detection based upon the known nuclidic parameters and the calculated γ -spectrum peak area with reference to a series of γ -ray emission reference sources. Certain decay products of radionuclides are still radioactive. These are referred to as mother and daughter radionuclides,

excluded from the calculation of radionuclidic purity. The radionuclidic purity should be stated with the date and hour when the measurement is made.

(2) **Determination of radiochemical purity** The radiochemical impurities of radiopharmaceutical preparation may be produced from the decomposition of the preparation itself or in the process of production. Radiochemical purity determination includes the separation of different chemical components and the measurement of the corresponding radioactivities.

Method 1 Carry out the method of ascending paper chromatography (Appendix V A), using a suitable amount of sample or proceed as described in the individual monograph if necessary. Apply the carrier solution on the base line, allow it to dry and then apply the sample solution on the same position. After developing and removal of the paper, dry it in air, determine the distribution of radioactivity on the chromatogram with a suitable apparatus. Calculate the R_f value and radiochemical purity by the following expression.

In the identification of individual radiopharmaceuticals, the word "about" means that the measured R_f value should be within $\pm 10\%$ of the specified value.

$$\text{Radiochemical purity (\%)} = \frac{\text{Net counts of radioactivity of specified chemical identity}}{\text{Sum of net counts of radioactivity on the chromatogram}} \times 100\%$$

Method 2 Carry out the paper electrophoresis (wet method) or electrophoresis on cellulose acetate membrane (Appendix V F). Apply the carrier solution on the base line as described in the individual monograph and followed by the sample solution on the same position if necessary. The base line is 1.5 cm from the anode or cathode support of the electrophoresis apparatus. Remove the paper or membrane after the specified time interval, dry it in air, determine and calculate the radiochemical purity as described under method 1.

Method 3 Carry out the method of ascending paper chromatography (Appendix V A) described in the individual monograph, using multiple separating system. After developing and removing of the paper, dry it in air, determine the distribution of radioactivity on chromatograms applied in each separating system with a suitable apparatus. In case the radioactive chemical impurities B and C contained in radiopharmaceutical A, B and (A+C) may be separated in separating system 1; C and (A+B) being separated in system 2; the radiochemical purity of sample A is calculated by the following expression:

$$\begin{aligned} B\% &= \frac{\text{net radioactive counts of B peak}}{\text{Sum of net radioactive counts of paper tested with system 1}} \times 100\% \\ C\% &= \frac{\text{net radioactive counts of C peak}}{\text{Sum of net radioactive counts of paper tested with system 2}} \times 100\% \\ A\% &= 100\% - (B + C)\% \end{aligned}$$

In addition, other separating analytical methods, which can separate various radiochemical impurities, can also be used for measurement of radiochemical purity after being validated, such as HPLC, column chromatography and thin-layer chromatography, etc.

4. Test for Particulate Matter

The diameter and distribution of the particulate matter or particles should be tested for the radiopharmaceutical preparations which are produced as colloidal solution or suspension. Usually, particles of nm in diameter are

microscope.

Electronic microscopical measurement Mount the solution being examined or an appropriate amount of dilute solution on a copper wire gauze of 3 mm (300 pores) which is coated with film suitable for mounting the specimen. Allow it to dry, observe directly or by photographing. Select an area where the particulate matter is distributed uniformly and measure at random the diameters of more than 100 particles. Calculate the diameter and distribution of particulate matter or particles with reference to both electronic and optical magnifying powers.

Microscopical measurement Mount the solution being examined or an appropriate amount of dilute solution in a blood cell counter and place it on the microscope stage. Observe the homogeneity of the distribution of particulate matter at first with eye piece $\times 10$, objective lens ($\times 10$), then observe with objective lens ($\times 40$) at the selected representing field or by photographing. Measure at random diameters of over 100 particles. Calculate the percentage distribution and the diameters of the particles in the preparation being examined.

5. Determination of pH value

The pH value of the solutions of radiopharmaceutical preparations must be in the definite scope. It is determined by a pH meter or a precise pH test paper to be checked.

Method of pH test paper Drop a drop of the solutions of radiopharmaceutical preparations on a precise pH test paper, compare the colour with the standard colour plate.

Method of pH meter Carry out the Determination of pH value (Appendix VI H) in a defensive condition.

6. Measurement of radioactivity and radioactive concentration

In the field of pharmaceutical sciences specific apparatus has been developed for the measurement of radioactivity, using dose calibrator with well-type ionization chamber as the detector. The apparatus has been calibrated carefully for release with reference radiation sources comply with the requirements for such measurement with the total indeterminacy no greater than $\pm 5\%$ (fiducial probability 99.7%). The apparatus should be calibrated periodically to ensure the accuracy of measurement.

(1) Measurement of radioactivity and radioactive concentration of γ -ray emitting nuclides

1) It is essential to safeguard the apparatus being operated under normal working conditions. Preheat the apparatus sufficiently and set it under the conditions required for the measurement of the nuclide concerned to measure the background reading or zero point adjustment.

2) Place the preparation being examined, accurately measured, into a glass vial of about 22.3 mm in external

diameter and about 1 mm in thickness of the wall. Mount the vial into the ionization chamber under identical geometrical conditions as that for calibration.

3) Carry out the measurements for 10 times consecutively, calculate the average value and subtract from it the background reading correspondingly as the radioactivity of the sample A.

4) The radioactive concentration of the preparation being examined C is calculated by the following equation:

$$C = A/V$$

Where V is the volume of the preparation being examined.

(2) Measurement of the radioactivity and radioactive concentration of β -ray emitting nuclide

The dose calibrator must be calibrated with a standard source, using the same condition described under the measurement of the substance being examined, and then may be used directly for the measurement. The procedure and calculation of results are similar to that described under γ -ray emitting radio nuclides.

1) The dose calibrator must comply with the requirements of the measuring apparatus enforced by the Government and calibrated and certificated by the National Bureau of Technical Supervision.

2) The date and time of measurement should be printed and the results should be within 90.0%-110.0%, or the range specified in the individual monograph, of the labelled value of radioactivity.

3) The dose calibrator must be stable and reliable, with detection source of long half-life nuclide (e.g. ^{137}Cs).

7. Other Requirements for the Radiopharmaceutical Preparations

(1) **Containers** Solutions of radiopharmaceutical preparations should be stored in vials with rubber closure for multiple injections. The radiation dose rate on the surface of the containers complies with the requirement for protection against ionization radiation.

(2) **Expiry date** The designated expiry date brings with the date at which the radioactivity is expressed on the label. It is not recommended to use beyond the expiry date or in any case, an extraordinary condition is observed within the expiry date.

(3) **Label and insert** The label of radiopharmaceutical preparations should indicate the name of the preparation, the name of manufacturer, batch number and indication of radioactive. The insert should indicate the name of the preparation, the chemical state, the date of production, batch number, radioactive concentration with the date and hour when the measurement was made, content (ml), total radioactivity, expiry date, name of manufacturer and the indication of radioactive.

Physical Characteristics of Radionuclides

Nuclide	Half-life period	Particle energies and transition probabilities			γ transition parameters		
		Type of decay	energy/MeV	Transition probability/%	Type of decay	energy/MeV	Transition probability/%
^{137}Cs	30.2 y ($^{137\text{m}}\text{Ba}$; 2.55 min)	e^+	0.004	7.8	X	0.005	1
			0.026	0.8			
		e^-	0.624	8	γ	0.032-0.037	7
			0.656	1.4		0.661	85.4
		β^-	0.660	0.4			
			0.511 Φ	94.6			
^{51}Cr	27.7 d	e^+	1.173 Φ	5.2	X		
			0.0004	144		0.0005	0.33
			0.004	67		0.005	22.3

continue

Nuclide	Half-life period	Particle energies and transition probabilities			γ transition parameters		
		Type of decay	energy/MeV	Transition probability/%	Type of decay	energy/MeV	Transition probability/%
⁵⁷ Co	271 d	e _A	0.0007	249	X	0.0007	0.8
		e _A +e _C	0.005-0.007	175		0.007	56
		e _C	0.014	8.9	γ	0.014	9.5
			0.115	1.9		0.122	85.6
			0.129	1.4		0.136	10.6
⁵⁸ Co	70.8 d	e _A	0.0007	117	X	0.0007	0.4
		β^+	0.006	49.4	γ	0.006	26.2
			0.475 [Ⓢ]	15		0.511	30 [Ⓢ]
						0.811	99.4
						0.864	0.7
⁶⁰ Co	5.27 y	β^-	0.318 [Ⓢ]	99.9	γ	1.173	99.9
						1.332	100
¹⁸ F	109.7 min	β^+	0.633	97	γ	0.511	1.94
		e _A +e _C		3			
⁶⁶ Ga	9.4 h	e _A	0.001	56	X	0.001	0.3
			0.008	21		0.008-0.010	19
		β^+	0.361 [Ⓢ]	1	γ	0.511	113 [Ⓢ]
			0.720-	1.1		0.834	6
			0.820 [Ⓢ]	4.1		1.039	38
			0.924 [Ⓢ]	0.4		1.333	1.3
			1.780 [Ⓢ]	50		1.918	2.2
			4.153 [Ⓢ]			2.190	5.8
						2.422	2
						2.752	23.5
						4.295	3.5
⁶⁷ Ga	3.26 d	e _A	0.001	169	X	0.001	1
			0.007-0.010	60		0.008-0.010	55
		e _C	0.081-0.084	27	γ	0.091-0.093	38.5
			0.090-0.093	6		0.185	22
			0.175	0.4		0.209	2.4
		β^-	0.290 [Ⓢ]	1		0.300	16.5
			0.966 [Ⓢ]	98.9		0.394	4.5
						0.494	0.09
						0.888	0.14
¹⁹⁸ Au	2.70 d	e _A	0.005-0.015	2.1	X	0.008-0.015	1.3
		e _C	0.329	2.9	γ	0.069-0.083	2.8
			0.397	1		0.412	95.6
			0.408	0.34		0.676	0.8
		β^-	0.290 [Ⓢ]	1		1.088	0.2
			0.966 [Ⓢ]	98.9			
¹⁹⁹ Au	3.14 d	e _A	0.005-0.015	21	X	0.008-0.015	12.8
		e _A +e _C	0.035-0.054	4.1	γ	0.050	0.33
		e _C	0.075	10.5	X	0.068-0.080	15.4
			0.125	5.5	γ	0.158	36.9
			0.144	17.1		0.208	8.4
			0.155-0.158	5.8			
			0.193	2			
		β^-	0.245 [Ⓢ]	18.9			
			0.294 [Ⓢ]	66.4			
¹¹¹ In	2.8 d	e _A	0.002-0.004	101	X	0.003-0.004	6.3
			0.018-0.027	16		0.023-0.028	82.4

continue

Nuclide	Half-life period	Particle energies and transition probabilities			γ transition parameters		
		Type of decay	energy/MeV	Transition probability/%	Type of decay	energy/MeV	Transition probability/%
^{111}In			0.167-0.171 0.219 0.241-0.245	1.2 4.9 0.9		0.245	94.2
$^{114\text{m}}\text{In}$	49.5 d (^{114}In ; 72 s)	e_A, e_C β^-	1.99	95	X γ	0.023-0.028 0.190 0.558 0.725	40 17.7 4.6 4.6
^{123}I	13.2 h	e_A	0.002-0.005 0.021-0.031 0.127 0.154 0.158	98 12 13.6 1.8 0.4	X γ	0.003-0.005 0.027-0.032 0.159 0.346 0.440 0.505 0.529 0.538	8 87 83.4 0.1 0.4 0.3 1.4 0.4
^{124}I	4.2 d	e_A e_C β^+	0.003 0.023 0.571 0.810 1.532 2.135	64 8 0.3 0.3 11.3 11.3	X γ	0.004 0.027-0.031 0.511 0.606 0.723 1.325 1.376 1.509 1.691	6 59 46 [Ⓢ] 61 10 1.5 1.7 3 10.5
^{125}I	60.1 d	$e_A + e_C$	0.002-0.005 0.021-0.035	236 33	X γ	0.003-0.005 0.027 0.031 0.035	15 114 25 6.7
^{126}I	13.0 d	e_A e_C β^- β^+	0.003 0.022 0.354 0.634 0.371 [Ⓢ] 0.862 [Ⓢ] 1.252 [Ⓢ] 0.134 [Ⓢ]	43.5 5.7 0.5 0.1 3.6 32 8 3.3	X γ	0.004 0.027-0.031 0.388 0.491 0.511 0.666 0.754 0.880 1.420	4.3 40 34 2.9 6.7 [Ⓢ] 33 4.2 0.8 0.3
^{131}I	8.04 d	e_A e_C β^-	0.003 0.025 0.045 0.075-0.079 0.250 0.330 1.359 0.248a 0.304a 0.334a 0.606a 0.807a	5.1 0.6 3.5 0.6 0.25 1.5 0.25 2.1 0.6 7.4 89.4 0.4	X γ	0.004 0.029-0.034 0.080 0.284 0.365 0.637 0.722	0.6 5 2.6 6.1 81.2 7.3 1.8
^{85}Kr	10.7 y	β^-	0.173 [Ⓢ] 0.687 [Ⓢ]	0.43 99.57	γ	0.514	0.43
^{201}Pb	9.4 h	$e_A e_C$	(*)	(*)	X γ	0.070-0.073 0.083 0.130 0.221	68 19 1.3 70

continue

Nuclide	Half-life period	Particle energies and transition probabilities			γ transition parameters		
		Type of decay	energy/MeV	Transition probability/%	Type of decay	energy/MeV	Transition probability/%
^{201}Pb						0.361 0.406 0.585 0.692 0.767 0.826 0.908 0.946	9.9 2.0 3.5 2.7 3.3 2.3 6 7.5
^{203}Pb	2.17 d	e_A ec	0.008 0.055 0.194 0.316	54 3 13 0.5	X γ	0.010 0.070-0.073 0.083 0.279 0.401 0.681	36 58 19 80 3.4 0.7
^{197m}Hg	23.8 h	e_A $e_A + ec$ ec	0.005-0.014 0.050-0.080 0.116-0.130 0.150 0.161 0.198	75 36 50 51 21 1.6	X γ	0.008-0.015 0.067-0.083 0.130 0.134 0.164 0.279	44 40.5 0.23 34 0.32 5.1
^{197}Hg	64.1 h	e_A $e_A + ec$	0.005-0.014 0.050-0.080	91 84	X γ	0.008-0.017 0.067-0.080 0.077 0.191 0.269	52 73 18.3 0.57 0.05
^{203}Hg	46.8 d	e_A ec β^-	0.005-0.015 0.055-0.085 0.194 0.264 0.276 0.212	9.3 0.44 13.4 3.9 1.2 100	X γ	0.009-0.015 0.071-0.085 0.279	5.4 13 81.4
^{99}Mo	66.0 h	$e_A + ec$ ec β^-	0.002 0.015-0.020 0.119-0.121 0.137-0.140 0.436 $^\Phi$ 0.848 $^\Phi$ 1.214 $^\Phi$	110 7 9.5 1.5 16.6 1.2 82	X γ	0.002 0.018-0.021 0.140 0.181 0.366 0.740 0.778 0.823	0.7 14 91 6 1.2 12.3 4.4 0.13
^{32}P	14.3 d	β^-	1.71 $^\Phi$	100			
^{103}Ru	39.3 d (^{103m}Ru ; 56.1 min)	e_A $e_A + ec$ ec β^-	0.002 0.017 0.036-0.039 0.112 0.225 0.722	77 11 91 6.4 87 6	X γ	0.003 0.020-0.023 0.053 0.295 0.444 0.497 0.557 0.610	4 7.7 0.4 0.3 0.4 89.7 0.8 5.6
^{75}Se	118.5 d	e_A ec	0.001 0.009 0.013	136 44 4.3	X γ	0.001 0.011 0.066	1 57 1

continue

Nuclide	Half-life period	Particle energies and transition probabilities			γ transition parameters		
		Type of decay	energy/MeV	Transition probability/%	Type of decay	energy/MeV	Transition probability/%
⁷⁵ Se			0.054 0.085 0.095 0.109 0.124 0.134 0.253 0.268	0.4 2.7 0.4 0.7 1.6 0.2 0.4 0.2		0.121 0.136 0.199 0.265 0.280 0.304 0.401	17.5 61 1.5 59.4 25.2 1.3 11.3
⁸⁹ Sr	50.5 d	β^-	1.492 [ⓓ]	100			
⁹⁰ Sr	29.1 y	β^-	0.546 [ⓓ]	100			
⁹⁰ Sr/ ⁹⁰ Y	29.1 y (⁹⁰ Y; 64.0 h)	β^-	0.546 [ⓓ] 2.284 [ⓓ]	100 100			
^{99m} Tc	6.02 h	$e_A + e_C$ e_A	0.002 0.015-0.020 0.119-0.121 0.137-0.140	100 2.1 9.5 1.5	X γ	0.002 0.018-0.021 0.140	0.5 7.2 89.3
⁹⁹ Tc	2.14×10^5 y	β^-	0.29 [ⓓ]	100			
²⁰⁰ Tl	1.09 d	e_A	(*)	(*)	X γ	0.069-0.070 0.080-0.083 0.368 0.579 0.661 0.828 0.886 1.206 1.226 1.274 1.363 1.515	66 19 88.4 14 2.3 11 2 30.0 3.4 3.3 3.5 4.1
²⁰¹ Tl	3.05 d	e_A e_C $e_A + e_C$ e_C	0.005-0.015 0.015-0.020 0.027-0.032 0.052-0.085 0.120-0.123 0.132-0.135 0.153-0.155 0.164-0.167	77 19 6.4 27.3 1.3 0.4 2.8 0.8	X γ X γ	0.008-0.015 0.031-0.032 0.069-0.071 0.079-0.083 0.135 0.166-0.167	45 0.6 75 21 2.8 10.7
²⁰² Tl	12.2 d	e_A	(*)	(*)	X γ	0.069-0.071 0.080-0.083 0.440	65 19 95
³ H	12.3 y	β^-	0.019 [ⓓ]	100			
^{131m} Xe	11.9 d	$e_A e_C$	0.003 0.025 0.129 0.158 0.163	26 6.8 61 28.6 8.2	X γ	0.004 0.029-0.034 0.164	3 54 1.92
¹³³ Xe	5.29 d	e_A e_C β^-	0.004 0.025 0.045 0.075 0.266 [ⓓ] 0.346 [ⓓ]	50 6 52 8.5 0.7 99.3	X γ	0.004 0.030-0.035 0.081	6 47 37
^{133m} Xe	2.19 d	e_A e_C	0.004 0.025 0.198 0.228	70 7.1 64 21	X γ	0.004 0.030-0.035 0.233	8 57 10.3

continue

Nuclide	Half-life period	Particle energies and transition probabilities			γ transition parameters		
		Type of decay	energy/MeV	Transition probability/%	Type of decay	energy/MeV	Transition probability/%
^{133m}Xe			0.232	5			
^{65}Zn	243.9 d	e_A β^+	0.001	127	X	0.001	0.8
			0.007-0.010	48		0.008-0.010	38.7
			0.330 ^①	1.46	γ	0.511	2.92 ^②
						1.115	50.75

① Maximum energy of the beta spectrum.

② Maximum intensity corresponding to a total annihilation in the source.

 e_A : Auger electrons. e_c : Conversion electrons.

(*) No precise values are known for the moment.

y=year, d=day, h=hour, min=minute, s=second

Appendix XIV Statistical Methods for Biological Assays

1. Introduction

Biological methods are used for the assay of certain pharmaceutical products whose potency cannot be adequately determined by chemical or physical means.

This chapter presents mainly the basic principles and general requirements to be observed, the assay design and statistical method to be adopted in a biological assay. The assay procedure, experimental condition and some other specifications are described under individual monographs.

Standard Preparation Ch. P. standard preparations (S) are available for biological assays, the potency of (S) is expressed in Unit which is equivalent to the corresponding International Unit.

Test Preparation Test preparation (T) or (U) is a pharmaceutical products whose potency is to be assayed. The pharmacological properties of (T) or (U) should be essentially similar to those of the standard preparation. A_T or A_U is the labelled or assumed potency of (T) or (U).

Ratio of Equally Effective Doses Biological assays are carried out by comparing the responses produced by the standard preparation (S) and the test preparation (T) when applied as stimuli to living matter at the same time and under the same condition. From the results of an assay, the doses of (S) and (T) producing equal response—the equally effective doses (d_S , d_T) can be calculated and the potency of (T) is estimated from the ratio of equally effective doses (R), i. e.

R is the ratio of d_S and d_T . $R = d_S/d_T$.

M is the difference between logarithm of d_S and d_T . $M = \lg d_S - \lg d_T = x_S - x_T$. $R = \text{antilog } M$.

P_T is the estimated potency of (T) obtained by multiplying the value of R or antilog M by assumed potency A_T .

$P_T = A_T \cdot R = A_T \cdot \text{antilog } M$. P_T is expressed as u/mg, u/ml etc.

Control of Biological Variation Biological assays are subject to random errors due to the inherent variability of biological responses. In order to control and minimize the biological variation and reduce the error of an assay, the following conditions must be noticed.

(1) The living matter used in an assay should be of the same species and same source, bred in a uniform environment or cultured under uniform condition.

(2) When the totality of individual unit appears to be reasonably homogeneous, allocate the individual unit to different doses by random process. If the individuals in subgroup, such as body weight, Petri dishes, sex, litter are likely to be more homogeneous than the totality of individual unit, allocation will be made by arranging the individuals in contiguous subgroups at random to different doses.

(3) When the assay design requires to segregate the variation between subgroups or blocks such as between litters or Petri dishes, the member in each subgroup is selected at random for each dose.

Error Variance The residual error of an assay is obtained by subtracting the variations allowed for in the design (e.g. variations between doses) from the total variation in response. Error variance (s^2) is the mean square of residual error which is obtained by dividing the sum of squares of residual error by its degrees of freedom.

The value of s^2 will affect the value of standard error of M (S_M) and the range of fiducial limits.

Validity Test For parallel line assay, it is required that the relation between the logarithm of doses and responses (or transformed responses) can be represented by a straight line in a certain range of doses, and the line for the test preparation must be parallel to that for the standard preparation. If the dose-response line of (S) or (T) is not significantly deviated from a straight line and the two lines are not significantly deviated from parallelism, the assay result is said to be statistically valid, the calculation methods described in this chapter can be used to estimate the potency of the test preparation and its fiducial limits.

Fiducial Limits of Error The required precision of a biological assay is expressed in terms of fiducial limits (FL). The fiducial limits for M are $M \pm t \cdot S_M$, where S_M is the standard error of M, t is a value depending on the degrees of freedom (f) of s^2 (Table 1).

Table 1 Degrees of freedom and the corresponding values of t (P=0.95)

f	t	f	t	f	t	f	t
3	3.18	8	2.31	14	2.15	30	2.04
4	2.78	9	2.26	16	2.12	40	2.02
5	2.57	10	2.23	18	2.10	60	2.00
6	2.45	11	2.20	20	2.09	120	1.98
7	2.37	12	2.18	25	2.06	∞	1.96

In Ch. P., the fiducial limits are calculated with reference to a probability of 0.95, i. e., the true potency would be expected to lie between the upper and lower fiducial limits ($P=0.95$). The precision of an assay is expressed in $FL\%$ which is the average distance between the upper and lower fiducial limits expressed as a percentage of the estimated P_T or R . The value of $FL\%$ is prescribed for each assay method in Ch. P., if the result of an assay does not comply with the required $FL\%$, the experiment should be repeated. $FL\%$ may be reduced as much as practicable by increasing the number of animals or Petri dishes; reducing the weight or age variation of animals; changing the doses etc.

The results of n repeated assays, including the one with a $FL\%$ in excess of that specified in the monograph, can be combined to obtain a single value.

2. Direct Assay

In a direct assay, the threshold dose of standard or test preparation which produces some fixed effect is being measured. The assay of digitalis with pigeons is an example of such an assay.

In an assay of digitalis, x_s and x_T are the logarithm of the minimum lethal dose of (S) and (T) for each pigeon, their mean value \bar{x}_s and \bar{x}_T are taken as the equally effective doses, n_s and n_T are the number of pigeons treated with standard and test preparation respectively.

(1) Calculation of potency

$$M = \bar{x}_s - \bar{x}_T \quad (1)$$

$$R = \text{antilog}(\bar{x}_s - \bar{x}_T) = \text{antilog } M \quad (2)$$

$$P_T = R \cdot A_T \quad (3)$$

(2) Error variance and fiducial limits

$$s^2 = \frac{\sum x_s^2 - \frac{(\sum x_s)^2}{n_s} + \sum x_T^2 - \frac{(\sum x_T)^2}{n_T}}{n_s + n_T - 2} \quad (4)$$

$$f = n_s + n_T - 2$$

$$S_M = \sqrt{s^2 \cdot \frac{n_s + n_T}{n_s \cdot n_T}} \quad (5)$$

$$FL \text{ of } R = \text{antilog} (M \pm t \cdot S_M) \quad (6)$$

$$FL \text{ of } P_T = A_T \cdot \text{antilog} (M \pm t \cdot S_M) \quad (7)$$

$$FL\% \text{ of } R(\text{or } P_T) = \frac{\text{Upper limit of } R(\text{or } P_T) - \text{Lower limit of } R(\text{or } P_T)}{2 R(\text{or } 2 P_T)} \times 100\% \quad (8)$$

When two or more test preparations (T, U...) are compared with the standard preparation simultaneously, the combined error variance (s^2) of (S), (T), (U)... is calculated as follows:

$$s^2 = \frac{\sum x_s^2 - \frac{(\sum x_s)^2}{n_s} + \sum x_T^2 - \frac{(\sum x_T)^2}{n_T} + \sum x_U^2 - \frac{(\sum x_U)^2}{n_U} + \dots}{n_s - 1 + n_T - 1 + n_U - 1 + \dots} \quad (9)$$

$$f = n_s - 1 + n_T - 1 + n_U - 1 + \dots$$

Example 1 Direct assay of digitalis using pigeons (MLD method)

The assay is carried out as described in the Biological Assay of Digitalis (Appendix XIII K). The substance being examined is digitalis powder, $A_T=10$ Units/g. The results of test are shown in table 1-1.

Table 1-1 An assay of digitalis powder

S		T	
$MLD_s (d_s)$	x_s	$MLD_T (d_T)$	x_T
Units/kg body wt.	$\lg(d_s \times 10)$	Units/kg body wt.	$\lg(d_T \times 10)$
1.15	1.061	1.11	1.045
1.01	1.004	1.23	1.090
1.10	1.041	1.06	1.025
1.14	1.057	1.31	1.117
1.06	1.025	0.94	0.973
0.95	0.978	1.36	1.134
$\sum x_s$	6.166	$\sum x_T$	6.384
\bar{x}_s	1.028	\bar{x}_T	1.064

$$M = 1.028 - 1.064 = -0.036$$

$$R = \text{antilog}(-0.036) = 0.9204$$

$$P_T = 10 \times 0.9204 = 9.20 \text{ Units/g}$$

$$s^2 = \frac{1.061^2 + 1.004^2 + \dots + 0.978^2 - \frac{6.166^2}{6} + 1.045^2 + 1.090^2 + \dots + 1.134^2 - \frac{6.384^2}{6}}{6+6-2}$$

$$= 0.002373$$

$$S_M = \sqrt{0.002373 \times \frac{6+6}{6 \times 6}} = 0.02812$$

$$f = 6+6-2 = 10 \quad t = 2.23$$

$$FL \text{ of } P_T = 10 \text{ antilog}(-0.036 \pm 2.23 \times 0.02812) = 7.97 - 10.6 \text{ Units/g}$$

$$FL\% \text{ of } P_T = \frac{10.6 - 7.97}{2 \times 9.20} \times 100 = 14.3\%$$

3. Parallel Line Assay Based on Quantitative Responses

When the magnitude of response which varies with the amount of dose is measurable, it is known as a quantitative response. Parallel line assay can be used only when the relation between the logarithm of dose and response (or transformed response) can be represented by a straight line over a certain range of doses, and the straight line for (T) must be parallel to that for (S).

In a parallel line assay, the dose structure of (S, T) may be (2, 2) or (3, 3) which are generally termed as (*k, k*) assay; the dose structure of (S, T, U) may be (2, 2, 2) or (3, 3, 3) which are generally termed as (*k, k, k*) assay. When the number of doses of (S) is not equal to that of (T), (*k, k'*) assay is resulted. Ordinarily the (*k, k*) structure is used for parallel line assay, but when the dose of (T) or (S) used is very different from the right dose, it is possible that the response of the largest or smallest dose may fall outside the linear zone. In such circumstances, the response to the largest or smallest dose should be omitted and (3, 2) or (2, 3) assay is resulted. Therefore, in (*k, k'*) assay, *k* is only one more or one less than *k'*.

Either in (*k, k*) assay, (*k, k, k*) assay or in (*k, k'*) assay, the preceding *k* always represents the number of doses of (S), the *k* or *k'* behind is the number of doses of (T) or (U). Therefore $K = k + k$ or $K = k + k'$ or $K = k + k + k$. In this chapter, the calculation used for parallel line assays is a simplified method, therefore, the following requirements should be observed:

- (1) The ratio of adjacent doses (*r*) of (S) and (T) in an assay must be constant, usually (1 : 0.8)-(1 : 0.5). $\lg r = L$.
- (2) The number of responses (*m*) to each dose must be equal.

(1) **Assay design** ① *Random design* In this type of assay design, no restriction on the variability of subgroups is applied. The test animals or other experimental units are allocated randomly to different doses, only the variation caused by dose levels can be segregated from the assay result.

② *Random block design* In this type of design, the test animals or other experimental units are further divided into blocks, such as litters of experimental animal or Petri dishes in a microbiological assay. Random block design requires that every dose is applied once in every block (litter or Petri dish) and is only suitable when the block is large enough to accommodate all doses. In this design, the error variance may be reduced by segregating the variation between blocks.

③ *Cross-over design* This design is useful when the single animal used in an experiment can be tested on two occasions separated at suitable time interval. The cross over design used in (2, 2) parallel line assay is known as twin crossover test, in which two doses of standard preparation and of a test preparation are used. Animals are divided randomly into four groups with equal number of animal in each group, and each animal in every group is marked for identification. In the first part of the test, each group receives one of the doses of (S) and (T). Animals which received one preparation in the first part of the test receive the other preparation in the second part of the test, and animals receiving small doses in one part of the test receive large doses in the other. Thus the precision of the experiment can be increased by eliminating the different effect between animals and the different responses at the two stages of the test. The arrangement of doses for twin cross-over design is shown in the following table

	group 1	group 2	group 3	group 4
1st test	d_{S_1}	d_{S_2}	d_{T_1}	d_{T_2}
2nd test	d_{T_2}	d_{T_1}	d_{S_2}	d_{S_1}

(2) Variance analysis and validity test

For random and random block design

① Enter the value of the measured responses or their transformations (*y*) into Table 2. *K* is the total number of doses and *m* is the number of *y* in each dose. In randomized block design, the variation between rows (*m*) represents the variation between blocks, *n* is the total number of responses, $n = mK$.

Table 2 The value of y in different dose groups

		Number of doses					Sum
		(1)	(2)	(3)	...	(K)	
Between blocks	1	$y_{1(1)}$	$y_{1(2)}$	$y_{1(3)}$...	$y_{1(k)}$	$\sum y_1$
	2	$y_{2(1)}$	$y_{2(2)}$	$y_{2(3)}$...	$y_{2(k)}$	$\sum y_2$
	3	$y_{3(1)}$	$y_{3(2)}$	$y_{3(3)}$...	$y_{3(k)}$	$\sum y_3$

	m	$y_{m(1)}$	$y_{m(2)}$	$y_{m(3)}$...	$y_{m(k)}$	$\sum y_m$
Sum		$\sum y_{(1)}$	$\sum y_{(2)}$	$\sum y_{(3)}$...	$\sum y_{(k)}$	$\sum y$

② *Replacement of missing value and rejection of aberrant value* When an accident leads to the loss of one or more responses, the number of responses (m) in each dose will not be equal. The balance may be restored by one of the following procedures:

For random design, the missing value can be replaced with the arithmetic mean of other responses to the same dose. If there are one or two surplus responses in one dose, reject the surplus response by random selection. For randomized block design, the missing value can be replaced with a value calculated from equation (10):

$$y = \frac{KC + mR - G}{(K-1)(m-1)} \quad (10)$$

Where C is The sum of responses in the dose group containing the missing value;

R is the sum of responses in the row containing the missing value;

G is the sum of all responses recorded in the assay;

K is the total number of doses;

m is the number of blocks used in the assay.

When there are enough blocks (litters or dishes) used in the design, it is preferable to omit the whole block in which the missing value lies.

Each replacement of a missing value causes a loss of 1 degree of freedom for error variance, and the number of missing values should not be more than 5% of the total number of responses.

When the largest or smallest response in one of the doses is questionable, the following aberrant value test should be applied.

Let y_a be the supposed aberrant value, arrange the responses in the dose in order of magnitude from y_a to y_m ($y_a, y_2, y_3, \dots, y_{m-2}, y_{m-1}, y_m$). If y_a is the largest value, the series is in descending order; if y_a is the smallest value, the series is in ascending order.

Calculate the value of J with the following equations:

When $m=3-7$,

$$J_1 = \frac{y_2 - y_a}{y_m - y_a} \quad (11)$$

When $m=8-13$,

$$J_2 = \frac{y_3 - y_a}{y_{m-1} - y_a} \quad (12)$$

When $m=14-20$,

$$J_3 = \frac{y_3 - y_a}{y_{m-2} - y_a} \quad (13)$$

If the calculated value of J exceeds the critical value shown in Table 3, y_a can be judged as an aberrant value and rejected.

Table 3 The value of J for aberrant value test

m	3	4	5	6	7		
J_1	0.98	0.85	0.73	0.64	0.59		
m	8	9	10	11	12	13	
J_2	0.78	0.73	0.68	0.64	0.61	0.58	
m	14	15	16	17	18	19	20
J_3	0.60	0.58	0.56	0.54	0.53	0.51	0.50

③ *Variance analysis* For randomized block design, the sum of squares of total variation is divided into components of 'between doses', 'between blocks' and 'residual error'. The values for sum of squares were obtained using the following equations.

$$\text{Total} = \sum y^2 - \frac{(\sum y)^2}{mK} \quad (14)$$

$$\text{Between doses} = \frac{\sum [\sum y_{(k)}]^2}{m} - \frac{(\sum y)^2}{mK} \quad (15)$$

$$f_{\text{between doses}} = K - 1$$

$$\text{Between blocks} = \frac{\sum (\sum y_m)^2}{K} - \frac{(\sum y)^2}{mK} \quad (16)$$

$$f_{\text{between blocks}} = m - 1$$

$$\text{Residual error} = \text{total} - \text{between doses} - \text{between blocks} \quad (17)$$

$$f_{\text{residual error}} = (K-1)(m-1)$$

The mean squares for each component are calculated by dividing the sum of squares of each component by its degrees of freedom. The mean square for residual error is the error variance (s^2) of the assay.

$$s^2 = \frac{\text{sum of squares for error}}{f \text{ for error}} \quad (18)$$

or

$$s^2 = \frac{Km \sum y^2 - K \cdot \sum [\sum y_{(k)}]^2 - m \cdot \sum [\sum y_m]^2 + (\sum y)^2}{Km(K-1)(m-1)} \quad (19)$$

$$f = (K-1)(m-1)$$

For random design, it is only necessary to calculate the sum of squares for total, between doses and residual error, using equations (14), (15) and (20).

$$\text{Residual error} = \text{total} - \text{between doses} \quad (20)$$

$$f_{\text{residual error}} = K(m-1)$$

and s^2 is obtained from equation (18) or (21).

$$s^2 = \frac{m \sum y^2 - \sum [\sum y_{(k)}]^2}{Km(m-1)} \quad (21)$$

$$f = K(m-1)$$

④ *Validity test* For (2.2) and (2.2.2) assays, the between doses component can be subdivided into terms of preparations, regression and parallelism; for ($k.k$) assays other than (2.2) assay and ($k.k.k$) assays other than (2.2.2) assay, additional terms of quadratic and difference of quadratics are required. For ($k.k$) and ($k.k'$) assays, calculate $m \cdot \sum C_i^2$ and $\sum [C_i \cdot \sum y_{(k)}]$ for each term, using the equations shown in Table 4. The sum of squares for each component is obtained from equation (22).

Table 4 Orthogonal coefficient for validity tests of ($k.k$) and ($k.k'$) assay

Design	Source of variation	Orthogonal coefficient(C_i)								$m \cdot \sum C_i^2$	$\sum [C_i \cdot \sum y_{(k)}]$
		S_1	S_2	S_3	S_4	T_1	T_2	T_3	T_4		
(2.2)	Preparations	-1	-1			1	1			4 m	$T_2 + T_1 - S_2 - S_1$
	Regression	-1	1			-1	1			4 m	$T_2 - T_1 + S_2 - S_1$
	Parallelism	1	-1			-1	1			4 m	$T_2 - T_1 - S_2 + S_1$
(3.3)	Preparations	-1	-1	-1		1	1	1		6 m	$T_3 + T_2 + T_1 - S_3 - S_2 - S_1$
	Regression	-1	0	1		-1	0	1		4 m	$T_3 - T_1 + S_3 - S_1$
	Parallelism	1	0	-1		-1	0	1		4 m	$T_3 - T_1 - S_3 + S_1$
	Quadratic	1	-2	1		1	-2	1		12 m	$T_3 - 2T_2 + T_1 + S_3 - 2S_2 + S_1$
	Difference of Quadratics	-1	2	-1		1	-2	1		12 m	$T_3 - 2T_2 + T_1 - S_3 + 2S_2 - S_1$
(4.4)	Preparations	-1	-1	-1	-1	1	1	1	1	8 m	$T_4 + T_3 + T_2 + T_1 - S_4 - S_3 - S_2 - S_1$
	Regression	-3	-1	1	3	-3	-1	1	3	40 m	$3T_4 + T_3 - T_2 - 3T_1 + 3S_4 + S_3 - S_2 - 3S_1$
	Parallelism	3	1	-1	-3	-3	-1	1	3	40 m	$3T_4 + T_3 - T_2 - 3T_1 - 3S_4 - S_3 + S_2 + 3S_1$
	Quadratic	1	-1	-1	1	1	-1	-1	1	8 m	$T_4 - T_3 - T_2 + T_1 + S_4 - S_3 - S_2 + S_1$
	Difference of Quadratics	-1	1	1	-1	1	-1	-1	1	8 m	$T_4 - T_3 - T_2 + T_1 - S_4 + S_3 + S_2 - S_1$
(3.2)	Preparations	-2	-2	-2		3	3			30 m	$3(T_2 + T_1) - 2(S_3 + S_2 + S_1)$
	Regression	-2	0	2		-1	1			10 m	$T_2 - T_1 + 2(S_3 - S_1)$
	Parallelism	1	0	-1		-2	2			10 m	$2(T_2 - T_1) - S_3 + S_1$
	Quadratics	1	-2	1		0	0			6 m	$S_3 - 2S_2 + S_1$

continue

Design	Source of variation	Orthogonal coefficient(C_i)								$m \cdot \sum C_i^2$	$\sum [C_i \cdot \sum y_{(k)}]$
		S_1	S_2	S_3	S_4	T_1	T_2	T_3	T_4		
(4.3)	Preparations	-3	-3	-3	-3	4	4	4		84 m	$4(T_3+T_2+T_1)-3(S_4+S_3+S_2+S_1)$
	Regression	-3	-1	1	3	-2	0	2		28 m	$2(T_3-T_1)+3(S_4-S_1)-S_2+S_3$
	Parallelism	3	1	-1	-3	-5	0	5		70 m	$5(T_3-T_1)-3(S_4-S_1)-S_3+S_2$
	Quadratic	3	-3	-3	3	2	-4	2		60 m	$2(T_3+T_1)-4T_2+3(S_4-S_3-S_2+S_1)$
	Difference of Quadratics	-1	1	1	-1	1	-2	1		10 m	$T_3-2T_2+T_1-S_4+S_3+S_2-S_1$

Notes: For (2.3) or (3.4) assay, calculate $m \cdot \sum C_i^2$ and $\sum [C_i \cdot \sum y_{(k)}]$ by interchanging the orthogonal coefficient of (S) and (T) in (3.2) or (4.3) assay.

In Table 4 $S_1, S_2, \dots, T_1, T_2, \dots$ are the total responses for each dose of (S) and (T) corresponding to the term $\sum y_{(k)}$ in table 2. The subscript 1, 2, 3... are used to represent the respective dose level and 1 is always the smallest dose.

$$\text{Sum of squares for each component} = \frac{[\sum C_i \cdot \sum y_{(k)}]^2}{m \cdot \sum C_i^2} \quad (22)$$

$$f=1$$

For (k. k. k) assays, calculate the sum of squares of preparation by equation (23) and (24).

For (2.2.2) assay

$$\text{Sum of squares(preparations)} = \frac{(S_2+S_1)^2 + (T_2+T_1)^2 + (U_2+U_1)^2}{2m} - \frac{(\sum y)^2}{mK} \quad (23)$$

$$f=2$$

For (3.3.3) assay

$$\text{Sum of squares(preparations)} = \frac{(S_1+S_2+S_3)^2 + (T_1+T_2+T_3)^2 + (U_1+U_2+U_3)^2}{3m} - \frac{(\sum y)^2}{mK} \quad (24)$$

$$f=2$$

For calculation the sum of squares for components other than preparations, calculate $m \cdot \sum C_i^2$ and $\sum [C_i \cdot \sum y_{(k)}]$ by the equations shown in Table 5.

Table 5 Orthogonal coefficient for validity tests of (k. k. k) assay

Design	Source of variation	Orthogonal coefficient(C_i)									$m \cdot \sum C_i^2$	$\sum [C_i \cdot \sum y_{(k)}]$
		S_1	S_2	S_3	T_1	T_2	T_3	U_1	U_2	U_3		
(2.2.2)	Regression	-1	1		-1	1		-1	1		6 m	$S_2-S_1+T_2-T_1+U_2-U_1$
	Parallelism	1	-1		-1	1					4 m	$T_2-T_1-S_2+S_1$
		1	-1					-1	1		4 m	$U_2-U_1-S_2+S_1$
					1	-1		-1	1		4 m	$U_2-U_1-T_2+T_1$
(3.3.3)	Regression	-1	0	1	-1	0	1	-1	0	1	6 m	$U_3-U_1+T_3-T_1+S_3-S_1$
	Parallelism	1	0	-1	-1	0	1				4 m	$T_3-T_1-S_3+S_1$
		1	0	-1				-1	0	1	4 m	$U_3-U_1-S_3+S_1$
					1	0	-1	-1	0	1	4 m	$U_3-U_1-T_3+T_1$
	Quadratic	1	-2	1	1	-2	1	1	-2	1	18 m	$U_3-2U_2+U_1+T_3-2T_2+T_1+S_3-2S_2+S_1$
	Difference of quadratics	-1	2	-1	1	-2	1				12 m	$T_3-2T_2+T_1-S_3+2S_2-S_1$
		-1	2	-1				1	-2	1	12 m	$U_3-2U_2+U_1-S_3+2S_2-S_1$
					-1	2	-1	1	-2	1	12 m	$U_3-2U_2+U_1-T_3+2T_2-T_1$

The sum of squares for regression and parallelism is obtained from equation (22). The sum of squares of quadratic and difference of quadratics is calculated from equation (25).

$$\text{Quadratic and difference of quadratics} = \frac{2 \sum [\sum (C_i \cdot \sum y_{(k)})]^2}{\sum (m \cdot \sum C_i^2)} \quad (25)$$

$$f=2$$

The mean square of each term is obtained by dividing the sum of squares of each term by its degrees of freedom.

Table 6 is a model of validity test for (3.3) assay, randomized block design.

Table 6 Validity test for (3, 3) assay, randomized block design

Source of variation	Degrees of freedom(<i>f</i>)	Sum of squares	Mean Square	<i>F</i>	<i>P</i>
Preparations	1	equation(22)	Sum of squares/ <i>f</i>	Mean square/ <i>s</i> ²	
Regression	1	equation(22)	Sum of squares/ <i>f</i>	Mean square/ <i>s</i> ²	
Parallelism	1	equation(22)	Sum of squares/ <i>f</i>	Mean square/ <i>s</i> ²	
Quadratic	1	equation(22)	Sum of squares/ <i>f</i>	Mean square/ <i>s</i> ²	
Difference of quadratics	1	equation(22)	Sum of squares/ <i>f</i>	Mean square/ <i>s</i> ²	
Doses	<i>K</i> - 1	equation(15)	Sum of squares/ <i>f</i>	Mean square/ <i>s</i> ²	
Blocks	<i>m</i> - 1	equation(16)	Sum of squares/ <i>f</i>	Mean square/ <i>s</i> ²	
Error	(<i>K</i> - 1)(<i>m</i> - 1)	equation(17)	Sum of squares/ <i>f</i> (<i>s</i> ²)		
Total	<i>mK</i> - 1	equation(14)			

In Table 6, the *F* ratio is the mean square of each variable expressed as a ratio of *s*², and the significance of these values are assessed by use of Table 7.

Table 7 The *F* distribution table

		<i>f</i> ₁ Degrees of freedom for numerator								
		1	2	3	4	6	12	20	40	∞
Degrees of freedom for denominator	1	161 4052	200 4999	216 5403	225 5625	234 5859	244 6106	248 6208	251 6286	254 6366
	2	18.51 98.49	19.00 99.00	19.16 99.17	19.25 99.25	19.33 99.33	19.41 99.42	19.44 99.45	19.47 99.48	19.50 99.50
	3	10.13 34.12	9.55 30.82	9.28 29.46	9.12 28.71	8.94 27.91	8.74 27.05	8.66 26.69	8.60 26.41	8.53 26.12
	4	7.71 21.20	6.94 18.00	6.59 16.69	6.39 15.98	6.16 15.21	5.91 14.37	5.80 14.02	5.71 13.74	5.63 13.46
	5	6.61 16.26	5.79 13.27	5.41 12.06	5.19 11.39	4.95 10.67	4.68 9.89	4.56 9.55	4.46 9.29	4.36 9.02
	6	5.99 13.74	5.14 10.92	4.76 9.78	4.53 9.15	4.28 8.47	4.00 7.72	3.87 7.39	3.77 7.14	3.67 6.88
	7	5.59 12.25	4.74 9.55	4.35 8.45	4.12 7.85	3.87 7.19	3.57 6.47	3.44 6.15	3.34 5.90	3.23 5.65
	8	5.32 11.26	4.46 8.65	4.07 7.59	3.84 7.01	3.58 6.37	3.28 5.67	3.15 5.36	3.05 5.11	2.93 4.86
	9	5.12 10.56	4.26 8.02	3.86 6.99	3.63 6.42	3.37 5.80	3.07 5.11	2.93 4.80	2.82 4.56	2.71 4.31
	10	4.96 10.04	4.10 7.56	3.71 6.55	3.48 5.99	3.22 5.39	2.91 4.71	2.77 4.41	2.67 4.17	2.54 3.91
	15	4.54 8.68	3.68 6.36	3.29 5.42	3.06 4.89	2.79 4.32	2.48 3.67	2.33 3.36	2.21 3.12	2.07 2.87
	20	4.35 8.10	3.49 5.85	3.10 4.94	2.87 4.43	2.60 3.87	2.28 3.23	2.12 2.94	1.99 2.69	1.84 2.42
	30	4.17 7.56	3.32 5.39	2.92 4.51	2.69 4.02	2.42 3.47	2.09 2.84	1.93 2.55	1.79 2.29	1.62 2.01
	40	4.08 7.31	3.23 5.18	2.84 4.31	2.61 3.83	2.34 3.29	2.00 2.66	1.84 2.37	1.69 2.11	1.51 1.81
	60	4.00 7.08	3.15 4.98	2.76 4.13	2.52 3.65	2.25 3.12	1.92 2.50	1.75 2.20	1.59 1.93	1.39 1.60
	∞	3.84 6.64	2.99 4.60	2.60 3.78	2.37 3.32	2.09 2.80	1.75 2.18	1.57 1.87	1.40 1.59	1.00 1.00

The upper values: *P* = 0.05

The lower values: *P* = 0.01

If the calculated *F* value is larger than the tabulated value at the level of probability of *P* = 0.05 or *P* = 0.01, the value being tested is said to be significant at the level of *P* = 0.05 or highly significant at the level of *P* = 0.01.

The assay result is said to be valid if the outcome of the test is as follows.

The regression term should be highly significant (*P* < 0.01).

The deviation from parallelism should not be significant (*P* > 0.05).

When 3 or more dose levels are used in (*k, k*) or (*k, k, k*) assay, the quadratic and difference in quadratics should not be significant (*P* > 0.05).

The significant level for the term of preparations is not used for assessing the validity of an assay, but a highly significant *F* ratio for preparations may indicate that the choice of assumed potency is not a good one. The estimated potency may serve as a guide for the choice of assumed potency when the assay is repeated.

For twin cross-over design

and every animal of each group is tested on two separated occasions, therefore $2 \times 4m$ value of responses are obtained. Enter the $2 \times 4m$ values into the form of Table 8.

Table 8 The value of y for twin cross-over test

	1 st group			2 nd group			3 rd group			4 th group			
	Test (1)	Test (2)	Σ (1)+(2)	Test (1)	Test (2)	Σ (1)+(2)	Test (1)	Test (2)	Σ (1)+(2)	Test (1)	Test (2)	Σ (1)+(2)	
	d_{S_1}	d_{T_2}		d_{S_2}	d_{T_1}		d_{T_1}	d_{S_2}		d_{T_2}	d_{S_1}		
y	$y_{S_1(1)}$ \vdots	$y_{T_2(2)}$ \vdots	$y_{(1)}+y_{(2)}$ \vdots	$y_{S_2(1)}$ \vdots	$y_{T_1(2)}$ \vdots	$y_{(1)}+y_{(2)}$ \vdots	$y_{T_1(1)}$ \vdots	$y_{S_2(2)}$ \vdots	$y_{(1)}+y_{(2)}$ \vdots	$y_{T_2(1)}$ \vdots	$y_{S_1(2)}$ \vdots	$y_{(1)}+y_{(2)}$ \vdots	Σ
Σy	$S_{1(1)}$	$T_{2(2)}$		$S_{2(1)}$	$T_{1(2)}$		$T_{1(1)}$	$S_{2(2)}$		$T_{2(1)}$	$S_{1(2)}$		S_1 S_2 T_1 T_2

(II) *Replacement of missing value* In twin cross-over test, each animal has two values of measured response, if one value of an animal is lost, the total two values of that animal will be considered to be missed. Replace the two missing value separately with the arithmetic mean of the other responses to the same dose of the test or reject the one surplus value of other doses in each test by random selection.

Each replacement of a missing value causes a loss of 1 degree of freedom for error variance. The number of missing value should not be more than 5% of the total number of responses and the missing value in one dose should not be more than 1.

(III) *Variance analysis* For twin cross-over design, the sum of square of total variation of $2 \times 4m$ responses can be divided into variation of between animals (inter-animal variation) and variation of intra-animal.

Sum of squares of

$$\text{Total} = \Sigma y^2 - \frac{(\Sigma y)^2}{2 \times 4m} \quad (26)$$

$$f_{(\text{Total})} = 2 \times 4m - 1$$

Sum of square of inter-animal variation is calculated by equation (27) using the value in the third column of each group in Table 8

$$\text{Inter-animal} = \frac{\Sigma [y_{(1)} + y_{(2)}]^2}{2} - \frac{(\Sigma y)^2}{2 \times 4m} \quad (27)$$

$$f_{(\text{inter-animal})} = 4m - 1$$

Subtract inter-animal variation from the total variation, the residue is the sum of square of intra-animal variation.

Calculate $m \cdot \Sigma C_i^2$ and $\Sigma (C_i \cdot \Sigma y)$ of each component by multiplying the sum of total response for each test of the four groups in Table 8 ($S_{1(1)}$, $S_{2(1)}$, $T_{1(1)}$, $T_{2(1)}$, $S_{1(2)}$, $S_{2(2)}$, $T_{1(2)}$, $T_{2(2)}$) by the orthogonal coefficient shown in Table 9.

Sum of square of each component in Table 9 is obtained by $\frac{[\Sigma (C_i \cdot \Sigma y)]^2}{m \cdot \Sigma C_i^2}$.

Table 9 Orthogonal coefficient for validity test of twin cross-over design

Source of variation	Test(1)				Test(2)				$m \cdot \Sigma C_i^2$	$\Sigma(C_i \cdot \Sigma y)$
	$S_{1(1)}$	$S_{2(1)}$	$T_{1(1)}$	$T_{2(1)}$	$S_{1(2)}$	$S_{2(2)}$	$T_{1(2)}$	$T_{2(2)}$		
	Orthogonal coefficient C_i									
Preparation*	-1	-1	1	1	-1	-1	1	1	8 m	$T_{2(1)}+T_{1(1)}-S_{2(1)}-S_{1(1)}+T_{2(2)}+T_{1(2)}-S_{2(2)}-S_{1(2)}$
Regression *	-1	1	-1	1	-1	1	-1	1	8 m	$T_{2(1)}-T_{1(1)}+S_{2(1)}-S_{1(1)}+T_{2(2)}-T_{1(2)}+S_{2(2)}-S_{1(2)}$
Parallelism	1	-1	-1	1	1	-1	-1	1	8 m	$T_{2(1)}-T_{1(1)}-S_{2(1)}+S_{1(1)}+T_{2(2)}-T_{1(2)}-S_{2(2)}+S_{1(2)}$
Time of test*	-1	-1	-1	-1	1	1	1	1	8 m	$T_{2(2)}+T_{1(2)}+S_{2(2)}+S_{1(2)}-T_{2(1)}-T_{1(1)}-S_{2(1)}-S_{1(1)}$
Time×preparation	1	1	-1	-1	-1	-1	1	1	8 m	$T_{2(2)}+T_{1(2)}-S_{2(2)}-S_{1(2)}-T_{2(1)}-T_{1(1)}+S_{2(1)}+S_{1(1)}$
Time×regression	1	-1	1	-1	-1	1	-1	1	8 m	$T_{2(2)}-T_{1(2)}+S_{2(2)}-S_{1(2)}-T_{2(1)}+T_{1(1)}-S_{2(1)}+S_{1(1)}$
Time×parallelism*	-1	1	1	-1	1	-1	-1	1	8 m	$T_{2(2)}-T_{1(2)}-S_{2(2)}+S_{1(2)}-T_{2(1)}+T_{1(1)}+S_{2(1)}-S_{1(1)}$

The degrees of freedom for each component is 1.

* mean the four components of intra-animal variation, the remaining three components are inter-animal variation.

Sum of square of error variance for intra-animal (error I) and inter-animal (error II) are calculated by equation (28) and equation (29)

$$\text{Error(I)} = \text{Total} - \text{Inter-animal} - \text{Preparation} - \text{Regression} - \text{Time} - \text{Time} \times \text{parallelism} \quad (28)$$

$$f_{\text{error(I)}} = f_{\text{Total}} - f_{\text{inter-animal}} - f_{\text{preparation}} - f_{\text{regression}} - f_{\text{time}} - f_{\text{time} \times \text{parallelism}}$$

$$= 4(m-1)$$

$$\text{Error(II)} = \text{Inter-animal} - \text{Parallelism} - \text{Time} \times \text{Preparation} - \text{Time} \times \text{regression} \quad (29)$$

$$f_{\text{error(II)}} = f_{\text{inter-animal}} - f_{\text{parallelism}} - f_{\text{time} \times \text{preparation}} - f_{\text{time} \times \text{regression}}$$

(IV) *Validity test* The result of validity test for twin cross-over design is shown in Table 10.

Table 10 Validity test for twin cross-over design

source of variation	f	sum of square	mean square	F	P
Parallelism	1	equation(22)	sum of square/ f	mean square/ s_{II}^2	
Time \times preparation	1	equation(22)	sum of square/ f	mean square/ s_{II}^2	
Time \times regression	1	equation(22)	sum of square/ f	mean square/ s_{II}^2	
Error(II)	$4(m-1)$	equation(29)	sum of square/ $f(s_{II}^2)$		
Inter-animal	$4m-1$	equation(27)	sum of square/ f	mean square/ s^2	
Preparation	1	equation(22)	sum of square/ f	mean square/ s^2	
Regression	1	equation(22)	sum of square/ f	mean square/ s^2	
Time of test	1	equation(22)	sum of square/ f	mean square/ s^2	
Time \times parallelism	1	equation(22)	sum of square/ f	mean square/ s^2	
Error(I)	$4(m-1)$	equation(28)	sum of square/ $f(s^2)$	mean square/ s^2	
Total	$2 \times 4m-1$	equation(26)			

In table 10, the mean square for each component is obtained by dividing the sum of square of each component by its degrees of freedom. F ratio for three inter-animal components (In the upper part of Table 10) is the mean square for each component expressed as a ratio of mean square of Error (II) - (s_{II}^2) and the F ratio for three intra-animal components (The lower part of table 10) is the mean square for each component expressed as a ratio of mean square of error (I) s^2 . The significance of F value are assessed in the same way as that for other parallel line assays.

Assay results are said to be statistically valid if the outcome of these tests is as follows:

The terms of regression, parallelism and preparation are assessed in the same way as that of (2.2) assay. The three interaction components—time \times preparation, time \times regression, time \times parallelism—indicate the variation of these components (preparation, parallelism, regression) from the first test to the second test, if the F value of these components obtained are significantly high, care should be taken in interpreting the results of the assay, and if possible, the assay should be repeated.

(3) Estimation of potency and fiducial limits

For (k, k), (k, k') and (k, k, k) assays, calculate the values of V , W , D , A , B and g by use of the equations listed in Table 11, and calculate R , S_M , FL by use of equations (30)-(33).

$$R = D \cdot \text{antilog } \frac{IV}{W} \quad (30)$$

$$S_M = \frac{I}{W^2(1-g)} \sqrt{ms^2[(1-g)AW^2 + BV^2]} \quad (31)$$

$$FL \text{ of } R = \text{antilog } \left[\frac{\lg R}{1-g} \pm t \cdot S_M \right] \quad (32)$$

$$FL \text{ of } P_T = A_T \cdot \text{antilog } \left[\frac{\lg R}{1-g} \pm t \cdot S_M \right] \quad (33)$$

Calculate P_T by use of equation (3) and its $FL\%$ by use of equation (8).

Table 11 Equations used for paralld line assay

Design	(S)	(T)	V	W	D	A	B	g
2. 2	$ds_1 ds_2$	$d_{T_1} d_{T_2}$	$\frac{1}{2}(T_1 + T_2 - S_1 - S_2)$	$\frac{1}{2}(T_2 - T_1 + S_2 - S_1)$	$\frac{ds_2}{dT_2}$	1	1	$\frac{t^2 s^2 m}{W^2}$
3. 3	$ds_1 ds_2 ds_3$	$d_{T_1} d_{T_2} d_{T_3}$	$\frac{1}{3}(T_1 + T_2 + T_3 - S_1 - S_2 - S_3)$	$\frac{1}{4}(T_3 - T_1 + S_3 - S_1)$	$\frac{ds_3}{dT_3}$	$\frac{2}{3}$	$\frac{1}{4}$	$\frac{t^2 s^2 m}{4W^2}$
4. 4	$ds_1 ds_2 ds_3 ds_4$	$d_{T_1} d_{T_2} d_{T_3} d_{T_4}$	$\frac{1}{4}(T_1 + T_2 + T_3 + T_4 - S_1 - S_2 - S_3 - S_4)$	$\frac{1}{20}[(T_3 - T_2 + S_3 - S_2) + 3(T_4 - T_1 + S_4 - S_1)]$	$\frac{ds_4}{dT_4}$	$\frac{1}{2}$	$\frac{1}{10}$	$\frac{t^2 s^2 m}{10W^2}$
3. 2	$ds_1 ds_2 ds_3$	$d_{T_1} d_{T_2}$	$\frac{1}{2}(T_2 + T_1) - \frac{1}{3}(S_1 + S_2 + S_3)$	$\frac{1}{5}[(T_2 - T_1) + 2(S_3 - S_1)]$	$\frac{ds_3}{dT_2} \cdot \frac{1}{\sqrt{r}}$	$\frac{5}{6}$	$\frac{2}{5}$	$\frac{2t^2 s^2 m}{5W^2}$
2. 3	$ds_1 ds_2$	$d_{T_1} d_{T_2} d_{T_3}$	$\frac{1}{3}(T_1 + T_2 + T_3) - \frac{1}{2}(S_1 + S_2)$	$\frac{1}{5}[2(T_3 - T_1) + 2(S_2 - S_1)]$	$\frac{ds_2}{dT_3} \cdot \sqrt{r}$			
4. 3	$ds_1 ds_2 ds_3 ds_4$	$d_{T_1} d_{T_2} d_{T_3}$	$\frac{1}{3}(T_1 + T_2 + T_3) - \frac{1}{4}(S_1 + S_2 + S_3 + S_4)$	$\frac{1}{14}[2(T_3 - T_1) + (S_3 - S_2) + 3(S_4 - S_1)]$	$\frac{ds_4}{dT_3} \cdot \frac{1}{\sqrt{r}}$	$\frac{7}{12}$	$\frac{1}{7}$	$\frac{t^2 s^2 m}{7W^2}$
3. 4	$ds_1 ds_2 ds_3$	$d_{T_1} d_{T_2} d_{T_3} d_{T_4}$	$\frac{1}{4}(T_1 + T_2 + T_3 + T_4) - \frac{1}{5}(S_1 + S_2 + S_3)$	$\frac{1}{14}[2(S_3 - S_1) + (T_3 - T_2) + 3(T_4 - T_1)]$	$\frac{ds_3}{dT_4} \cdot \sqrt{r}$			

continue								
Design	(S)	(T)	V	W	D	A	B	g
2. 2. 2	$ds_1 ds_2$	$dT_1 dT_2$	$\frac{1}{2}(T_1 + T_2 - S_1 - S_2)$	$\frac{1}{3}(T_2 - T_1 + U_2 - U_1 + S_2 - S_1)$	$\frac{ds_2}{dT_2}$	1	$\frac{2}{3}$	$\frac{2t^2 s^2 m}{3W^2}$
		$dU_1 dU_2$	$\frac{1}{2}(U_1 + U_2 - S_1 - S_2)$		$\frac{ds_2}{dU_2}$			
3. 3. 3	$ds_1 ds_2 ds_3$	$dT_1 dT_2 dT_3$	$\frac{1}{3}(T_1 + T_2 + T_3 - S_1 - S_2 - S_3)$	$\frac{1}{6}(T_3 - T_1 + U_3 - U_1 + S_3 - S_1)$	$\frac{ds_3}{dT_3}$	$\frac{2}{3}$	$\frac{1}{6}$	$\frac{t^2 s^2 m}{6W^2}$
		$dU_1 dU_2 dU_3$	$\frac{1}{3}(U_1 + U_2 + U_3 - S_1 - S_2 - S_3)$		$\frac{ds_3}{dU_3}$			

For twin cross-over design, 2m values of measured responses for each dose of (S) and (T) are obtained. Calculate V, W, D, and g by use of equations for (2. 2) assay in table 11 using the sum of 2m responses for each dose (the values of S_1 , S_2 , T_1 , T_2 in table 8). Calculate S_M by equation (34)

$$S_M = \frac{I}{W^2(1-g)} \sqrt{2ms^2[(1-g)W^2 + V^2]} \quad (34)$$

$$g = \frac{s^2 \cdot t^2 \cdot 2m}{W^2}$$

Example 2 Parallel line assay of HCG by uterus weight method in mice, random design (3. 3. 3)

S is the standard preparation of HCG;

T is HCG bulk substance, $A_T = 2500$ Units/mg;

U is HCG for injection, $A_U = 500$ Units/ampoule.

The assay result is shown in Table 2-1.

Table 2-1 An assay of HCG

$r = 1 : 0.6$, $I = \lg r = 0.222$ (3. 3. 3) assay; $K = 9$, $m = 15$

Dose Units/mouse	ds_1 0.135	ds_2 0.225	ds_3 0.375	dT_1 0.135	dT_2 0.225	dT_3 0.375	dU_1 0.144	dU_2 0.240	dU_3 0.400	
Uterine weight mg/10 g(body weight) y	9.31	33.70	15.10	20.80	25.70	35.60	26.20	10.00	55.00	
	17.50	56.80	47.20	16.40	6.37	48.40	10.00	40.20	41.70	
	21.90	44.60	51.80	5.66	38.30	41.90	19.22	22.30	15.40	
	14.60	32.30	47.30	9.50	46.80	44.70	22.00	40.50	53.60	
	8.20	16.70	49.90	9.27	43.40	29.80	20.70	50.90	53.70	
	11.00	6.17	47.20	7.56	27.80	38.80	23.20	23.50	33.00	
	24.40	41.50	47.10	15.40	26.00	37.40	18.70	19.60	44.30	
	16.80	36.20	45.10	20.30	27.20	33.70	12.60	27.20	44.70	
	29.90	9.83	46.40	11.50	27.30	35.40	20.90	30.30	23.00	
	8.95	20.00	52.90	22.20	11.90	47.90	19.10	58.80	31.60	
	17.80	22.00	32.50	20.60	33.40	14.60	19.40	55.30	49.20	
	18.00	60.60	56.40	13.90	29.00	49.80	14.50	40.70	55.30	
	13.70	6.43	39.50	12.60	6.43	14.50	11.40	35.40	23.80	
	8.82	26.00	8.08	7.25	27.80	42.00	16.20	15.20	21.80	
	17.80	34.80	37.10	15.80	17.70	11.50	20.80	28.70	36.00	
$\Sigma y_{(k)}$	238.68 S_1	447.63 S_2	623.58 S_3	208.74 T_1	395.10 T_2	526.00 T_3	274.92 U_1	498.60 U_2	582.10 U_3	Σy 3795.35

① Sum of squares

$$K = 9, m = 15$$

$$\text{Total} = 9.31^2 + 17.50^2 + \dots + 23.80^2 + 21.80^2 + 36.00^2 - \frac{(3795.35)^2}{9 \times 15} = 29868.26$$

$$f = 9 \times 15 - 1 = 134$$

$$\text{Between doses} = \frac{238.68^2 + 447.63^2 + \dots + 582.10^2}{15} - \frac{(3795.35)^2}{9 \times 15} = 12336.55$$

$$f = 9 - 1 = 8$$

$$\text{Error} = 29868.26 - 12336.55 = 17531.71$$

$$f = 134 - 8 = 126$$

② Variance analysis and validity test

$$\begin{aligned}\text{Sum of squares (preparations)} &= \frac{(238.68+447.63+623.58)^2}{3 \times 15} + \frac{(274.92+498.60+582.10)^2}{3 \times 15} - \frac{(3795.35)^2}{9 \times 15} = 633.23 \\ f &= 2\end{aligned}$$

The results of variance analysis are shown in Table 2-2; the results of validity test are shown in Table 2-3.

Table 2-2 Variance analysis for HCG assay (3. 3. 3)

Source of variation	$\Sigma y_{(k)}$									$m \cdot \Sigma C_i^2$	$\Sigma[G \cdot \Sigma y_{(k)}]$	Sum of squares			
	S_1	S_2	S_3	T_1	T_2	T_3	U_1	U_2	U_3			$\frac{[\Sigma(C_i \cdot \Sigma y_{(k)})]^2}{m \cdot \Sigma C_i^2}$	$\frac{2\Sigma[\Sigma(C_i \cdot \Sigma y_{(k)})]^2}{\Sigma(m \cdot \Sigma C_i^2)}$		
	Orthogonal coefficient C_i														
Regression	-1	0	1	-1	0	1	-1	0	1	6×15	1009.34	11319.64			
Parallelism	1	0	-1	-1	0	1				4×15	-67.54		119.08		
	1	0	-1				-1	0	1	4×15	-77.72				
				1	0	-1	-1	0	1	4×15	-10.08				
Quadratic	1	-2	1	1	-2	1	1	-2	1	18×15	-228.64	193.62			
Difference of quadratics	-1	2	-1	1	-2	1				12×15	-22.46		71.0		
	-1	2	-1				1	-2	1	12×15	-107.18				
				-1	2	-1	1	-2	1	12×15	-87.72				

Table 2-3 Validity test of HCG assay (3. 3. 3)

Source of variation	Degree of freedom(f)	Sum of squares	Mean square	F	P
Preparations	2	633.23	316.6	2.28	>0.05
Regression	1	11319.64	11319.64	81.35	<0.01
Parallelism	2	119.08	59.54	<1	>0.05
Quadratic	1	193.62	193.62	1.39	>0.05
Difference of quadratics	2	71.00	35.50	<1	>0.05
Doses	8	12336.55	1542.07	11.08	<0.01
Error	126	17531.71	139.14(s^2)		
Total	134	29868.26			

Conclusion The regression was highly significant, the deviation from parallelism, the quadratic and difference of quadratics were not significant. Therefore, the assay result was satisfactory.

③ Potency and fiducial limits

$$\begin{aligned}r &= 1 : 0.6 & I &= 0.222 \\ s^2 &= 139.14 & f &= 126 & t &= 1.98 \\ V_T &= \frac{1}{3}(208.74+395.10+526.00-238.68-447.63-623.58) = -60.017 \\ W &= \frac{1}{6}(526.00-208.74+623.58-238.68+582.10-274.92) = 168.223 \\ g &= \frac{139.14 \times 1.98^2 \times 15}{6 \times (168.223)^2} = 0.048 \\ R_T &= \frac{0.375}{0.375} \cdot \text{antilog}\left(\frac{-60.017}{168.223}\right) \times 0.222 = 0.833 \\ P_T &= 2500 \times 0.833 = 2082.5 \text{ Units/mg} \\ S_{M_T} &= \frac{0.222}{(168.223)^2 (1-0.048)} \times \sqrt{15 \times 139.14 \left[(1-0.048) \frac{2}{3} \times 168.223^2 + \frac{1}{6} (-60.017)^2 \right]} \\ &= 0.05129 \\ FL \text{ of } R_T &= \text{antilog} \left[\frac{\lg 0.833}{(1-0.048)} \pm 1.98 \times 0.05129 \right] = 0.653-1.043 \\ FL \text{ of } P_T &= 2500(0.653-1.043) = 1632.5-2607.5 \text{ Units/mg} \\ FL\% \text{ of } P_T &= \frac{2607.5-1632.5}{2 \times 2082.5} \times 100 = 23.4\% \\ V_U &= \frac{1}{3}(274.92+498.60+582.10-238.68-447.63-623.58) = 15.243 \\ W &= 168.223 \quad g = 0.048 \\ R_U &= \frac{0.375}{0.400} \text{ antilog} \left(\frac{15.243}{168.223} \times 0.222 \right) = 0.982 \\ P_U &= 500 \times 0.982 = 491.0 \text{ Units/ampoule}\end{aligned}$$

$$S_{Mu} = \frac{0.222}{168.223^2(1-0.048)} \times \sqrt{15 \times 139.14 \left[(1-0.048) \frac{2}{3} \times 168.223^2 + \frac{1}{6} \times 15.243^2 \right]}$$

$$= 0.05051$$

$$FL \text{ of } R_U = \text{antilog} \left[\frac{\lg 0.982}{(1-0.048)} \pm 1.98 \times 0.05051 \right] = 0.779 - 1.235$$

$$FL \text{ of } P_U = 500(0.779 - 1.235) = 389.5 - 617.5 \text{ Units/ampoule}$$

$$FL\% \text{ of } P_U = \frac{617.5 - 389.5}{2 \times 491.0} \times 100 = 23.2\%$$

Calculate s^2 from equation(21)

$$s^2 = \frac{15(9.31^2 + 17.50^2 + \dots + 21.80^2 + 36.00^2) - (238.68^2 + 447.63^2 + \dots + 582.10^2)}{9 \times 15(15-1)}$$

$$= 139.14$$

Example 3 Parallel line assay of neomycin, randomized block design (3.3) assay

S is the standard preparation of neomycin;

T is neomycin bulk substance, $A_T = 670$ Units/mg.

The assay result is shown in Table 3-1.

Table 3-1 An assay of neomycin

Units/ml	d_{S_1} 8.0	d_{S_2} 10.0	d_{S_3} 12.5	d_{T_1} 8.0	d_{T_2} 10.0	d_{T_3} 12.5	Σy_m
y	16.05	16.20	16.50	15.80	16.35	16.60	97.50
	16.20	16.45	16.65	16.20	16.45	16.70	98.65
	16.00	16.45	16.70	16.05	16.35	16.70	98.25
	15.95	16.35	16.60	16.00	16.25	16.60	97.75
	15.70	16.25	16.60	15.85	16.25	16.60	97.25
	15.55	16.20	16.55	15.70	16.20	16.60	96.80
	15.65	16.20	16.40	15.80	16.15	16.40	96.60
	15.90	16.10	16.45	15.80	16.10	16.50	96.85
	15.60	16.00	16.30	15.70	15.95	16.30	95.85
$\Sigma y_{(k)}$	142.60 S_1	146.20 S_2	148.75 S_3	142.90 T_1	146.05 T_2	149.00 T_3	875.50

① Sum of squares

$$K=6, m=9$$

$$\text{Total} = 16.05^2 + 16.20^2 + \dots + 16.50^2 + 16.30^2 - \frac{(875.5)^2}{9 \times 6} = 5.4709$$

$$f = 9 \times 6 - 1 = 53$$

$$\text{Between doses} = \frac{(142.60)^2 + (146.20)^2 + \dots + (146.05)^2 + (149.00)^2}{9} - \frac{(875.5)^2}{9 \times 6} = 4.1926$$

$$f = 6 - 1 = 5$$

$$\text{Between dishes} = \frac{(97.50)^2 + (98.65)^2 + \dots + (96.85)^2 + (95.85)^2}{6} - \frac{(875.5)^2}{9 \times 6} = 1.0018$$

$$f = 9 - 1 = 8$$

$$\text{Error} = 5.4709 - 4.1926 - 1.0018 = 0.2765$$

$$f = 53 - 5 - 8 = 40$$

② Variance analysis and validity test

The results of variance analysis are shown in Table 3-2; the results of validity test are shown in Table 3-3.

Table 3-2 Variance analysis for neomycin in assay (3.3)

Source of variation	$\Sigma y_{(k)}$						$m \cdot \Sigma C_i^2$	$\Sigma [C_i \cdot \Sigma y_{(k)}]$	$\frac{\text{Sum of squares } [\Sigma (C_i \cdot \Sigma y_{(k)})]^2}{m \cdot \Sigma C_i^2}$
	S_1 142.60	S_2 146.20	S_3 148.75	T_1 142.90	T_2 146.05	T_3 149.00			
	Orthogonal coefficient C_i								
Preparations	-1	-1	-1	+1	+1	+1	9×6	0.4000	0.002963
Regression	-1	0	+1	-1	0	+1	9×4	12.25	4.168
Parallelism	+1	0	-1	-1	0	+1	9×4	0.05000	0.00006944
Quadratic	+1	-2	+1	+1	-2	+1	9×12	1.250	0.01447
Difference of quadratics	-1	+2	-1	+1	-2	+1	9×12	0.8500	0.006690

Table 3-3 Validity test for neomycin assay (3.3)

Source of variation	Degrees of freedom(<i>f</i>)	Sum of squares	Mean square	<i>F</i>	<i>P</i>
Preparations	1	0.002963	0.002963	<1	>0.05
Regression	1	4.168	4.168	602.9	<0.01
Parallelism	1	0.00006944	0.00006944	<1	>0.05
Quadratic	1	0.01447	0.01447	2.1	>0.05
Difference of quadratics	1	0.006690	0.006690	<1	>0.05
Doses	5	4.1926	0.8385	121.3	<0.01
Dishes	8	1.0028	0.1252	18.1	<0.01
Error	40	0.2765	0.006912(<i>s</i> ²)		
Total	53	5.4709			

Conclusion The regression was highly significant, the deviation from parallelism, the quadratic and difference of quadratics were not significant. Therefore, the assay result was satisfactory. The difference between dishes was highly significant ($P < 0.01$), the precision of the assay would be increased by segregating the variation between dishes from the total.

③ Potency and fiducial limits

$$r=1:0.8 \quad I=0.0969 \quad s^2=0.006912 \quad f=40 \quad t=2.02 \quad (P=0.95)$$

$$V=\frac{1}{3}(142.90+146.05+149.00-142.6-146.2-148.75)=0.1333$$

$$W=\frac{1}{4}(149.0-142.9+148.75-142.6)=3.0625$$

$$g=\frac{2.02^2 \times 0.006912 \times 9}{4 \times 3.0625^2}=0.007$$

$$R=\frac{12.5}{12.5} \text{ antilog } \frac{0.1333}{3.0625} \times 0.0969=1.01$$

$$P_T=1.010 \times 670 \text{ Units/mg}=676.70 \text{ Units/mg}$$

$$S_M=\frac{0.0969}{3.0625^2(1-0.007)} \times \sqrt{9 \times 0.006912 \left[(1-0.007) \times \frac{2}{3} \times 3.0625^2 + \frac{1}{4} \times 0.1333^2 \right]}=0.006469$$

$$FL \text{ of } R=\text{antilog} \left[\frac{\lg 1.010}{(1-0.007)} \pm 2.02 \times 0.006469 \right]=0.980-1.041$$

$$FL \text{ of } P_T=670 \times 0.980-670 \times 1.041=656.60-697.47 \text{ Units/mg}$$

$$FL\% \text{ of } P_T=\frac{697.47-656.60}{2 \times 676.70} \times 100=3.0\%$$

$$s^2=\frac{6 \times 9(16.05^2+16.20^2+\dots+16.50^2+16.30^2)}{6 \times 9(6-1)(9-1)} - \frac{6(142.6^2+\dots+149.0^2)-9(97.5^2+\dots+95.85^2)+875.5^2}{6 \times 9(6-1)(9-1)}$$

$$=0.006912$$

$$f=(6-1)(9-1)=40$$

Example 4 Parallel line assay of oxytocin, randomized block design (2.2)

S is the standard preparation of oxytocin;
T is oxytocin injection, $A_T=10$ Units/ml.
 The assay result is shown in Table 4-1.

Table 4-1 An assay of oxytocin injection

Doses Units	d_{s_1} 0.0068 (0.34 ml)	d_{s_2} 0.009 (0.45 ml)	d_{T_1} 0.0080 (0.40 ml)	d_{T_2} 0.0106 (0.53 ml)	Σy_m
<i>y</i>	39.5	68.0	41.0	71.0	219.5
	37.0	62.5	36.0	53.0	188.5
	35.0	63.0	37.0	62.0	197.0
	31.5	58.0	34.5 (15.0)	60.0	184.0
	30.0	50.0	35.0	60.0	175.0
	$\Sigma y_{(k)}$				
	173.0 S_1	301.5 S_2	183.5 T_1	306.0 T_2	964.0

① Disposal of an aberrant value

In Table 4-1, the response value of 3rd column (d_{T_1}) 4th row (15) is rather small, and the aberrant value test is applied. Arrange the responses to d_{T_1} in ascending order: 15.0, 35.0, 36.0, 37.0, 41.0.

$$m=5 \quad y_a=15 \quad y_2=35 \quad y_m=41$$

$$J_1=\frac{y_2-y_a}{y_m-y_a}=\frac{35-15}{41-15}=0.77$$

In Table 3, when $m=5$, $J_1=0.73$, smaller than the calculated J_1 (0.77). Therefore, y_* can be rejected and the missing value replaced by a value calculated as follows:

$$\begin{aligned} C &= 149 & R &= 149.5 & G &= 929.5 \\ K &= 4 & m &= 5 \\ y &= \frac{4 \times 149 + 5 \times 149.5 - 929.5}{(4-1)(5-1)} = 34.5 \end{aligned}$$

② Sum of squares

$$\text{Total} = 39.5^2 + 37.0^2 + \dots + 60.0^2 + 60.0^2 - \frac{964.0^2}{5 \times 4} = 3600.20$$

$$f = 5 \times 4 - 1 = 19$$

$$\text{Between doses} = \frac{173.0^2 + 301.5^2 + 183.5^2 + 306.0^2}{5} - \frac{964.0^2}{5 \times 4} = 3163.10$$

$$f = 4 - 1 = 3$$

$$\text{Between blocks} = \frac{219.5^2 + 188.5^2 + \dots + 184.0^2 + 175.0^2}{4} - \frac{964.0^2}{5 \times 4} = 285.82$$

$$f = 5 - 1 = 4$$

$$\text{Error} = 3600.20 - 3163.10 - 285.82 = 151.28$$

The replacement of a missing value causes a loss of 1 degree of freedom, therefore, $f = 19 - 3 - 4 - 1 = 11$, $s^2 = 151.28/11 = 13.75$

③ Variance analysis and validity test

The results of variance analysis are shown in Table 4-2; the results of validity test are shown in Table 4-3.

Table 4-2 Variance analysis for an assay of oxytocin injection

Source of variation	$\Sigma y_{(k)}$				$m \cdot \Sigma C_i^2$	$\Sigma [C_i \cdot \Sigma y_{(k)}]$	$\frac{[\Sigma (C_i \cdot \Sigma y_{(k)})]^2}{m \cdot \Sigma C_i^2}$
	S_1	S_2	T_1	T_2			
	173.0	301.5	183.5	306.0			
	Orthogonal coefficient C_i						
Preparations	-1	-1	1	1	5×4	15.0	11.25
Regression	-1	1	-1	1	5×4	251.0	31150.05
Parallelism	1	-1	-1	1	5×4	-6.00	1.80

Table 4-3 Validity test for an assay of oxytocin injection

Source of variation	f	Sum of squares	Mean square	F	P
Preparations	1	11.25	11.25	<1	>0.05
Regression	1	3150.05	3150.05	229.06	<0.01
Parallelism	1	1.80	1.80	<1	>0.05
Doses	3	3163.10	1054.37	76.67	<0.01
Blocks	4	285.82	71.46	5.20	<0.05
Error	11	151.27	13.75 (s^2)		>0.01
Total	19	3600.20			

Conclusion The regression was highly significant, the deviation from parallelism was not significant. Therefore, the assay result was satisfactory.

④ Potency and fiducial limits

$$r = 1 : 0.75 \quad I = 0.125 \quad s^2 = 13.75$$

$$f = 11 \quad t = 2.20$$

$$V = \frac{1}{2} (183.5 + 306.0 - 173.0 - 301.5) = 7.5$$

$$W = \frac{1}{2} (306.0 - 183.5 + 301.5 - 173.0) = 125.5$$

$$g = \frac{13.75 \times 2.20^2 \times 5}{125.5^2} = 0.021$$

$$R = \frac{0.009}{0.0106} \text{ antilog } \frac{7.5}{125.5} \times 0.125 = 0.864$$

$$P_T = 10 \times 0.864 = 8.64 \text{ Units/ml}$$

$$S_M = \frac{0.125}{125.5^2(1-0.021)} \sqrt{5 \times 13.75[(1-0.021)125.5^2 + 7.5^2]} = 0.008362$$

$$FL \text{ of } R = \text{antilog} \left[\frac{\lg 0.864}{(1-0.021)} \pm 2.20 \times 0.008362 \right] = 0.826-0.899$$

$$FL \text{ of } P_T = 10 \times (0.826-0.899) = 8.26-8.99 \text{ Units/ml}$$

$$FL\% \text{ of } P_T = \frac{8.99-8.26}{2 \times 8.64} \times 100 = 4.2\%$$

Example 5 Parallel line assay of insulin—Blood sugar depression method in mice, twin cross-over design

S is the standard preparation of insulin

T is the test preparation of insulin, $A_T = 27$ Units/mg.

d_{S_1} : 25 mu/ml, 0.25 ml/mouse d_{T_1} : 25 mu/ml, 0.25 ml/mouse

d_{S_2} : 50 mu/ml, 0.25 ml/mouse d_{T_2} : 50 mu/ml, 0.25 ml/mouse

$r = 1 : 0.5$ $I = 0.301$

y is value of blood glucose (mg%).

The assay result is shown in Table 5-1

Table 5-1 The data of an assay of insulin

	Group 1			Group 2			Group 3			Group 4				
	Test(1)	Test(2)	Test (1)+(2)	Test(1)	Test(2)	Test (1)+(2)	Test(1)	Test(2)	Test (1)+(2)	Test(1)	Test(2)	Test (1)+(2)		
	d_{S_1}	d_{T_2}		d_{S_2}	d_{T_1}		d_{T_1}	d_{S_2}		d_{T_2}	d_{S_1}			
	$y_{S_1(1)}$	$y_{T_2(2)}$	$y_{(1)}+y_{(2)}$	$y_{S_2(1)}$	$y_{T_1(2)}$	$y_{(1)}+y_{(2)}$	$y_{T_1(1)}$	$y_{S_2(2)}$	$y_{(1)}+y_{(2)}$	$y_{T_2(1)}$	$y_{S_1(2)}$	$y_{(1)}+y_{(2)}$		
y	103.99	87.01	191.00	83.21	110.13	202.64	116.54	85.82	202.36	105.37	128.92	234.29		
	113.21	104.61	217.82	61.05	78.53	137.58	94.19	77.72	171.91	73.40	126.95	200.35		
	106.94	100.26	207.20	85.56	139.40	224.96	92.82	100.26	193.08	74.38	106.19	180.57		
	94.19	96.10	190.29	76.54	126.95	203.49	103.99	79.89	183.88	72.42	100.26	172.68		
	103.99	74.56	178.55	76.54	97.49	174.03	113.21	87.01	200.22	66.54	90.77	157.31		
	92.82	82.27	175.09	78.70	130.90	209.60	101.05	100.26	201.31	106.94	109.35	216.29		
	108.50	87.01	195.51	72.42	93.34	165.76	106.94	122.99	229.93	98.31	103.22	201.53		
	89.09	84.64	173.73	77.52	121.24	198.73	92.82	82.27	175.09	113.21	132.88	246.09		
	131.45	93.34	224.79	76.54	110.93	187.47	98.31	91.95	190.26	61.83	89.58	151.41		
	111.64	88.20	199.84	64.58	94.72	159.30	127.53	106.19	233.72	95.56	110.93	206.49	Total	
Σy_i	1055.82 $S_{1(1)}$			752.66 $S_{2(1)}$			934.36 $S_{2(2)}$			1099.05 $S_{1(2)}$			S_1	2154.87
													S_2	1687.02
				1110.90 $T_{1(2)}$			1047.40 $T_{1(1)}$						T_1	2158.30
	898.00 $T_{2(2)}$									867.96 $T_{2(1)}$			T_2	1765.96
Σy														7766.15

① Sum of square

$$\text{Total} = 103.99^2 + 113.21^2 + \dots + 89.58^2 + 110.93^2 - \frac{(7766.15)^2}{2 \times 4 \times 10} = 25865.8223$$

$$f_{\text{Total}} = 2 \times 4 \times 10 - 1 = 79$$

$$\text{inter-animal} = 191.00^2 + 217.82^2 + \dots + 151.41^2 + 206.49^2 - \frac{(7766.15)^2}{2 \times 4 \times 10} = 11320.6387$$

$$f_{\text{inter-animal}} = 4 \times 10 - 1 = 39$$

② Calculate $m \cdot \sum C_i^2$, $\sum (C_i \cdot \sum y_i)$ and sum of squares of each component of Table 5-1 by use of equations in Table 9, and equation (22) (18)

The sum of square of error (I) and error (II) are obtained by equation (28) (29).

$$\text{Error(I)} = 25865.8223 - 11320.6387 - 84.8102 - 9249.0855 - 1267.7893 - 369.4991 = 3573.9995$$

$$f = 4 \times (10 - 1) = 36$$

$$\text{Error(II)} = 11320.6387 - 71.2720 - 215.7917 - 137.8388 = 110895.7362$$

$$f = 4 \times (10 - 1) = 36$$

The result of variance analysis and validity test are shown in Table 5-2 and 5-3.

Table 5-2 Variance analysis for insulin, twin cross-over design

Source of variation	$\Sigma y_{(1)}$				$\Sigma y_{(2)}$				$m \cdot \Sigma C_i^2$	$\Sigma(C_i \cdot \Sigma y)$	Sum of square $\frac{[\Sigma(C_i \cdot \Sigma y)]^2}{m \cdot \Sigma C_i^2}$
	$S_{1(1)}$	$S_{2(1)}$	$T_{1(1)}$	$T_{2(1)}$	$S_{1(2)}$	$S_{2(2)}$	$T_{1(2)}$	$T_{2(2)}$			
	1055.82	752.66	1047.40	867.96	1099.05	934.36	1110.90	898.00			
	$(C_i \cdot \Sigma y)$										
Preparation *	-1	-1	1	1	-1	-1	1	1	10×8	82.37	84.8102
Regression *	-1	1	-1	1	-1	1	-1	1	10×8	-860.19	9249.0855
Parallelism	1	-1	-1	1	1	-1	-1	1	10×8	75.51	71.2720
Times of test *	-1	-1	-1	-1	1	1	1	1	10×8	318.47	1267.7893
Time×Preparation	1	1	-1	-1	-1	-1	1	1	10×8	-131.39	215.7917
Time×regression	1	-1	1	-1	-1	1	-1	1	10×8	105.01	137.8388
Time×parallelism *	-1	1	1	-1	1	-1	-1	1	10×8	-171.93	369.4991

* mean the four components of intra-animal variation, the remaining three components are inter-animal variation.

Table 5-3 Validity test of insulin

Source of variation	f	Sum of square	Mean square	F	P
Parallelism	1	71.2720	71.2720	<1	>0.05
Time×Preparation	1	215.7917	215.7917	<1	>0.05
Time×regression	1	137.8388	137.8388	<1	>0.05
Error(II)	36	10895.7362	302.6593(s_{II}^2)		
Inter-animal	39	11320.6387	290.2728	2.92	
Preparation	1	84.8102	84.8102	<1	>0.05
Regression	1	9249.0855	9249.0855	93.16	<0.01
Time of test	1	1267.7893	1267.7893	12.77	<0.01
Time×Parallelism	1	369.4991	369.4991	3.72	>0.05
Error(I)	36	3573.9995	99.2778(s^2)		
Total	79	25865.8223			

Conclusion The regression was highly significant, the deviation from parallelism was not significant, the assay result was satisfactory. The variance between two tests was highly significant, thus the precision of the assay was increased by eliminating the effects of difference between animals at the two stages of the test.

③ Potency and fiducial limits

$$r=1:0.5 \quad I=0.301 \quad s^2=99.2778 \quad f=36 \quad t=2.03$$

$$V=\frac{1}{2}(1765.96+2158.30-1687.02-2154.87)=41.185$$

$$W=\frac{1}{2}(1765.96-2158.30+1687.02-2154.87)=-430.095$$

$$R=\frac{50}{50}\text{antilog}\left(\frac{41185}{-430.095} \times 0.301\right)=0.936$$

$$P_T=27 \times 0.936=25.27 \text{ Units/mg}$$

$$g=\frac{99.2778 \times 2.03^2 \times 2 \times 10}{(-430.095)^2}=0.044$$

$$S_M=\frac{0.301}{(-430.095)^2(1-0.044)} \sqrt{2 \times 10 \times 99.2778[(1-0.044)(-430.095)^2+41.185^2]} \\ =0.03204$$

$$FL \text{ of } R=\text{antilog}\left[\frac{\lg 0.936}{(1-0.044)} \pm 2.03 \times 0.03204\right]=0.803-1.084$$

$$FL \text{ of } P_T=27(0.803-1.084)=21.68-29.27 \text{ Units/mg}$$

$$FL\% \text{ of } P_T=\left(\frac{29.27-21.68}{2 \times 25.27} \times 100\right)\%=15.0\%$$

4. Combination of Potency Estimates

When the same test preparation has been assayed n times, it is necessary to combine the n estimated potencies to obtain a mean potency and its fiducial limits.

In the combination of n estimates, the following points should be observed:

(1) The n estimates were independent and each obtained from a separate assay of the same method, under the same experimental condition.

(2) The estimated log potency (M) should be corrected by assumed potency (A_T) before they are combined.

Calculated the mean of the combined log P_T by the following method.

Homogeneity of n estimates of log potency: The homogeneity of n log potencies is assessed by χ^2 test.

$$\chi^2 = \sum WM^2 - \frac{(\sum WM)^2}{\sum W} \quad (35)$$

$$f = n - 1$$

Where M is the logarithm of the potency estimates and W is the reciprocal of its S_M .

$$W = \frac{1}{S_M^2} \quad (36)$$

If the calculated value of χ^2 is smaller than the tabulated value of $\chi^2_{0.05}$ corresponding to $n-1$ degrees of freedom (shown in Table 12), the potencies are homogeneous, the weighted mean potency of n estimates and its FL are obtained by equation (37)-(41), where \bar{M} is the weighted mean potency of $\lg P_T$.

$$\bar{M} = \frac{\sum WM}{\sum W} \quad (37)$$

$$S_{\bar{M}} = \sqrt{\frac{1}{\sum W}} \quad (38)$$

$$FL \text{ of } \bar{M} = \bar{M} \pm t \cdot S_{\bar{M}} \quad (39)$$

$$\bar{P}_T = \text{antilog } \bar{M} \quad (40)$$

$$FL \text{ of } \bar{P}_T = \text{antilog } (\bar{M} \pm t \cdot S_{\bar{M}}) \quad (41)$$

For equation (39) and (41), the appropriate value of t (in Table 1) is that corresponding to the sum of the numbers of f for the s^2 in the n individual assays

If the calculated value of χ^2 is greater than the tabulated value of $\chi^2_{0.05}$ in Table 12, the potencies are heterogeneous. The combined mean potency and the FL of n estimates are obtained by equation (42) (43) and equation (39)-(41).

$$\bar{M} = \frac{\sum M}{n} \quad (42)$$

$$S_{\bar{M}} = \frac{S_M}{\sqrt{n}} = \sqrt{\frac{\sum M^2 - \frac{(\sum M)^2}{n}}{n(n-1)}} \quad (43)$$

$$f = n - 1$$

Table 12 The value of χ^2 ($P=0.05$)

f	χ^2	f	χ^2	f	χ^2
1	3.84	11	19.7	21	32.7
2	5.99	12	21.0	22	33.9
3	7.82	13	22.4	23	35.2
4	9.49	14	23.7	24	36.4
5	11.1	15	25.0	25	37.6
6	12.6	16	26.3	26	38.9
7	14.1	17	27.6	27	40.1
8	15.5	18	28.9	28	41.3
9	16.9	19	30.1	29	42.6
10	18.3	20	31.4	30	43.8

Example 6 Combination of 5 estimates of Heparin

The assay results are shown in Table 6-1

Table 6-1 The data of 5 assay results of Heparin

P_T (Units/mg)	$M(\lg P_T)$	S_M	$W\left(\frac{1}{S_M^2}\right)$	WM	WM^2
189.28	2.2771	0.0289	1197.30	2726.37	6208.22
180.13	2.2556	0.0144	4822.53	10877.70	24535.74
189.72	2.2781	0.0105	9070.29	20663.03	47072.44
185.27	2.2678	0.00633	24957.01	56597.51	128351.83
181.25	2.2583	0.0278	1293.93	2922.08	6598.94
Σ			41341.06	93786.69	212767.17

$$\chi^2 = 212767.17 - \frac{93786.69^2}{41341.06} = 1.86$$

$$f = 5 - 1 = 4$$

The calculated χ^2 (1.86) is smaller than the tabulated value ($\chi_{(4),0.05}^2 = 9.49$).

$$\bar{M} = \frac{93786.69}{41341.06} = 2.2686$$

$$\bar{P}_T = \text{antilog } 2.2686 = 185.61 \text{ Units/mg}$$

$$S_M = \sqrt{\frac{1}{41341.06}} = 0.00492$$

$$f = 5 \times 24 = 120, t = 1.96$$

$$FL \text{ of } \bar{P}_T = \text{antilog } (2.2686 \pm 1.96 \times 0.00492) \\ = 181.53 - 189.78 \text{ Units/mg}$$

$$FL\% = \left(\frac{189.78 - 181.53}{2 \times 185.61} \times 100 \right) \% = 2.2\%$$

Example 7 Combination of 6 estimates of Insulin

The assay results are shown in Table 7-1.

Table 7-1 The data of 6 assay results of Insulin

P_T (Units/mg)	$M(\lg P_T)$	M^2	S_M	$W\left(\frac{1}{S_M^2}\right)$	WM	WM^2
25.91	1.4135	1.9980	0.09603	108.44	153.28	216.66
23.15	1.3646	1.8621	0.006202	25997.79	35476.59	48411.35
27.48	1.4390	2.0707	0.02609	1469.10	2114.04	3042.10
28.39	1.4532	2.1118	0.03177	990.75	1439.76	2092.26
27.56	1.4403	2.0745	0.03560	789.04	1136.46	1636.84
25.79	1.4115	1.9923	0.03181	988.26	1394.93	1968.95
Σ	8.5221	12.1094		30343.38	41715.06	57368.16

$$\chi^2 = 57368.16 - \frac{41715.06^2}{30343.38} = 19.70$$

$$f = 6 - 1 = 5 \quad \chi_{(5),0.05}^2 = 11.1$$

The calculated χ^2 (19.70) is greater than the tabulated value (11.1), the 6 estimates are heterogeneous.

$$\bar{M} = \frac{8.5221}{6} = 1.4203$$

$$\bar{P}_T = \text{antilog } 1.4203 = 26.32 \text{ Units/mg}$$

$$S_M = \sqrt{\frac{1.4135^2 + 1.3646^2 + \dots + 1.4115^2 - \frac{8.5221^2}{6}}{6(6-1)}} = 0.013$$

$$f = 6 - 1 = 5 \quad t = 2.57$$

$$FL \text{ of } \bar{P}_T = \text{antilog } (1.4203 \pm 2.57 \times 0.013) = 24.37 - 28.43 \text{ Units/mg}$$

$$FL\% = \left(\frac{28.43 - 24.37}{2 \times 26.32} \times 100 \right) \% = 7.7\%$$

5. Glossary of Symbols

A_T	The assumed or labelled potency of test preparation (T)
C	Incomplete sum of response in a column containing the missing value
C_i	Orthogonal coefficient used in validity test
$d_{S_1}, d_{S_2} \dots$	Dose levels of the standard preparation (S)
$d_{T_1}, d_{T_2} \dots$	Dose levels of the test preparation (T)
F	The mean square of each variable expressed as a ratio of s^2
FL	Fiducial limits
$FL\%$	Percentage of fiducial limits
f	Degrees of freedom
G	Incomplete sum of response in an assay excluding the missing value
g	Index of regression significance
I	Logarithm of the ratio between adjacent doses (r)
K	Total number of doses of S and T
$k \cdot k'$	Number of doses of S or T
M	Logarithm of the potency ratio (R)
m	Number of responses to each dose
n	Total number of responses to S and T
n_S	Number of responses to S
n_T	Number of responses to T
P	Probability
P_T, P_U	Estimated potency of test preparation (T, U)
R	Estimated potency ratio before correction by assumed potency, $R = \text{antilog } M$
R	Incomplete sum of response in a row containing the missing value
r	Ratio of adjacent doses
S	Standard preparation
$S_1, S_2 \dots$	Sum of the responses to each dose of standard preparation
S_M	Standard error of M
s^2	Error variance
T	Test preparation
$T_1, T_2 \dots$	Sum of the responses of each dose of test preparation
U	Another symbol used to represent test preparation
$U_1, U_2 \dots$	Sum of the responses to each dose of U
x	Logarithm of dose
x_S	Logarithm of minimum effective dose of S
x_T	Logarithm of minimum effective dose of T
\bar{x}_S	Mean log minimum effective dose of S
\bar{x}_T	Mean log minimum effective dose of T
y	Individual response or transformed response
y_1, y_m	Observed response listed in order of magnitude
$\sum y_{(k)}$	Sum of the responses to each dose of S or T
$\sum y_{(m)}$	Sum of the responses to each block or row

A white crystalline powder; odourless; tasteless; when slowly heated, sublimes but does not decompose. Soluble in boiling water, sodium hydroxide solution or sodium carbonate solution; slightly soluble in water; practically insoluble in ethanol, chloroform or ether.

Ascorbic Acid [$C_6H_8O_6$ 176.13]

Complies with the requirements prescribed in the monograph of the Chinese Pharmacopoeia.

Auric Chloride [$HAuCl_4 \cdot 3H_2O$ 393.83]

Bright yellow or orange crystals.

Soluble in water, ethanol or ether; slightly soluble in chloroform.

Azo Violet [$C_{12}H_9N_3O_4$ 259.22]

A reddish-brown powder.

Soluble in acetic acid, sodium hydroxide solution or toluene.

Barbital [$C_8H_{12}N_2O_3$ 184.19]

White crystals or powder; taste, slightly bitter.

Soluble in hot water, ethanol, ether or alkaline solution.

Barbital Sodium [$C_8H_{11}N_2NaO_3$ 206.18]

White crystals or powder; taste, bitter.

Soluble in water; slightly soluble in ethanol; insoluble in ether.

Barium Chloride [$BaCl_2 \cdot 2H_2O$ 244.26]

White crystals or granules.

Freely soluble in water or methanol; practically insoluble in ethanol, acetone or ethyl acetate.

Barium Hydroxide [$Ba(OH)_2 \cdot 8H_2O$ 315.46]

White crystals; absorbs carbon dioxide easily to form barium carbonate.

Freely soluble in water; slightly soluble in ethanol.

Barium Nitrate [$Ba(NO_3)_2$ 261.34]

White crystals or crystalline powder; burns and detonates when being in contact, rubbing or bumping with organic substances.

Soluble in water; slightly soluble in ethanol.

Barium Perchlorate [$Ba(ClO_4)_2 \cdot 3H_2O$ 390.32]

Colourless crystals. Poisonous.

Soluble in water or methanol; slightly soluble in ethanol, ethyl acetate or acetone; practically insoluble in ether.

Beef Extract

A yellowish-brown to dark brown pasty substance; odour, characteristic of beef; taste sour.

Soluble in water.

Chloride Not more than 6% of the total solids, calculated as NaCl.

Nitrate Decolourize a solution of beef extract (1→10) by boiling with active charcoal, filter, add 1 drop of the filtrate to 3 drops of a solution of diphenylamine in sulfuric acid (1→100), no blue colour is developed.

Ethanol insoluble substance To 25 ml of a solution of beef extract (1→10) add 50 ml of ethanol, shake thoroughly and filter, wash the residue with dilute ethanol (2→3), dry it at 105°C for 2 hours, the residue is not more than 10% of the total solids.

Ethanol soluble nitrogen The nitrogen content of the filtrate obtained in the test for ethanol insoluble substance is not less than 6% of the ethanol soluble substance.

Total solids Mix 10 ml of a solution of beef extract (1→10) with clean sand or asbestos, dry at 105°C for 16 hours, the residue is not less than 0.75 g.

Residue on ignition Not more than 30% of the total solids (Appendix VIII N).

Beef Hemoglobin

Dark brown crystals or crystalline powder.

Soluble in water or dilute acid.

Purity One band should be obtained after developing by electrophoresis on cellulose acetate membrane.

Total Nitrogen Not less than 16.0% (Appendix VII D, Method 1).

Loss on drying When dried to constant weight at 105°C, loses not more than 10.5% of its weight.

Residue on ignition Not more than 1.0% (Appendix VIII N).

Benzalkonium Chloride A white or pale yellow powder or gelatinous flakes.

Very soluble in water, ethanol or acetone; slightly soluble in benzene; practically insoluble in ether.

Benzene [C_6H_6 78.11]

A colourless clear liquid; odour, characteristic; inflammable.

Miscible with ethanol, ether, acetone, carbon tetrachloride, carbon disulfide or acetic acid; slightly soluble in water.

Boiling point: 80.1°C.

Benzidine Acetate [$C_{14}H_{16}N_2O_2$ 244.29]

White or pale yellow crystals or powder.

Soluble in water, acetic acid or hydrochloric acid; very slightly soluble in ethanol.

Benzoic Acid [C_6H_5COOH 122.12]

Complies with the requirements prescribed in monograph of the Chinese Pharmacopoeia.

Benzoquinone [$C_6H_4O_2$ 108.10]

Yellow crystals; odour, characteristic; sublimable.

Soluble in ethanol or ether; slightly soluble in water.

Benzoyl-DL-argrinylnaphthylamine Hydrochloride

[$C_{23}H_{25}N_5O_2 \cdot HCl$ 439.94]

White crystals.

Soluble in water or ethanol.

Benzoyl Chloride [C_6H_5COCl 140.57]

A colourless, clear liquid; irritant; corrosive; fuming on exposure to moist air; its vapour is corrosive and lachrymatory. Miscible with ether, benzene, carbon disulfide or oil; decomposes in water or ethanol.

Bismuth Subnitrate [$4BiNO_3(OH)_2 \cdot BiO(OH)$ 1461.99]

A white powder; heavy; odourless; tasteless; slightly hygroscopic.

Soluble in hydrochloric acid, nitric acid, dilute sulfuric acid or acetic acid; practically insoluble in water or ethanol.

Bis(cyclohexanone)oxalyldihydrazone [$C_{14}H_{22}N_4O_2$ 278.36]

White crystals.

Soluble in hot methanol or ethanol; insoluble in water.

Borax [$Na_2B_4O_7 \cdot 10H_2O$ 381.37]

White crystals or granules; hard.

Soluble in water and glycerin; insoluble in ethanol or acid.

Boric Acid [H_3BO_3 61.83]

White transparent crystals or a crystalline powder; with pear-like luster.

Freely soluble in hot water, hot ethanol or hot glycerin; soluble in water or ethanol; slightly soluble in acetone or ether.

Brilliant Green [$C_{27}H_{33}N_2 \cdot HSO_4$ 482.64]

Lustrous golden crystals.

Soluble in water or ethanol, the colour of solution is green.

Bromine [Br_2 159.81]

A deep red liquid, odour, asphyxiating irritant; fuming; freely volatile.

Miscible with ethanol, chloroform, ether benzene or carbon disulfide; slightly soluble in water.

Bromocresol Green [$C_{21}H_{14}Br_4O_5S$ 698.02]

A pale yellow or brown powder.

Soluble in ethanol or dilute alkaline solution; insoluble in

water.

Bromocresol Purple [$C_{21}H_{16}Br_2O_5S$ 540.23]

A pale yellow or pale red crystalline powder.
Soluble in ethanol or dilute alkaline solution; insoluble in water.

Bromophenol Blue [$C_{19}H_{10}Br_4O_5S$ 669.97]

A yellow powder.
Soluble in ethanol, ether, benzene or dilute alkaline solution; slightly soluble in water.

Bromothymol Blue [$C_{27}H_{28}Br_2O_5S$ 624.39]

A white or pale red crystalline powder.
Freely soluble in ethanol, dilute alkaline solution or ammonia solution; slightly soluble in water.

2,3-Butanedione [$C_4H_6O_2$ 86.09]

A yellowish-green liquid; odour, characteristic.
Miscible with ethanol or ether; soluble in water.

Butanol (*n*-Butanol) [$CH_3(CH_2)_3OH$ 74.12]

A clear, colourless liquid; odour, characteristic; inflammable; highly refractive.
Miscible with ethanol, ether or benzene; soluble in water.
Boiling point: 117-118°C.

t-Butanol [$(CH_3)_3COH$ 74.12]

White crystals, or liquid when contain small amount of water; odour, camphor like; hygroscopic; inflammable.
Miscible with ethanol or ether; soluble in water.
Boiling point: 82.4°C.

Butanone [$CH_3COC_2H_5$ 72.11]

A colourless liquid; freely volatile; inflammable; azeotropic with water; acutely irritant to mucous membrane of nose and eyes.
Miscible with ethanol or ether.

Butyl Acetate [$CH_3COO(CH_2)_3CH_3$ 116.16]

A clear, colourless liquid.
Miscible with ethanol or ether; insoluble in water.

Butylated Hydroxytoluene [$C_{15}H_{24}O$ 220.4]

Colourless crystals or a white crystalline powder.
Melting point: about 70°C.

Cadmium Acetate [$Cd(C_2H_3O_2)_2 \cdot 2H_2O$ 266.53]

White crystals.
Freely soluble in water; soluble in ethanol; very slightly soluble in ether.

Cadmium Iodide [CdI_2 366.22]

White or pale yellow crystals or a crystalline powder.
Soluble in water, ethanol, ether, ammonia solution or acids.

Cadmium Nitrate [$Cd(NO_3)_2 \cdot 4H_2O$ 308.49]

White needle or prismatic crystals; hygroscopic. Hypergolic and detonable when mixed with organic substances.
Freely soluble in water, soluble in ethanol, acetone or ethyl acetate; practically insoluble in concentrated nitric acid.

Calcein [$C_{30}H_{24}N_2Na_2O_{13}$ 666.51]

A bright yellow powder.
Soluble in water; insoluble in dehydrated ethanol or ether.

Calcium Carbonate [$CaCO_3$ 100.09]

A white crystalline powder.
Soluble in acid; insoluble in water and ethanol.

Calcon Carboxylic Acid

Brown to black colour crystals or a brown powder.
Freely soluble in alkaline solution and ammonia solution; slightly soluble in water.

Calcium Chloride [$CaCl_2 \cdot 2H_2O$ 147.01]

White granules or lumps; hygroscopic.
Freely soluble in water or ethanol.

Calcium Hydroxide [$Ca(OH)_2$ 74.09]

A white crystalline powder; absorbs carbon dioxide easily to form calcium carbonate.
Slightly soluble in water.

Calcium Sulfate [$CaSO_4 \cdot 2H_2O$ 172.17]

A white crystalline powder.
Soluble in solutions of ammonium salts, sodium thiosulfate, sodium chloride or acids; insoluble in water or ethanol.

Calcon [$C_{20}H_{13}N_2NaO_5S$ 416.39]

A brown or brownish-black powder.
Soluble in water or ethanol.

Camphor Sulfonic Acid [$C_{10}H_{16}O_4S$ 232.30]

White column or crystals.
Slightly soluble in glycerin, glacial acetic acid or ethyl acetate; very slightly soluble in ethanol; practically insoluble in ether.

Carbon Disulfide [CS_2 76.14]

A clear, colourless liquid; the pure substance has an ether-like odour; the usual commercial grade has a foul smell; inflammable; decomposes on standing for a long time.
Freely soluble in ethanol or ether; insoluble in water. It can dissolve iodine, bromine, sulphur, fat, rubber etc.
Boiling point: 46.5°C.

Carbon Tetrachloride [CCl_4 153.82]

A clear, colourless liquid; odour, characteristic; heavy.
Miscible with ethanol, chloroform, ether or benzene; very slightly soluble in water.

Casein

A white or pale yellow granular powder; odourless.
Insoluble in water or other neutral solvent; freely soluble in solutions of alkali hydroxide.
Alkalinity Shake 1 g of the casein with 20 ml of water for 10 minutes and filter, the filtrate exhibits no alkaline reaction with litmus paper.
Nitrogen 15.2%-16.0%, calculated on the dried basis (Appendix VII D).
Fats Not more than 0.5% (Appendix VII H).
Water soluble matter Not more than 0.1%.
Residue on ignition Not more than 1% (Appendix VII N).
Loss on drying Not more than 10.0% (Appendix VII L).

Catechol [$C_6H_6O_2$ 110.11]

Colourless or pale grey crystals or a crystalline powder; volatilizes with steam.
Freely soluble in water, ethanol or benzene.

Catechol Violet [$C_{10}H_{14}O_7S$ 386.38]

A reddish-brown crystalline powder with metallic lustre.
Freely soluble in water or ethanol.

Ceric Ammonium Nitrate [$(NH_4)_2Ce(NO_3)_6$ 548.22]

Reddish-orange crystals; strong oxidizing agent.
Soluble in water or ethanol; insoluble in concentrated nitric acid.

Ceric Ammonium Sulfate [$(NH_4)_4Ce(SO_4)_4 \cdot 2H_2O$ 633]

A yellow or orange-yellow crystalline powder.
Soluble in solutions of acid; slightly soluble in water; insoluble in acetic acid.

Ceric Sulfate [$Ce(SO_4)_2$ 332.24]

Deep yellow crystals.
Soluble in hot acid solution; slightly soluble in water, decomposes with the formation of basic salt.

Cerous Nitrate [$Ce(NO_3)_3 \cdot 6H_2O$ 434.22]

White, transparent crystals.
Soluble in water, ethanol or acetone.

Cetrimonium Bromide [$C_{16}H_{33}N(CH_3)_3Br$ 364.45]

A white crystalline powder.

Soluble in water; slightly soluble in ethanol; insoluble in ether.

Chloral Hydrate [$C_2H_3Cl_3O_2$ 165.40]

White crystals; odour, pungent; irritant to skin; volatilizes gradually on exposure to air; turns to yellow after long time storage.

Soluble in ethanol, chloroform or ether; soluble in water with hydrolysis.

Chloramine T [$C_7H_7ClNNaO_2S \cdot 3H_2O$ 281.69]

A white crystalline powder; odour, faintly chlorine-like.

Soluble in water; insoluble in chloroform or benzene.

Chlorinated Lime (Bleaching powder)

Complies with the requirements prescribed in monograph of the Chinese Pharmacopoeia.

p-Chloroaniline [C_6H_5ClN 127.57]

White or deep yellow crystals.

Soluble in hot water, ethanol, acetaldehyde or acetone.

Chloroform [$CHCl_3$ 119.38]

A colourless, clear liquid; heavy; refractive; volatilizes easily.

Miscible with ethanol, ether, benzene or petroleum benzin; slightly soluble in water.

Chloroform, Alcohol Free [$CHCl_3$ 119.38]

Wash 500 ml of chloroform with three portions of water, each of 50 ml. Dry the chloroform layer over anhydrous sodium sulfate for 12 hours, filter with absorbent cotton and distill. This solution should be freshly prepared.

p-Chlorophenol [C_6H_5ClO 128.56]

White crystals; odour, phenolic.

Freely soluble in ethanol or ether; slightly soluble in water.

Chloroplatinic Acid [$H_2PtCl_6 \cdot 6H_2O$ 517.91]

Orange red crystals; highly deliquescent.

Freely soluble in water; soluble in chloroform, acetone or ether.

Cholesterol [$C_{27}H_{46}O$ 386.66]

Monohydrate of cholesterol is white or pale yellow laminar crystals; anhydrous cholesterol is obtained at 70-80°C; it turns to yellow on exposure to air.

Soluble in benzene, petroleum benzin or vegetable oil; slightly soluble in ethanol; practically insoluble in water.

Chrome Azurol S [$C_{23}H_{13}Cl_2Na_3O_9S$ 605.31]

A brown powder.

Soluble in water to form a brownish-yellow solution; shows lower solubility in ethanol than in water with reddish-brown colour.

Chromium Trioxide [CrO_3 99.99]

Dark red crystals; powerful oxidizing agent and corrosive; hygroscopic; may cause inflame in contact with organic substances.

Freely soluble in water; soluble in sulfuric acid.

Chromotropic Acid [$C_{10}H_8O_8S_2 \cdot 2H_2O$ 356.33]

White crystals.

Soluble in water.

Cinchonine [$C_{19}H_{22}N_2O$ 294.40]

White crystals or a powder; taste, slightly bitter; darkens on exposure to light.

Soluble in ethanol or chloroform; slightly soluble in ether; practically insoluble in water.

Citric Acid [$C_6H_8O_7 \cdot H_2O$ 210.14]

White crystals or granules; efflorescent; hygroscopic.

Freely soluble in water or ethanol.

Cobaltous Acetate [$Co(C_2H_3O_2)_2 \cdot 4H_2O$ 249.08]

Violet-red crystals.

Soluble in water, ethanol, dilute acid or amyl acetate.

Cobaltous Chloride [$CoCl_2 \cdot 6H_2O$ 237.93]

Red or purplish-red crystals.

Freely soluble in water or ethanol; soluble in acetone; slightly soluble in ether.

Cobaltous Nitrate [$Co(NO_3)_2 \cdot 6H_2O$ 291.03]

White crystals or crystalline granules.

Freely soluble in water or ethanol; slightly soluble in acetone or ammonia solution.

Concentrated Ammonia Solution (Strong ammonia solution)

[NH_4OH 35.05]

A colourless, clear liquid; corrosive; contains 25%-28% (g/g) of NH_3 . Miscible with ethanol or ether.

Congo Red [$C_{32}H_{22}N_6Na_2O_6S_2$ 696.68]

A reddish-brown powder.

Soluble in water or ethanol.

Coomassie Brilliant Blue G 250 [$C_{47}H_{48}N_3NaO_7S_2$

854.04]

A violet crystalline powder.

Soluble in hot water or ethanol; slightly soluble in water.

Coomassie Brilliant Blue R 250 [$C_{45}H_{44}N_3NaO_7S_2$

825.99]

A violet powder.

Soluble in hot water or ethanol; insoluble in water.

m-Cresol Purple [$C_{21}H_{18}O_5S$ 382.44]

A reddish-yellow or brownish-green powder.

Freely soluble in methanol, ethanol or sodium hydroxide solution; slightly soluble in water.

Cresol Red [$C_{21}H_{18}O_5S$ 382.44]

A deep red, reddish-brown or dark green powder.

Freely soluble in ethanol or dilute sodium hydroxide solution; slightly soluble in water.

Crystal Violet [$C_{25}H_{30}ClN_3$ 407.99]

A dull green powder with metallic luster.

Soluble in water, ethanol or chloroform; insoluble in ether.

Cupric Acetate [$Cu(C_2H_3O_2)_2 \cdot H_2O$ 199.65]

Dark green crystals.

Soluble in water or ethanol; slightly soluble in ether or glycerin.

Cupric Chloride [$CuCl_2 \cdot 2H_2O$ 170.48]

Pale Bluish-green crystals.

Soluble in water, ethanol or methanol; slightly soluble in acetone or ethyl acetate.

Cupric Nitrate [$Cu(NO_3)_2 \cdot 3H_2O$ 241.60]

Blue, columnar crystals; burns and detonates when heated, rubbed or bumped with pulverized carbon, sulphur or other combustible substances.

Soluble in water or ethanol.

Cupric Sulfate [$CuSO_4 \cdot 5H_2O$ 249.69]

Blue crystals, granules or crystalline powder.

Soluble in water; slightly soluble in ethanol.

Cupric Sulfate, Anhydrous [$CuSO_4$ 159.61]

Greyish-white or greenish-white crystals or an amorphous powder; hygroscopic.

Soluble in water; practically insoluble in ethanol.

Curcuma Powder (Turmeric Powder)

A powder of the rhizome of *Curcuma longa* L. (Fam. Gingeraceae), containing 5% volatile oil, yellow curcumin, starch and resin.

Cyclohexane [C_6H_{12} 84.16]

A colourless, clear liquid; inflammable.

Miscible with methanol, ethanol, acetone, ether, benzene or carbon tetrachloride; practically insoluble in water.

Boiling point; 80.7°C.

Cysteine Hydrochloride [$\text{CH}_2(\text{SH})\text{CH}(\text{NH}_2)\text{COOH} \cdot \text{HCl}$ 157.62]

White crystals.

Soluble in water or ethanol.

L-Cystine [$\text{C}_6\text{H}_{12}\text{N}_2\text{O}_4\text{S}_2$ 240.30]

White crystals.

Soluble in acid or alkali solution; practically insoluble in water or ethanol.

Dextrin

Complies with the requirements prescribed in monograph of the Chinese Pharmacopoeia.

p-Diaminobenzene (*p*-Phenylenediamine) [$\text{C}_6\text{H}_4(\text{NH}_2)_2$ 108.14]

White or pale red crystals; darkens on exposure to air; sublimes easily on heating.

Soluble in ethanol, chloroform or ether; slightly soluble in water.

Diaminobenzidine Hydrochloride [$\text{C}_{12}\text{H}_{14}\text{N}_4 \cdot 4\text{HCl} \cdot 2\text{H}_2\text{O}$ 396.14]

A white or grey powder.

Soluble in water, its aqueous solution is readily oxidized and discoloured.

2,3-Diaminonaphthalene (2,3-Naphthalene diamine)

[$\text{C}_{10}\text{H}_8\text{N}_2$ 158.20]

Foliceous crystals.

Soluble in ethanol or ether.

Diammonium Hydrogen Phosphate [$(\text{NH}_4)_2\text{HPO}_4$ 132.06]

White crystals or a crystalline powder.

It loses ammonia on exposure to air and turns into ammonium dihydrogen phosphate.

Soluble in water; insoluble in ethanol.

Dibutyl Phthalate [$\text{C}_{16}\text{H}_{22}\text{O}_4$ 278.35]

A colourless or pale yellow oily liquid.

Freely soluble in ethanol, acetone, ether or benzene; practically insoluble in water.

Dichloromethane [CH_2Cl_2 84.93]

A colourless liquid; odour, ether-like.

Miscible with ethanol, ether or dimethylformamide; sparingly soluble in water.

Boiling point; 40-41°C.

2,6-Dichloroindophenol Sodium [$\text{C}_{12}\text{H}_6\text{Cl}_2\text{NNaO}_2 \cdot 2\text{H}_2\text{O}$ 326.11]

Grass green, fluorescent crystals or a dark green powder.

Freely soluble in water or ethanol; insoluble in chloroform or ether.

2,6-Dichloroquinone Chlorimide [$\text{C}_6\text{H}_2\text{Cl}_3\text{NO}$ 210.45]

A greyish-yellow crystalline powder.

Freely soluble in chloroform or ether; soluble in hot ethanol or dilute sodium hydroxide solution; insoluble in water.

Diethylamine [$(\text{C}_2\text{H}_5)_2\text{NH}$ 73.14]

A colourless liquid; odour, ammonia-like; strongly alkaline; corrosive; freely volatile; inflammable.

Miscible with water or ethanol.

Digitonin [$\text{C}_{56}\text{H}_{92}\text{O}_{29}$ 1229.33]

White crystals.

Sparingly soluble in dehydrated ethanol; slightly soluble in ethanol; practically insoluble in water, chloroform or ether.

2,7-Dihydroxynaphthalene (2,7-Naphthalenediol)

[$\text{C}_{10}\text{H}_8\text{O}_2$ 160.17]

White needle or scale crystals; the colour of solution darkens quickly on exposure to air.

Soluble in hot water, ethanol or ether; slightly soluble in chloroform or benzene.

3,5-Dihydroxy Toluene [$\text{C}_7\text{H}_8\text{O}_2 \cdot \text{H}_2\text{O}$ 142.14]

White crystals; easily oxidized to red in air; odour, unpleasant; taste, sweet.

Soluble in water or ethanol; slightly soluble in benzene, chloroform or carbon disulfide.

p-Dimethylaminobenzaldehyde [$\text{C}_9\text{H}_{11}\text{NO}$ 149.19]

White or pale yellow crystals; odour, characteristic; gradually turns to red on exposure to light.

Soluble in ethanol, acetone, chloroform, ether or acetic acid; slightly soluble in water.

Dimethylformamide [$\text{HCON}(\text{CH}_3)_2$ 73.09]

A colourless liquid with slight ammonia odour.

Miscible with water, ethanol, chloroform or ether.

Dimethylglyoxime [$\text{CH}_3\text{C}(\text{NOH})\text{C}(\text{NOH})\text{CH}_3$ 116.12]

A white powder.

Soluble in ethanol or ether; insoluble in water.

N,N-Dimethyl-p-phenylenediamine Dihydrochloride

[$\text{C}_8\text{H}_{12}\text{N}_2 \cdot 2\text{HCl}$ 209.12]

A white or greyish-white crystalline powder; darkens gradually on exposure to air; hygroscopic.

Soluble in water or ethanol.

Dimethylsulfoxide [$(\text{CH}_3)_2\text{SO}$ 78.14]

A colourless, viscous liquid; very hygroscopic; taste, slightly bitter; violent reaction occurs in contact with chlorine at room temperature.

Soluble in water, ethanol, acetone, chloroform, ether or benzene.

Dimethyl Yellow [$\text{C}_{14}\text{H}_{15}\text{N}_3$ 225.29]

A golden yellow crystalline powder.

Soluble in ethanol, chloroform, ether, benzene, petroleum ether or sulfuric acid; insoluble in water.

2,4-Dinitroaniline [$\text{C}_6\text{H}_5\text{N}_2\text{O}_4$ 183.12]

Yellow or yellowish-green crystals.

Soluble in chloroform or ether; slightly soluble in ethanol; insoluble in water.

m-Dinitrobenzene [$\text{C}_6\text{H}_4(\text{NO}_2)_2$ 168.11]

A pale yellow crystal; inflammable.

Freely soluble in chloroform, ethyl acetate or benzene; soluble in ethanol; slightly soluble in water.

3,5-Dinitrobenzoic Acid [$\text{C}_7\text{H}_4\text{N}_2\text{O}_6$ 212.12]

White or pale yellow crystals; volatilizes with steam.

Freely soluble in ethanol or glacial acetic acid; slightly soluble in water, ether, benzene or carbon disulfide.

2,4-Dinitrochlorobenzene [$\text{C}_6\text{H}_3\text{ClN}_2\text{O}_4$ 202.55]

Yellow crystals. It may cause explosion when heated to high temperature.

Freely soluble in hot ethanol; soluble in ether, benzene or carbon disulfide; insoluble in water.

2,4-Dinitrophenol [$\text{C}_6\text{H}_4\text{N}_2\text{O}_5$ 184.11]

Yellow, rhombic crystals; sublimes on heating.

Soluble in ethanol, ether, chloroform or benzene; very slightly soluble in cold water.

2,4-Dinitrophenylhydrazine [$\text{C}_8\text{H}_8\text{H}_4\text{O}_4$ 198.14]

A red crystalline powder; stable in acid solution, unstable in alkaline solution.

Soluble in hot ethanol, ethyl acetate, aniline or dilute mineral acids; slightly soluble in water and ethanol.

Diethyl Phthalate [$\text{C}_{12}\text{H}_{16}\text{O}_4$ 390.56]

A colourless or pale yellow oily liquid; odour, slight characteristic.

Miscible with organic solvent; insoluble in water.

Diethyl Sodium Sulfosuccinate [$C_{20}H_{37}NaO_7S$ 444.57]

White, wax-like solids.

Soluble in water, methanol, acetone, benzene, or carbon tetrachloride. Easily hydrolyzes in alkaline solution.

Dioxane [$C_4H_8O_2$ 88.11]

A colourless liquid; odour, ether-like; inflammable; freely absorbs oxygen to form peroxide.

Miscible with water or most of organic solvents.

Boiling range: 100-103°C.

Diphenylamine [$(C_6H_5)_2NH$ 169.23]

White crystals; odour, aromatic; gradually discolours on exposure to light.

Soluble in ether, benzene, glacial acetic acid or carbon disulfide; insoluble in water.

Diphenylcarbazine [$C_6H_5NHNHCONHNHC_6H_5$ 242.28]

A white, crystalline powder; gradually turns to red in air.

Soluble in hot ethanol, acetone or glacial acetic acid; very slightly soluble in water.

Dipotassium Hydrogen Phosphate [K_2HPO_4 174.18]

White granules or a crystalline powder.

Freely soluble in water; slightly soluble in ethanol.

2,2'-Dipyridyl [$C_5H_4N \cdot C_5H_4N$ 156.19]

A white or pale red crystalline powder.

Freely soluble in ethanol, chloroform, benzene or petroleum benzin; slightly soluble in water.

Disodium Edetate [$C_{10}H_{14}N_2Na_2O_8 \cdot 2H_2O$ 372.24]

A white crystalline powder.

Soluble in water; very slightly soluble in ethanol.

Disodium Hydrogen Phosphate [$Na_2HPO_4 \cdot 12H_2O$ 358.14]

White crystals or a granular powder; efflorescent.

Soluble in water; insoluble in ethanol.

Disodium Hydrogen Phosphate, Anhydrous [Na_2HPO_4 141.96]

A white crystalline powder; hygroscopic; it can absorb 2-7 mol of water on exposure to air for a long time.

Freely soluble in water; insoluble in ethanol.

Distilled Water, Ammonia Free

To 1000 ml of distilled water add 1 ml of dilute sulfuric acid and 1 ml of potassium permanganate TS, distil.

To 50 ml of the distillate add 1 ml of alkaline mercuric potassium iodide TS, no colour is produced.

Eosin Sodium [$C_{20}H_6Br_4Na_2O_5$ 691.86]

A red powder.

Freely soluble in water; an aqueous solution exhibits a red fluorescence; slightly soluble in ethanol; insoluble in ether.

Eriochrome Black T [$C_{20}H_{12}N_3NaO_7S$ 461.39]

A brownish-black powder.

Soluble in water or ethanol.

Ethanol [C_2H_5OH 46.07]

A clear, colourless liquid; freely volatile; inflammable.

Miscible with water, ether or benzene.

Ethanol, Absolute [C_2H_5OH 46.07]

A clear, colourless liquid; odour, alcoholic; inflammable; hygroscopic, it contains not more than 0.3% of water.

Miscible with water, acetone or ether.

Boiling point: 78.5°C.

Ether [$C_2H_5OC_2H_5$ 74.12]

A clear, colourless liquid; taste, paralysing sweet and astringent; freely volatile; inflammable; anaesthetic; oxidized to peroxide on exposure to light or on long storage.

Boiling point: 34.6°C

Ether Dehydrated [$(C_2H_5)_2O$ 74.12]

As described under Ether, but its water content is less than that of Ether.

Ethoxychrysoidine Hydrochloride [$C_{14}H_{16}N_4O \cdot HCl$ 292.77]

A deep reddish-brown or blackish-brown powder.

Soluble in water or ethanol.

Ethyl Acetate [$CH_3COOC_2H_5$ 88.11]

A clear, colourless liquid.

Miscible with acetone, chloroform or ether; soluble in water.

Ethyl Cyanoacetate [$CH_2(CN)COC_2H_5$ 113.12]

A colourless liquid; odour, characteristic of ester; taste, slightly sweet.

Miscible with ethanol or ether; soluble in ammonia solution or alkaline solution; insoluble in water.

Ethyl p-Hydroxybenzoate [$C_9H_{10}O_3$ 166.17]

White crystals; odourless; tasteless.

Soluble in ethanol, ether; slightly soluble in water.

Ethylene glycol monoethyl ether [$C_3H_8O_2$ 76.10]

Colourless liquid; odour, pleasant; toxic.

Miscible with water, ethanol, ether, glycerin, acetone and dimethylformamide.

Boiling point: 124.3°C.

N-Ethylmaleimide [$C_6H_7NO_2$ 125.12]

White crystals.

Freely soluble in ethanol or ether; slightly soluble in water.

Ethyl Tetrabromophenolphthalein Potassium [$C_{22}H_{13}Br_4KO_4$ 700.06]

Deep green or purplish-blue crystalline powder.

Soluble in water, ethanol or ether.

Fast Blue BB Salt [$C_{17}H_{18}ClN_3O_3 \cdot \frac{1}{2}ZnCl_2$ 415.96]

A pale cream-red powder

Ferric Ammonium Sulfate [$FeNH_4(SO_4)_2 \cdot 12H_2O$ 482.20]

White to pale violet crystals.

Soluble in water; insoluble in ethanol.

Ferric Chloride [$FeCl_3 \cdot 6H_2O$ 270.30]

Brownish-yellow or orange-yellow crystal-like mass; highly hygroscopic.

Freely soluble in water, ethanol, acetone, ether or glycerin.

Ferrous Sulfate [$FeSO_4 \cdot 7H_2O$ 278.02]

Pale blue crystals or granules.

Soluble in water; insoluble in ethanol.

Fluorane [$C_{20}H_{12}O_3$ 300.31]**Fluorescein** [$C_{20}H_{12}O_5$ 332.11]

An orange or red powder.

Soluble in hot ethanol, glacial acetic acid; in sodium carbonate solution or sodium hydroxide solution; insoluble in water, chloroform or benzene.

Formaldehyde Solution [$HCHO$ 30.03]

A colourless liquid; odour, pungent; it becomes muddy with polymerization when cooled. Slowly oxidized to formic acid on exposure to air. It contains about 37% of $HCHO$.

Miscible with water or ethanol.

Formamide [$HCONH_2$ 45.04]

A colourless, slightly viscous liquid with faint odour of ammonia; hygroscopic; irritant.

Miscible with water or ethanol.

Formic Acid [$HCOOH$ 46.03]

A clear, colourless liquid; odour, pungent; corrosive to skin. It contains not less than 85% of $HCOOH$.

Miscible with water, ethanol, ether or glycerin.

Formic Acid, Anhydrous [$HCOOH$ 46.03]

A clear, colourless liquid; odour, pungent; highly corrosive; strongly acidic; it contains not less than 98% of $HCOOH$.

Miscible with water, ethanol or ether.

Fuchsin Basic

Dark green crystals with metallic lustre.
Soluble in water or ethanol; insoluble in ether.

Furfural [$C_5H_4O_2$ 96.09]

A colourless or pale yellow oily liquid; easily turns to brown on exposure to air or light.
Miscible with water, ethanol or ether.

Gallic Acid [$C_7H_5O_5 \cdot H_2O$ 188.14]

White or pale brown crystals or a powder.
Soluble in hot water, ethanol or ether; insoluble in chloroform or benzene.

Gelatin

Complies with the requirements prescribed in monograph of the Chinese Pharmacopoeia.

Glucose [$C_6H_{12}O_6 \cdot H_2O$ 198.17]

Complies with the requirements prescribed in monograph of the Chinese Pharmacopoeia.

Glycerin (Glycerol) [$C_3H_8O_3$ 92.09]

A clear, colourless, viscous liquid; odourless; taste, sweet; hygroscopic.
Miscible with water or ethanol.

Glycine [$C_2H_5NO_2$ 75.07]

A white crystalline powder.
Soluble in water or pyridine; slightly soluble in ethanol; practically insoluble in ether.

Heptane [C_7H_{16} 100.20]

A colourless, clear liquid, inflammable.
Miscible with ethanol, chloroform or ether; insoluble in water.
Boiling point: 98.4°C.

n-Hexane [C_6H_{14} 86.18]

A clear, colourless liquid; odour, characteristic; highly volatile; irritant to respiratory tract.
Miscible with ethanol or ether, insoluble in water.
Boiling point: 69°C.

Holmium Oxide [Ho_2O_3 377.86]

Yellow solid; slightly hygroscopic; dissolves in acid with formation of a yellow salt.
Freely soluble in water.

Hydrazine Sulfate [$(NH_2)_2 \cdot H_2SO_4$ 130.12]

White crystals or powder.
Freely soluble in hot water; slightly soluble in water or ethanol.

Hydrochloric Acid [HCl 36.46]

A colourless, clear liquid; odour, pungent and characteristic; corrosive; fuming on exposure to air. It contains 36%-38% (g/g) of HCl.
Miscible with water or ethanol.

Hydrofluoric Acid [HF 20.01]

A colourless, fuming liquid; odour, pungent; highly corrosive to metal or glass.
Miscible with water or ethanol.

Hydrogen Peroxide Solution (30%) [H_2O_2 34.01]

A colourless, clear liquid; strong oxidizing agent and corrosive.
Miscible with water or ethanol.

Hydroquinone [$C_6H_4(OH)_2$ 110.11]

White or almost white crystals; discoloured on exposure to light.
Freely soluble in hot water; soluble in water, ethanol or ether.

p-Hydroxydiphenyl [$C_{12}H_{10}O$ 170.21]

Almost white crystals.

Freely soluble in ethanol or ether; soluble in alkali solution; insoluble in water.

Hydroxylamine Hydrochloride [$NH_2OH \cdot HCl$ 69.49]

White crystals; decomposes easily when moistened, corrosive.
Soluble in water, ethanol or glycerin.

p-Hydroxyphenylglycine [$C_8H_9NO_3$ 167.16]

White lustrous flakes.
Freely soluble in hydrochloric acid solution (1→5); soluble in acid or alkaline solution; practically insoluble in water, ethanol, ether, acetone, chloroform, benzene, glacial acetic acid or acetate ester.

8-Hydroxyquinoline [C_9H_7NO 145.16]

A white or pale yellow crystalline powder. Odour, phenolic; darkens easily on exposure to light.
Freely soluble in ethanol, acetone, chloroform or mineral acid; Practically insoluble in water.

Hypophosphorous Acid [H_3PO_2 66.00]

White, transparent crystals; colourless oily liquid is formed when over cooled; odourless; hygroscopic. It is a strong reducing agent.
Soluble in water, ethanol or ether.

Imidazole [$C_3H_4N_2$ 68.08]

White, nearly transparent Crystals.
Freely soluble in water, ethanol or pyridine;
Slightly soluble in benzene; very slightly soluble in petroleum ether.

Indigo Carmine [$C_{16}H_8N_2Na_2O_8S_2$ 466.36]

Blue crystals or powder with metallic lustre.
Soluble in water; insoluble in ethanol.

Iodine [I_2 253.81]

Purplish-black scale crystals or masses with metallic lustre.
Soluble in ethanol, ether or solution of potassium iodide; very slightly soluble in water.

Iodine Monochloride [ICl 162.36]

A brownish-red, oily liquid or dark-red crystals; strongly irritant; with odour of chlorine and iodine; corrosive and oxidative.

Iodine Pentoxide [I_2O_5 333.81]

A white crystalline powder; readily decomposes on exposure to light; hygroscopic.
Freely soluble in water to form iodic acid; insoluble in dehydrated ethanol, chloroform, ether or carbon disulfide.

Iodine Trichloride [ICl_3 233.26]

Yellow or pale brown crystals; odour, strongly pungent; volatile at room temperature; readily decomposes in contact with water; hygroscopic; corrosive.
Soluble in water, ethanol, ether or benzene.

Isoamyl Acetate [$CH_3COOCH_2CH_2CH(CH_3)_2$ 130.19]

A clear, colourless liquid; odour, characteristic resembling that of banana.
Miscible with ethyl acetate, ethanol, amyl alcohol, ether, benzene or carbon disulfide; very slightly soluble in water.

Isoamylol [$(CH_3)_2CHCH_2CH_2OH$ 88.15]

Colourless liquid; odour, characteristic; inflammable, miscible with organic solution; slightly soluble in water.
Boiling point: 132°C.

Isobutanol [$(CH_3)_2CHCH_2OH$ 74.12]

A colourless, clear liquid; strongly refractive; inflammable.
Miscible with water, ethanol or ether.
Boiling range: 107.3-108.3°C.

Isobutyl Acetate [$CH_3COOCH_2CH(CH_3)_2$ 116.16]

A colourless liquid; inflammable.
Miscible with ethanol or ether; insoluble in water.

Diethyl Sodium Sulfosuccinate [$C_{20}H_{37}NaO_7S$ 444.57]

White, wax-like solids.

Soluble in water, methanol, acetone, benzene, or carbon tetrachloride. Easily hydrolyzes in alkaline solution.

Dioxane [$C_4H_8O_2$ 88.11]

A colourless liquid; odour, ether-like; inflammable; freely absorbs oxygen to form peroxide.

Miscible with water or most of organic solvents.

Boiling range: 100-103°C.

Diphenylamine [$(C_6H_5)_2NH$ 169.23]

White crystals; odour, aromatic; gradually discolours on exposure to light.

Soluble in ether, benzene, glacial acetic acid or carbon disulfide; insoluble in water.

Diphenylcarbazide [$C_{18}H_{15}NHNHCONHNHC_6H_5$ 242.28]

A white, crystalline powder; gradually turns to red in air.

Soluble in hot ethanol, acetone or glacial acetic acid; very slightly soluble in water.

Dipotassium Hydrogen Phosphate [K_2HPO_4 174.18]

White granules or a crystalline powder.

Freely soluble in water; slightly soluble in ethanol.

2,2'-Dipyridyl [$C_5H_4N \cdot C_5H_4N$ 156.19]

A white or pale red crystalline powder.

Freely soluble in ethanol, chloroform, benzene or petroleum benzin; slightly soluble in water.

Disodium Edetate [$C_{10}H_{14}N_2Na_2O_8 \cdot 2H_2O$ 372.24]

A white crystalline powder.

Soluble in water; very slightly soluble in ethanol.

Disodium Hydrogen Phosphate [$Na_2HPO_4 \cdot 12H_2O$ 358.14]

White crystals or a granular powder; efflorescent.

Soluble in water; insoluble in ethanol.

Disodium Hydrogen Phosphate, Anhydrous [Na_2HPO_4 141.96]

A white crystalline powder; hygroscopic; it can absorb 2-7 mol of water on exposure to air for a long time.

Freely soluble in water; insoluble in ethanol.

Distilled Water, Ammonia Free

To 1000 ml of distilled water add 1 ml of dilute sulfuric acid and 1 ml of potassium permanganate TS, distil.

To 50 ml of the distillate add 1 ml of alkaline mercuric potassium iodide TS, no colour is produced.

Eosin Sodium [$C_{20}H_6Br_4Na_2O_5$ 691.86]

A red powder.

Freely soluble in water; an aqueous solution exhibits a red fluorescence; slightly soluble in ethanol; insoluble in ether.

Eriochrome Black T [$C_{20}H_{12}N_3NaO_7S$ 461.39]

A brownish-black powder.

Soluble in water or ethanol.

Ethanol [C_2H_5OH 46.07]

A clear, colourless liquid; freely volatile; inflammable.

Miscible with water, ether or benzene.

Ethanol, Absolute [C_2H_5OH 46.07]

A clear, colourless liquid; odour, alcoholic; inflammable; hygroscopic, it contains not more than 0.3% of water.

Miscible with water, acetone or ether.

Boiling point: 78.5°C.

Ether [$C_2H_5OC_2H_5$ 74.12]

A clear, colourless liquid; taste, paralysing sweet and astringent; freely volatile; inflammable; anaesthetic; oxidized to peroxide on exposure to light or on long storage.

Boiling point: 34.6°C

Ether Dehydrated [$(C_2H_5)_2O$ 74.12]

As described under Ether, but its water content is less than that of Ether.

Ethoxychrysoidine Hydrochloride [$C_{14}H_{16}N_4O \cdot HCl$ 292.77]

A deep reddish-brown or blackish-brown powder.

Soluble in water or ethanol.

Ethyl Acetate [$CH_3COOC_2H_5$ 88.11]

A clear, colourless liquid.

Miscible with acetone, chloroform or ether; soluble in water.

Ethyl Cyanoacetate [$CH_2(CN)COC_2H_5$ 113.12]

A colourless liquid; odour, characteristic of ester; taste, slightly sweet.

Miscible with ethanol or ether; soluble in ammonia solution or alkaline solution; insoluble in water.

Ethyl p-Hydroxybenzoate [$C_9H_{10}O_3$ 166.17]

White crystals; odourless; tasteless.

Soluble in ethanol, ether; slightly soluble in water.

Ethylene glycol monoethyl ether [$C_5H_{10}O_2$ 76.10]

Colourless liquid; odour, pleasant; toxic.

Miscible with water, ethanol, ether, glycerin, acetone and dimethylformamide.

Boiling point: 124.3°C.

N-Ethylmaleimide [$C_6H_7NO_2$ 125.12]

White crystals.

Freely soluble in ethanol or ether; slightly soluble in water.

Ethyl Tetrabromophenolphthalein Potassium [$C_{22}H_{13}Br_4KO_4$ 700.06]

Deep green or purplish-blue crystalline powder.

Soluble in water, ethanol or ether.

Fast Blue BB Salt [$C_{17}H_{18}ClN_3O_3 \cdot \frac{1}{2}ZnCl_2$ 415.96]

A pale cream-red powder

Ferric Ammonium Sulfate [$FeNH_4(SO_4)_2 \cdot 12H_2O$ 482.20]

White to pale violet crystals.

Soluble in water; insoluble in ethanol.

Ferric Chloride [$FeCl_3 \cdot 6H_2O$ 270.30]

Brownish-yellow or orange-yellow crystal-like mass; highly hygroscopic.

Freely soluble in water, ethanol, acetone, ether or glycerin.

Ferrous Sulfate [$FeSO_4 \cdot 7H_2O$ 278.02]

Pale blue crystals or granules.

Soluble in water; insoluble in ethanol.

Fluorane [$C_20H_{12}O_3$ 300.31]**Fluorescein** [$C_{20}H_{12}O_5$ 332.11]

An orange or red powder.

Soluble in hot ethanol, glacial acetic acid; in sodium carbonate solution or sodium hydroxide solution; insoluble in water, chloroform or benzene.

Formaldehyde Solution [$HCHO$ 30.03]

A colourless liquid; odour, pungent; it becomes muddy with polymerization when cooled. Slowly oxidized to formic acid on exposure to air. It contains about 37% of $HCHO$.

Miscible with water or ethanol.

Formamide [$HCONH_2$ 45.04]

A colourless, slightly viscous liquid with faint odour of ammonia; hygroscopic; irritant.

Miscible with water or ethanol.

Formic Acid [$HCOOH$ 46.03]

A clear, colourless liquid; odour, pungent; corrosive to skin. It contains not less than 85% of $HCOOH$.

Miscible with water, ethanol, ether or glycerin.

Formic Acid, Anhydrous [$HCOOH$ 46.03]

A clear, colourless liquid; odour, pungent; highly corrosive; strongly acidic; it contains not less than 98% of $HCOOH$.

Miscible with water, ethanol or ether.

Fuchsin Basic

Dark green crystals with metallic lustre.
Soluble in water or ethanol; insoluble in ether.

Furfural [$C_5H_4O_2$ 96.09]

A colourless or pale yellow oily liquid; easily turns to brown on exposure to air or light.
Miscible with water, ethanol or ether.

Gallic Acid [$C_7H_6O_5 \cdot H_2O$ 188.14]

White or pale brown crystals or a powder.
Soluble in hot water, ethanol or ether; insoluble in chloroform or benzene.

Gelatin

Complies with the requirements prescribed in monograph of the Chinese Pharmacopoeia.

Glucose [$C_6H_{12}O_6 \cdot H_2O$ 198.17]

Complies with the requirements prescribed in monograph of the Chinese Pharmacopoeia.

Glycerin (Glycerol) [$C_3H_8O_3$ 92.09]

A clear, colourless, viscous liquid; odourless; taste, sweet; hygroscopic.
Miscible with water or ethanol.

Glycine [$C_2H_5NO_2$ 75.07]

A white crystalline powder.
Soluble in water or pyridine; slightly soluble in ethanol; practically insoluble in ether.

Heptane [C_7H_{16} 100.20]

A colourless, clear liquid, inflammable.
Miscible with ethanol, chloroform or ether; insoluble in water.
Boiling point: 98.4°C.

n-Hexane [C_6H_{14} 86.18]

A clear, colourless liquid; odour, characteristic; highly volatile; irritant to respiratory tract.
Miscible with ethanol or ether; insoluble in water.
Boiling point: 69°C.

Holmium Oxide [Ho_2O_3 377.86]

Yellow solid; slightly hygroscopic; dissolves in acid with formation of a yellow salt.
Freely soluble in water.

Hydrazine Sulfate [$(NH_2)_2 \cdot H_2SO_4$ 130.12]

White crystals or powder.
Freely soluble in hot water; slightly soluble in water or ethanol.

Hydrochloric Acid [HCl 36.46]

A colourless, clear liquid; odour, pungent and characteristic; corrosive; fuming on exposure to air. It contains 36%-38% (g/g) of HCl .
Miscible with water or ethanol.

Hydrofluoric Acid [HF 20.01]

A colourless, fuming liquid; odour, pungent; highly corrosive to metal or glass.
Miscible with water or ethanol.

Hydrogen Peroxide Solution (30%) [H_2O_2 34.01]

A colourless, clear liquid; strong oxidizing agent and corrosive.
Miscible with water or ethanol.

Hydroquinone [$C_6H_4(OH)_2$ 110.11]

White or almost white crystals; discoloured on exposure to light.
Freely soluble in hot water; soluble in water, ethanol or ether.

p-Hydroxydiphenyl [$C_{12}H_{10}O$ 170.21]

Almost white crystals.

Freely soluble in ethanol or ether; soluble in alkali solution; insoluble in water.

Hydroxylamine Hydrochloride [$NH_2OH \cdot HCl$ 69.49]

White crystals; decomposes easily when moistened, corrosive.
Soluble in water, ethanol or glycerin.

p-Hydroxyphenylglycine [$C_8H_9NO_3$ 167.16]

White lustrous flakes.
Freely soluble in hydrochloric acid solution (1→5); soluble in acid or alkaline solution; practically insoluble in water, ethanol, ether, acetone, chloroform, benzene, glacial acetic acid or acetate ester.

8-Hydroxyquinoline [C_8H_7NO 145.16]

A white or pale yellow crystalline powder. Odour, phenolic; darkens easily on exposure to light.
Freely soluble in ethanol, acetone, chloroform or mineral acid; Practically insoluble in water.

Hypophosphorous Acid [H_3PO_2 66.00]

White, transparent crystals; colourless oily liquid is formed when over cooled; odourless; hygroscopic. It is a strong reducing agent.
Soluble in water, ethanol or ether.

Imidazole [$C_3H_4N_2$ 68.08]

White, nearly transparent Crystals.
Freely soluble in water, ethanol or pyridine; Slightly soluble in benzene; very slightly soluble in petroleum ether.

Indigo Carmine [$C_{16}H_8N_2Na_2O_8S_2$ 466.36]

Blue crystals or powder with metallic lustre.
Soluble in water; insoluble in ethanol.

Iodine [I_2 253.81]

Purplish-black scale crystals or masses with metallic lustre.
Soluble in ethanol, ether or solution of potassium iodide; very slightly soluble in water.

Iodine Monochloride [ICl 162.36]

A brownish-red, oily liquid or dark-red crystals; strongly irritant; with odour of chlorine and iodine; corrosive and oxidative.

Iodine Pentoxide [I_2O_5 333.81]

A white crystalline powder; readily decomposes on exposure to light; hygroscopic.
Freely soluble in water to form iodic acid; insoluble in dehydrated ethanol, chloroform, ether or carbon disulfide.

Iodine Trichloride [ICl_3 233.26]

Yellow or pale brown crystals; odour, strongly pungent; volatile at room temperature; readily decomposes in contact with water; hygroscopic; corrosive.
Soluble in water, ethanol, ether or benzene.

Isoamyl Acetate [$CH_3COOCH_2CH_2CH(CH_3)_2$ 130.19]

A clear, colourless liquid; odour, characteristic resembling that of banana.
Miscible with ethyl acetate, ethanol, amyl alcohol, ether, benzene or carbon disulfide; very slightly soluble in water.

Isoamylol [$(CH_3)_2CHCH_2CH_2OH$ 88.15]

Colourless liquid; odour, characteristic; inflammable.
Miscible with organic solution; slightly soluble in water.
Boiling point: 132°C.

Isobutanol [$(CH_3)_2CHCH_2OH$ 74.12]

A colourless, clear liquid; strongly refractive; inflammable.
Miscible with water, ethanol or ether.
Boiling range: 107.3-108.3°C.

Isobutyl Acetate [$CH_3COOCH_2CH(CH_3)_2$ 116.16]

A colourless liquid; inflammable.
Miscible with ethanol or ether; insoluble in water.

Isoniazid [$C_6H_7N_3O$ 137.14]

Complies with the requirements prescribed in monograph of the Chinese Pharmacopoeia.

Isooctane

See Trimethylpentane.

Isopentanol [$(CH_3)_2CHCH_2CH_2OH$ 88.15]

A colourless liquid; odour, characteristic; inflammable. Miscible with organic solvent; slightly soluble in water.

Isopropanol [$(CH_3)_2CHOH$ 60.10]

A colourless, clear liquid; odour, characteristic; taste, slightly bitter.

Miscible with water, ethanol or ether.

Boiling range: 82.0-83.0°C.

Isopropyl Ether [$C_6H_{14}O$ 102.18]

A colourless, clear liquid; inflammable.

Miscible with ethanol, ether, chloroform or benzene; slightly soluble in water.

Kerosene, Refined

A colourless or pale yellow oily liquid; odour, characteristic. Miscible with chloroform, benzene or carbon disulfate; insoluble in water or ethanol.

Wash 300 ml of commercial kerosene with 20 ml of crude sulfuric acid in a 500 ml separator for 4-5 times, until the acid layer is pale black, separate the kerosene layer and wash with water. Then wash it with 20 ml of sodium hydroxide solution (1→5), wash it with water and dehydrate with anhydrous calcium chloride, transfer it into a distilling flask, distil under an air condenser, on a sand bath. Collect the distillate in the range of 160-250°C.

Kieselguhr

A white or almost white powder; strongly adsorptive powder and good filter medium.

Insoluble in water, acid or alkali solution.

Lactic Acid [$CH_3CH(OH)COOH$ 90.08]

Complies with the requirements prescribed in monograph of the Chinese Pharmacopoeia.

Lanthanum Nitrate [$La(NO_3)_3 \cdot 6H_2O$ 433.01]

White crystals.

Soluble in water, ethanol or acetone.

Lead Acetate [$Pb(C_2H_3O_2)_2 \cdot 3H_2O$ 379.34]

White crystals or a powder.

Freely soluble in water or glycerin; soluble in ethanol.

Lead Monoxide [PbO 223.20]

A yellow to brownish-yellow powder or crystals.

At 300-500°C, it converts into Pb_3O_4 , but at higher temperature reverts to PbO .

Soluble in hot solution of sodium hydroxide, acetic acid or dilute nitric acid.

Lead Nitrate [$Pb(NO_3)_2$ 331.21]

White crystals; burns and detonates when in contact, rubbed or bumped with organic substances.

Soluble in water; slightly soluble in ethanol.

Lithium Carbonate [Li_2CO_3 73.89]

A white powder or crystals; light.

Soluble in dilute acid; slightly soluble in water; insoluble in ethanol or acetone.

Lithium Chloride [$LiCl$ 42.39]

A white crystalline powder.

Soluble in water, ethanol, acetone, ether, isoamyl alcohol or sodium hydroxide solution.

Lithium Lactate [$LiC_3H_5O_3$ 96.01]

A white powder; odourless.

Soluble in water.

Lithium Sulfate [$Li_2SO_4 \cdot H_2O$ 127.96]

White crystals.

Soluble in water; practically insoluble in ethanol.

Litmus

A blue powder or mass.

Partly soluble in water or ethanol.

Magnesium Chloride [$MgCl_2 \cdot 6H_2O$ 203.30]

White crystals or a powder; hygroscopic.

Soluble in water or ethanol.

Magnesium Nitrate [$Mg(NO_3)_2 \cdot 6H_2O$ 256.42]

White crystals; hygroscopic. Its aqueous solution is neutral, decomposes at 330°C, burns when mixed with inflammable organic substances, inflammable and detonable. Soluble in ethanol, ammonia or water.

Magnesium Sulfate [$MgSO_4 \cdot 7H_2O$ 246.48]

White crystals or a powder; efflorescent.

Freely soluble in water; slowly soluble in glycerin; slightly soluble in ethanol.

Malachite Green [$2C_{23}H_{25}N_2 \cdot 3C_2H_2O_4$ 929.04]

Green flake crystals with metallic lustre.

Freely soluble in hot water or ethanol; very slightly soluble in water.

Malonic Acid [$C_3H_4O_4$ 104.06]

White transparent crystals; strongly irritant.

Soluble in water, methanol, ethanol, ether or pyridine.

Maltose [$C_{12}H_{22}O_{11}$ 342.30]

White crystals (β -type); odour, sweet.

Freely soluble in water; slightly soluble in ethanol; insoluble in ether.

Specific rotation $[\alpha]_D^{20}$: +125°-+137°.

Manganese Dioxide [MnO_2 86.94]

Black crystals or a powder. It can cause burning or explosion when heated or rubbed with organic substances or other reductive substances.

Insoluble in water, nitric acid or cold sulfuric acid; soluble in nitric acid or dilute sulfuric acid in presence of hydrogen peroxide or oxalic acid.

Manganese Sulfate [$MnSO_4 \cdot H_2O$ 169.02]

Pink crystals.

Soluble in water; insoluble in ethanol.

Mannitol [$C_6H_{14}O_6$ 182.17]

White crystals; odourless; taste, sweet.

Soluble in water; slightly soluble in ethanol; practically insoluble in ether.

Mercuric Acetate [$Hg(C_2H_3O_2)_2$ 318.68]

White crystals or a powder; odour, resembling acetic acid.

Soluble in water or ethanol.

Mercuric Bromide [$HgBr_2$ 360.40]

White crystals or a crystalline powder.

Freely soluble in hot ethanol, hydrochloric acid, hydrobromic acid or solution of potassium bromide; slightly soluble in chloroform or ether.

Mercuric Chloride [$HgCl_2$ 271.50]

White crystals or a crystalline powder, slightly volatile at room temperature. It decomposes to mercurous chloride on exposure to light.

Soluble in water, ethanol, acetone or ether.

Mercuric Iodide, Red [HgI_2 454.40]

A emerald red powder; odourless; heavy

Soluble in ether, sodium thiosulfate solution and potassium iodide solution; slightly soluble in dehydrated ethanol; insoluble in water.

Mercuric Nitrate [$Hg(NO_3)_2 \cdot H_2O$ 342.62]

A white or slightly yellow crystalline powder, with an odour of nitric acid; hygroscopic.

Freely soluble in water or dilute acid; a precipitate of basic salt is formed in a large amount of water or boiling water.

Mercurous Nitrate [$\text{HgNO}_3 \cdot \text{H}_2\text{O}$ 280.61]

White crystals; usually with an odour of nitric acid.

Freely soluble in water or dilute nitric acid.

A precipitate of basic salt is formed in a large amount of water.

Mercury [Hg 200.59]

A silver-white lustrous, liquid metal; heavy; slightly volatile at room temperature; produces amalgam with metals other than iron.

Soluble in dilute nitric acid; insoluble in water.

Metaphthalein [$\text{C}_{32}\text{H}_{32}\text{N}_2\text{O}_{12}$ 636.58]

A pale yellow or pale brown powder.

Sensitivity To 10 mg add 1 ml of concentrated ammonia solution, dilute with water to 100 ml and mix well. Mix 5 ml of this solution with 95 ml of water, 4 ml of concentrated ammonia solution, 50 ml of ethanol and 0.1 ml of 0.1 mol/L barium chloride solution. The mixture turns to bluish-purple colour and should be colourless with adding 0.15 ml of 0.1 mol/L EDTA solution.

Methanol [CH_3OH 32.04]

A clear, colourless liquid; volatile; inflammable. It contains 0.1% of water.

Miscible with water, ethanol or ether.

Boiling range: 64-65°C.

Methanol, Anhydrous [CH_3OH 32.04]

A clear, colourless liquid; volatile; burns with a bluish flame without fume. It contains not more than 0.05% of water.

Miscible with water, ethanol or ether.

Boiling point: 64.7°C.

Methyl Acetate [$\text{CH}_3\text{COOCH}_3$ 74.08]

A clear, colourless liquid.

Miscible with water, ethanol or ether.

Methylamine Hydrochloride [$\text{CH}_3\text{NH}_2 \cdot \text{HCl}$ 67.52]

White or almost white crystals; hygroscopic.

Soluble in water or dehydrated ethanol.

N, N'-Methylene Bisacrylamide [$\text{C}_7\text{H}_{10}\text{N}_2\text{O}_2$ 154.17]

A white crystalline powder; hydrolyses in aqueous solution with formation of ammonia and acrylic acid.

Sparingly soluble in water.

Methylene Blue [$\text{C}_{16}\text{H}_{18}\text{ClN}_3\text{S} \cdot 3\text{H}_2\text{O}$ 373.90]

Deep emerald green crystals or a dark brown powder; with bronze lustre.

Freely soluble in hot water.

Methyl Isobutyl Ketone [$\text{CH}_3\text{COCH}_2\text{CH}(\text{CH}_3)_2$ 100.16]

A colourless liquid; inflammable.

Miscible with ethanol, ether or benzene; slightly soluble in water.

p-Methylaminophenol Sulfate [$\text{C}_6\text{H}_7\text{N}_2\text{O}_2 \cdot \text{H}_2\text{SO}_4$ 344.39]

White crystals; turns grey on exposure to light.

Soluble in water; insoluble in ethanol or ether.

Methyl p-Hydroxybenzoate [$\text{C}_8\text{H}_8\text{O}_3$ 152.14]

Colourless crystals or white crystalline powder; odourless or slightly irritant.

Soluble in ethanol, ether or acetone; slightly soluble in benzene or carbon tetrachloride; practically insoluble in water.

Methyl Orange [$\text{C}_{14}\text{H}_{14}\text{N}_3\text{NaO}_3\text{S}$ 327.34]

Orange crystals or a powder.

Freely soluble in hot water; practically insoluble in ethanol.

Methyl Red [$\text{C}_{15}\text{H}_{15}\text{N}_3\text{O}_2$ 269.30]

Purplish-red crystals.

Soluble in ethanol or acetic acid; insoluble in water.

Morphine, Anhydrous [$\text{C}_{17}\text{H}_{19}\text{NO}_3$ 285.34]

Rhombic, short columnar prism crystals (crystallized from anisole); decomposes at 254°C.

α -Naphthol (1-Naphthol) [$\text{C}_{10}\text{H}_7\text{OH}$ 144.17]

White, pale pink crystals or powder; odour, phenolic; darkens gradually on exposure to light.

Freely soluble in ethanol, chloroform, ether, benzene or alkali solution; slight soluble in water.

β -Naphthol (2-Naphthol) [$\text{C}_{10}\text{H}_7\text{OH}$ 144.17]

White or pale yellow crystals or a powder; odour, characteristic; discoloured easily on exposure to light.

Freely soluble in ethanol, ether, glycerin or sodium hydroxide solution; soluble in hot water; slightly soluble in water.

α -Naphtholbenzein [$\text{C}_{27}\text{H}_{20}\text{O}_3$ 392.45]

A reddish-brown powder.

Soluble in ethanol, ether, benzene or glacial acetic acid; insoluble in water.

α -Naphthylamine Hydrochloride [$\text{C}_{10}\text{H}_9\text{N} \cdot \text{HCl}$ 179.65]

A white crystalline powder; discoloured on exposure to air.

Soluble in water, ethanol or ether.

N-Naphthylethylenediamine Dihydrochloride [$\text{C}_{12}\text{H}_{14}\text{N}_2 \cdot 2\text{HCl}$ 259.18]

White or faintly red crystals.

Freely soluble in hot water, ethanol or dilute hydrochloric acid; slightly soluble in water, dehydrated ethanol or acetone.

Neutral Red [$\text{C}_{15}\text{H}_{17}\text{N}_4\text{Cl}$ 288.78]

A dark green or brownish-black powder.

Soluble in water or ethanol.

Nickel Ammonium Sulfate [$\text{NiSO}_4 \cdot (\text{NH}_4)_2\text{SO}_4 \cdot 6\text{H}_2\text{O}$ 394.99]

Bluish-green crystals.

Soluble in water; insoluble in ethanol.

Nickel Nitrate [$\text{Ni}(\text{NO}_3)_2 \cdot 6\text{H}_2\text{O}$ 290.79]

Green crystals. Its aqueous solution is acidic.

Freely soluble in water; soluble in ethanol or ethylene glycol; slightly soluble in acetone.

Nickel Sulfate [$\text{NiSO}_4 \cdot 7\text{H}_2\text{O}$ 280.86]

Green, transparent crystals.

Soluble in water or ethanol.

Nicotinyl L-tyrosyl-hydrazide [$\text{C}_{15}\text{H}_{16}\text{N}_4\text{O}_3$ 300.32]

White crystals.

Soluble in hot ethanol.

Ninhydrine [$\text{C}_9\text{H}_6\text{O}_4$ 178.14]

A white or pale yellow crystalline powder; hygroscopic; discoloured gradually on exposure to light and air.

Soluble in water or ethanol; slightly soluble in chloroform or ether.

Nitric Acid [HNO_3 63.01]

A colourless, clear liquid; fumes on exposure to air; odour, suffocating irritant; turns to brown with formation of nitrogen tetroxide on exposure to light.

It contains 69%-71% (g/g) of HNO_3 .

Miscible with water.

Nitric Acid, Fuming [HNO_3 63.01]

A clear, colourless or slightly yellowish-brown liquid; highly oxidative and corrosive; A reddish-yellow fog of nitrogen dioxide and nitrogen tetroxide is produced on contact

with air.

Miscible with water.

***p*-Nitroaniline** [$C_6H_5N_2O_2$ 138.13]

Yellow crystals or powder.

Freely soluble in methanol; soluble in ethanol or ether; insoluble in water.

Nitrobenzene [$C_6H_5NO_2$ 123.11]

A colourless or pale yellow oily liquid; odour, bitter almond-like.

Freely soluble in ethanol, ether, benzene or oil; very slightly soluble in water.

Nitromethane [CH_3NO_2 61.04]

A colourless, oily liquid; inflammable; its vapour forms explosive mixture with air.

Miscible with water, ethanol or alkali solution.

***p*-Nitrophenol** [$C_6H_5NO_3$ 139.11]

White or pale yellow crystals; sublimable; inflammable.

Freely soluble in ethanol, chloroform, ether or sodium hydroxide solution; slightly soluble in water.

***p*-Nitrophenyl-azo-resorcinol** [$C_{12}H_9N_3O_4$ 259.22]

A reddish-brown powder.

Slightly soluble in boiling ethanol, acetone, ethyl acetate and toluene; insoluble in water. Soluble in dilute alkali solution.

***n*-Octanol** [$CH_3(CH_2)_7OH$ 130.23]

A colourless liquid; odour, characteristically aromatic.

Miscible with ethanol, ether chloroform; insoluble in water.

Olive Oil

A pale yellow or slightly green liquid.

Orange IV [$C_{18}H_{14}N_3NaO_3S$ 375.38]

A yellow powder.

Soluble in water or ethanol.

Oxalic Acid [$H_2C_2O_4 \cdot 2H_2O$ 126.07]

White, transparent crystals or crystalline granules; efflorescent.

Freely soluble in water or ethanol; insoluble in chloroform or benzene.

Palladium Chloride [$PdCl_2$ 177.33]

Red, needle crystals; hygroscopic.

Soluble in water, ethanol, acetone or hydrobromic acid.

Pancreatic Digest of Casein

Yellow granules. Casein hydrolyzed with pancreatin decolourized and purified with active carbon. It is used as culture medium of bacteria, especially in test for sterility.

Pancreatin

Complies with the requirements prescribed in monograph of the Chinese Pharmacopoeia.

***n*-Pentanol** [$C_5H_{12}O$ 88.15]

A clear, colourless liquid; odour, characteristic and pungent. Its vapour can form explosive mixture with air.

Miscible with ethanol or ether; slightly soluble in water.

Boiling point: 138.1°C.

Pepsin

White to yellowish flakes or granules; taste, slightly sour and salty; hygroscopic.

Freely soluble in water; practically insoluble in ethanol, chloroform or ether.

Peptone

A yellow or pale yellow powder; odourless; taste, slightly bitter.

Soluble in water; insoluble in ethanol or ether.

Perchloric Acid [$HClO_4$ 100.46]

A colourless, clear liquid; strong oxidant; very hygroscopic; volatile and corrosive.

Miscible with water.

Petroleum Ether

A clear colourless liquid; odour, characteristic; inflammable; low boiling fractions of petroleum ether is highly volatile.

Miscible with anhydrous ethanol, ether or benzene; insoluble in water.

Boiling range: 30-60°C; 60-90°C; 90-120°C.

***o*-Phenanthroline** [$C_{12}H_8N_2 \cdot H_2O$ 198.22]

White or pale yellow crystals or a crystalline powder; darkens after long standing.

Soluble in ethanol or acetone; slightly soluble in water; insoluble in ether.

Phenol [C_6H_5O 94.11]

Complies with the requirements prescribed in monograph of the Chinese Pharmacopoeia.

Phenol, Liquefied

To 90 g of phenol add a little water, heat slowly on a water bath until liquefied, cool, add sufficient water to produce 100 ml.

Phenoxyethanol [$C_6H_5OCH_2CH_2OH$ 138.17]

A colourless, clear liquid; odour, aromatic.

Freely soluble in ethanol, ether or sodium hydroxide solution; slightly soluble in water.

Phenylhydrazine [$C_6H_5N_2$ 108.14]

A yellow oily liquid, turns to scale crystals at a temperature below 23°C; turns to brown on exposure to air and light; corrosive; inflammable.

Miscible with ethanol, ether, chloroform or benzene; soluble in dilute acid; slightly soluble in water or petroleum benzine.

Phenylhydrazine Hydrochloride [$C_6H_5N_2 \cdot HCl$ 144.60]

White or white transparent crystals; inflammable.

Freely soluble in water; soluble in ethanol, practically insoluble in ether.

Phloroglucinol [$C_6H_3(OH)_3 \cdot 2H_2O$ 162.14]

A white or pale yellow crystalline powder; taste, sweet. It turns to pale red on exposure to light.

Freely soluble in water.

Phenolphthalein [$C_{20}H_{14}O_4$ 318.33]

A white powder.

Soluble in ethanol; insoluble in water.

Phenolsulfonphthalein (Phenol red) [$C_{19}H_{14}O_5S$ 354.38]

A deep red crystalline powder.

Soluble in ethanol, solution of sodium hydroxide or sodium carbonate; insoluble in water, chloroform or ether.

Phosphorus Pentoxide [P_2O_5 141.94]

A white powder, odour alliaceous; corrosive; highly hygroscopic.

Phosphomolybdic Acid [$P_2O_5 \cdot 20MoO_3 \cdot 51H_2O$ 3939.49]

Bright yellow crystals.

Soluble in water, ethanol or ether.

Phosphoric Acid [H_3PO_4 98.00]

A clear, colourless, viscous liquid; corrosive.

Soluble in water.

Phosphotungstic Acid [$P_2O_5 \cdot 20WO_3 \cdot 28H_2O$ 5283.34]

White or pale yellow crystals.

Soluble in water, ethanol or ether.

***o*-Phthalaldehyde** [$C_8H_6O_2$ 134.13]

Pale yellow needle crystals.

Soluble in water, ethanol or ether; slightly soluble in

petroleum benzin.

Picrolonic Acid [$C_{10}H_8N_4O_5$ 264.21]

Yellow flake crystals.

Soluble in ethanol; slightly soluble in water.

Polyethylene Glycol 1500

A white or cream waxy solid; odour, characteristic; melts on heating.

Soluble in water or ethanol.

Polyethylene Glycol Adipate

$HO[CH_2CH_2OCO(CH_2)_4COO]_nH$

White powder or crystals.

Soluble in chloroform; insoluble in water, ethanol or ether.

Polysorbate 80

A pale red, oily liquid; odour, fat-like.

Soluble in water or most of organic solvents; insoluble in paraffin oil or vegetable oil.

Potassium Acetate [$KC_2H_3O_2$ 98.14]

White crystals or powder; hygroscopic.

Freely soluble in water or ethanol.

Potassium Alum [$AlK(SO_4)_2 \cdot 12H_2O$ 474.39]

White, transparent crystals or powder; odourless; taste, slightly sweet and astringent.

Freely soluble in glycerin or water; insoluble in ethanol or acetone.

Potassium Biphthalate [$KHC_8H_4(COO)_2$ 204.22]

A white crystalline powder.

Soluble in water; slightly soluble in ethanol.

Potassium Bisulfate [$KHSO_4$ 136.17]

White crystals; its aqueous solution is strongly acidic.

Soluble in water.

Potassium Bitartrate [$KHC_4H_4O_6$ 188.18]

A white, crystalline powder; taste, sour.

Freely soluble in hot water; insoluble in water or ethanol.

Potassium Bromate [$KBrO_3$ 167.00]

White crystals or powder.

Soluble in water; insoluble in ethanol.

Potassium Bromide [KBr 119.00]

A white crystalline powder.

Soluble in water, boiling ethanol or glycerin; slightly soluble in ethanol.

Potassium Carbonate [$K_2CO_3 \cdot 1\frac{1}{2}H_2O$ 165.23]

White crystals or granules.

Soluble in water; insoluble in ethanol.

Potassium Carbonate, Anhydrous [K_2CO_3 138.21]

White crystals or powder; hygroscopic.

Soluble in water; its aqueous solution is strongly alkaline; insoluble in ethanol.

Potassium Chlorate [$KClO_3$ 122.55]

White, transparent crystals or a powder.

Freely soluble in boiling water; soluble in water or glycerin; practically insoluble in ethanol.

Potassium Chloride [KCl 74.55]

White crystals or a crystalline powder.

Freely soluble in water or glycerin; slightly soluble in ethanol; insoluble in acetone or ether.

Potassium Chromate [K_2CrO_4 194.19]

Pale yellow crystals.

Soluble in water; insoluble in ethanol.

Potassium Cyanide [KCN 65.12]

White granules or clinkers.

Soluble in water; slightly soluble in ethanol.

Potassium Dichromate [$K_2Cr_2O_7$ 294.18]

Lustrous orange-red crystals; taste, bitter; strongly oxidative.

Soluble in water; insoluble in ethanol.

Potassium dihydrogen Phosphate [KH_2PO_4 136.09]

White crystals or a crystalline powder.

Soluble in water; insoluble in ethanol.

Potassium Ferricyanide [$K_3Fe(CN)_6$ 329.25]

Red crystals; decompose easily on exposure to light, air and acid.

Soluble in water; slightly soluble in ethanol.

Potassium Ferrocyanide [$K_4Fe(CN)_6 \cdot 3H_2O$ 422.39]

Yellow crystals or granules. Its aqueous solution readily deteriorates.

Soluble in water; insoluble in ethanol.

Potassium Hyaluronate

A white, loose, flocky mass or flake.

Freely soluble in water.

Loss on drying When dried to constant weight in vacuum over phosphorous pentoxide, loses not more than 10% of its weight.

Residue on ignition 14%-18% calculated on the dried basis.

Viscosity Kinematic viscosity of 0.15% aqueous solution, 5-6 mm²/s.

pH value 6.0-7.0, using 0.15% aqueous solution.

Total nitrogen 3%-4% calculated on the dried basis.

Potassium hydroxide [KOH 56.11]

White granules or sticks; absorbs carbon dioxide easily to form potassium carbonate; hygroscopic.

Soluble in water or ethanol.

Potassium Iodate [KIO_3 214.00]

White crystals or a crystalline powder.

Soluble in water or dilute sulfuric acid; insoluble in ethanol.

Potassium Iodide [KI 166.00]

White crystals or powder.

Soluble in water, ethanol, acetone or glycerin; insoluble in ether.

Potassium Naphthoquinone sulfonate [$C_{10}H_6KO_3S$ 276.31]

Golden yellow crystals.

Soluble in 50% ethanol; slightly soluble in water.

Potassium Nitrate [KNO_3 101.10]

White crystals or powder; burns and detonates when in contact, rubbed or bumped with organic substances.

Soluble in water; slightly soluble in ethanol.

Potassium Periodate [KIO_4 230.00]

A white, crystalline powder.

Soluble in hot water; slightly soluble in water.

Potassium Permanganate [$KMnO_4$ 158.03]

Dark purple crystals with metallic luster; strong oxidant; decomposes in ethanol, concentrated acids or other organic solvents with liberation of oxygen.

Soluble in water.

Potassium Sodium Tartrate [$KNaC_4H_4O_6 \cdot 4H_2O$ 282.22]

White, transparent crystals or a crystalline powder.

Soluble in water; insoluble in ethanol.

Potassium Sulfate [K_2SO_4 174.26]

White crystals or a crystalline powder.

Soluble in water or glycerin; insoluble in ethanol.

Potassium Tetroxalate (Potassium trihydrogen oxalate)

[$KH_3(C_2O_4)_2 \cdot 2H_2O$ 254.19]

White crystals or a crystalline powder.

Soluble in water; slightly soluble in ethanol.

Potassium Thiocyanate [KSCN 97.18]

White crystals.
soluble in water or ethanol.

Potato Starch [(C₆H₁₀O₅)_n]

A white, amorphous powder; odourless; tasteless; highly hygroscopic.
Insoluble in water and ethanol; forms slightly blue collosol in hot water.

Procaine Hydrochloride [C₁₃H₂₀N₂O₂ • HCl 272.78]

Complies with the requirements prescribed in monograph of the Chinese Pharmacopoeia.

Propanol [CH₃CH₂CH₂OH 60.10]

A clear, colourless liquid; inflammable.
Miscible with water, ethanol or ether.
Boiling point: 97.2°C.

Propylene Glycol [CH₃CH(OH)CH₂OH 76.10]

A colourless, viscous liquid; taste, slightly acid.
Miscible with water, acetone or chloroform.

Propyl *p*-Hydroxybenzoate [C₁₀H₁₂O₃ 180.20]

White crystals.
Freely soluble in ethanol or ether; Slightly soluble in boiling water; practically insoluble in water.

Protocatechuic Acid [C₇H₆O₄ 154.12]

White or faintly brown crystals; discoloured on exposure to air.
Soluble in ethanol or ether, slightly soluble in water.
Purified Water, Ammonia Free Distill 1000 ml of purified water with 1 ml of diluted sulphuric acid and 1 ml of potassium permanganate TS.

Pyridine [C₅H₅N 79.10]

A colourless, clear liquid; odour, disagreeable; taste, peppery; hygroscopic; inflammable.
Miscible with water, ethanol, ether or petroleum ether.

Pyridine, Anhydrous [C₅H₅N 79.10]

To 200 ml of pyridine reagent add 40 ml of benzene, mix well and distil on a sand bath. Collect the distillate at 115-116°C, tightly closed, spare.

Pyrogallol [C₆H₃(OH)₃ 126.11]

White lustrous crystals.
Soluble in water, ethanol or ether; slightly soluble in chloroform, benzene or carbon disulfide.

Quinaldine Red [C₂₁H₂₃IN₂ 430.33]

A deep red powder.
Soluble in ethanol; slightly soluble in water.

Quinalizarin [C₁₄H₈O₆ 272.21]

Red or dark red crystals or a powder with green metallic lustre.
Soluble in acetic acid with yellow colour; in sulfuric acid with bluish-violet colour; in aqueous alkaline solution with reddish-violet colour; insoluble in water.

Quinine Sulfate [(C₂₀H₂₄N₂O₂)₂ • H₂SO₄ • 2H₂O 782.96]

White, fine needle crystals; odourless; taste, very bitter; gradually discoloured on exposure to light; its aqueous solution yields neutral reactions.
Freely soluble in a mixture of chloroform-dehydrated ethanol (2 : 1); slightly soluble in water, ethanol, chloroform or ether.

Red Mercuric Iodide [HgI₂ 454.40]

A bright red powder; heavy; odourless.
Soluble in ether, sodium thiosulfate solution or potassium iodide solution; Slightly soluble in dehydrated ethanol; insoluble in water.

Resazurin [C₁₂H₇NO₄ 229.19]

Deep red crystals with green lustre.

Soluble in dilute sodium hydroxide solution; slightly soluble in ethanol or glacial acetic acid; insoluble in water or ether.

(*p*-Nitrophenyl-azo)-resorcinol [C₁₂H₉N₃O₄ 259.22]

A reddish-brown powder.
Slightly soluble in boiling ethanol, acetone, acetate ester or toluene; insoluble in water; soluble in dilute alkaline solution.

Resorcinol [C₆H₄(OH)₂ 110.11]

White transparent crystals; turns to pale red on exposure to light, air or in contact with iron.
Soluble in water, ethanol or ether.

Rhodamine B [C₂₈H₃₁ClN₂O₃ 479.02]

Green lustrous crystals or a reddish-violet powder.
Freely soluble in water with a bluish-red colour; its diluted solution is strongly fluorescent; freely soluble in ethanol; slightly soluble in hydrochloric acid or sodium hydroxide solution.

Salicylic Acid [C₇H₆O₃ 138.12]

White crystals or powder; taste, sweet followed by acid; gradually discolours on exposure to light; sublimes at 76°C.
Soluble in ethanol and ether; slightly soluble in water.

Salicylaldehyde [C₆H₄(OH)CHO 122.12]

A colourless or pale brown oily liquid; bitter almond-like odour.
Soluble in ethanol, ether and benzene; slightly soluble in water.

Sarcosylsin [C₁₃H₁₈Cl₂N₂O₂ 305.20]

Needle crystals.
Soluble in ethanol, propylene glycol or ethylene glycol, practically insoluble in water.

Selenious Acid [H₂SeO₃ 128.97]

White crystals; hygroscopic; reduced to selenium by most of the reducing agents.
Freely soluble in water or ethanol; insoluble in ammonia solution.

Semicarbazide Hydrochloride [NH₂CONHNH₂HCl 111.53]

White crystals.
Freely soluble in water; insoluble in ethanol and ether.

Silicic Acid [mSiO₂ • nH₂O]

A white, translucent, or milky white granules or pellets; hygroscopic; usually contains about 3%-7% of water; moisture absorbing capacity about 40%.

Silicotungstic Acid [SiO₂ • 12WO₃ • 26H₂O 3310.66]

White or pale yellow crystals; hygroscopic.
Freely soluble in water or ethanol.

Silver Diethyldithiocarbamate [(C₂H₅)₂NCS₂Ag 256.14]

Pale yellow crystals.
Freely soluble in pyridine; soluble in chloroform; insoluble in water, ethanol, acetone or benzene.

Silver Nitrate [AgNO₃ 169.87]

White, transparent, flaky crystals.
Freely soluble in ammonia solution; soluble in water or ethanol; slightly soluble in ether or glycerin.

Silver Oxide [Ag₂O 231.74]

A brownish-black powder; heavy; slowly decomposes on exposure to light; inflammable.
Freely soluble in dilute nitric acid or ammonia solution; practically insoluble in water or ethanol.

Soda Lime

A mixture of sodium hydroxide and calcium oxide, pink small granules with the addition of special indicator; the colour fades gradually on absorption of carbon dioxide.

Sodium Acetate [NaC₂H₃O₂ • 3H₂O 136.08]

White transparent crystals or white granules; efflorescent.
Soluble in water.

Sodium Acetate, Anhydrous $[\text{NaC}_2\text{H}_3\text{O}_2 \quad 82.03]$

A white powder; hygroscopic.
Freely soluble in water; soluble in ethanol.

Sodium Alizarinsulfonate $[\text{C}_{14}\text{H}_7\text{NaO}_7\text{S} \cdot \text{H}_2\text{O} \quad 360.28]$

An orange or yellowish-brown powder.
Freely soluble in water; slightly soluble in ethanol;
insoluble in chloroform or benzene.

Sodium Ammonium Phosphate $[\text{Na}(\text{NH}_4)_2\text{PO}_4 \cdot 4\text{H}_2\text{O} \quad 226.10]$

White crystals or granules; efflorescent and loss part of ammonia.

Soluble in water; insoluble in ethanol.

Sodium Bicarbonate $[\text{NaHCO}_3 \quad 84.01]$

A white crystalline powder.
Soluble in water; insoluble in ethanol.

Sodium Bisulfite $[\text{NaHSO}_3 \quad 104.06]$

A white crystalline powder; odour, resembling sulfur dioxide; oxidized to form sulfate on exposure to air.
Soluble in water; slightly soluble in ethanol.

Sodium Bitartrate $[\text{NaHC}_4\text{H}_4\text{O}_6 \cdot 2\text{H}_2\text{O} \quad 190.09]$

A white, crystalline powder.
Soluble in water; insoluble in ethanol.

Sodium Borohydride $[\text{NaBH}_4 \quad 37.83]$

A white crystalline powder; hygroscopic.
Soluble in water, ammonia solution, ethylenediamine or pyridine; insoluble in ether.

Sodium Bromide $[\text{NaBr} \quad 102.89]$

White crystals or a powder.
Soluble in water; slightly soluble in ethanol.

Sodium Carbonate $[\text{Na}_2\text{CO}_3 \cdot 10\text{H}_2\text{O} \quad 286.14]$

White transparent crystals.
Soluble in water or glycerin; insoluble in ethanol.

Sodium Carbonate, Anhydrous $[\text{Na}_2\text{CO}_3 \quad 105.99]$

White powder or granules; absorbs one mol of water on exposure to air.
Soluble in water; to produce strongly alkaline solution; insoluble in ethanol.

Sodium Carbonate, Monohydrate $[\text{Na}_2\text{CO}_3 \cdot \text{H}_2\text{O} \quad 124.00]$

White prismatic crystals; hygroscopic; loses water of crystallization at 100°C .
Freely soluble in water; insoluble in ethanol.

Sodium Carboxymethylcellulose

A white powder or small granules; hygroscopic; easily disperses and swells in hot water; the viscosity of a 1% solution is 0.005-2.0 Pa · s.

Sodium Chloride $[\text{NaCl} \quad 58.44]$

White crystals or a crystalline powder; hygroscopic.
Soluble in water and in glycerin; very slightly soluble in ethanol or hydrochloric acid.

Sodium Chromotropate $[\text{C}_{10}\text{H}_5\text{Na}_2\text{O}_8\text{S}_2 \cdot 2\text{H}_2\text{O} \quad 400.29]$

A white or grey powder.
Soluble in water with a pale brown colour.

Sodium Citrate $[\text{C}_6\text{H}_5\text{Na}_3\text{O}_7 \cdot 2\text{H}_2\text{O} \quad 294.10]$

White crystals or a powder.
Freely soluble in water; insoluble in ethanol.

Sodium Cobaltinitrite $[\text{Na}_3\text{Co}(\text{NO}_2)_6 \quad 403.94]$

A yellow or yellowish-brown crystalline powder; readily decomposes.
Very soluble in water; slightly soluble in ethanol.

Sodium Deoxycholate $[\text{C}_{24}\text{H}_{39}\text{NaO}_4 \quad 414.56]$

A white crystalline powder; odour, characteristic, resembling that of bile; taste, very bitter; hygroscopic.
Freely soluble in water; slight soluble in anhydrous ethanol; insoluble in ether.

Sodium Diethyldithiocarbamate $[(\text{C}_2\text{H}_5)_2\text{NCS}_2\text{Na} \cdot 3\text{H}_2\text{O} \quad 225.31]$

White crystals; its aqueous solution is alkaline and gradually decomposes to produce a turbidity due to the liberation of carbon disulfide in contact with acid.
Freely soluble in water; soluble in ethanol.

Sodium dihydrogen Phosphate $[\text{NaH}_2\text{PO}_4 \cdot \text{H}_2\text{O} \quad 137.99]$

White crystals or granules.
Freely soluble in water; practically insoluble in ethanol.

Sodium Ferricyanide, Ammoniated

$[\text{Na}_3[\text{Fe}(\text{CN})_5\text{NH}_3] \cdot 3\text{H}_2\text{O} \quad 325.98]$

Yellow crystals.
Soluble in water.

Sodium Fluoride $[\text{NaF} \quad 41.99]$

A white powder or cubic crystals.
Soluble in water; its aqueous solution is corrosive to glass; insoluble in ethanol.

Sodium Formate $[\text{HCOONa} \cdot 2\text{H}_2\text{O} \quad 104.04]$

White crystals; odour, faint formic acid; hygroscopic.
Soluble in water or glycerin; slightly soluble in ethanol.

Sodium Heptanesulfonate $[\text{C}_7\text{H}_{15}\text{NaO}_3\text{S}_3 \cdot \text{H}_2\text{O} \quad 220.27]$

Sodium Hexanesulfonate $[\text{C}_6\text{H}_{13}\text{NaO}_3\text{S} \quad 188.18]$

A white powder.
Soluble in water.

Sodium Hydrosulfite $[\text{Na}_2\text{S}_2\text{O}_4 \quad 174.11]$

A white or almost white powder; odour, characteristic; hygroscopic; decomposes and burns on exposure to air or heat.
Freely soluble in water; insoluble in ethanol.

Sodium Hydroxide $[\text{NaOH} \quad 40.00]$

White granules or flakes; easily absorbs carbon dioxide and water; hygroscopic.
Freely soluble in water, ethanol or glycerin.

Sodium Hypochlorite Solution $[\text{NaOCl} \quad 74.44]$

A clear, pale yellowish-green liquid; corrosive; strongly oxidative and alkaline.
Miscible with water.

Sodium Iodide $[\text{NaI} \quad 149.89]$

White crystals or a powder.
Soluble in water, ethanol or glycerin.

Sodium Laurylsulfate $[\text{CH}_3(\text{CH}_2)_{10}\text{CH}_2\text{OSO}_3\text{Na} \quad 288.38]$

White or pale yellow crystals or a powder; odour, characteristic; decomposes on exposure to moist and warm air. It is a mixture of 85% sodium laurylsulfate and other sodium alkyl sulfates.

Freely soluble in water, its 10% aqueous solution is not clear at low temperature; soluble in hot ethanol.

Sodium Molybdate $[\text{Na}_2\text{MoO}_4 \cdot 2\text{H}_2\text{O} \quad 241.95]$

A white crystalline powder; loses water of crystallization at 100°C .
Soluble in water.

Sodium β -Naphthalenesulfonate $[\text{C}_{10}\text{H}_7\text{NaO}_3\text{S} \quad 230.22]$

White crystals or powder.
Soluble in water; insoluble in ethanol.

Sodium 1,2-Naphthoquinone-4-sulfonate $[\text{C}_{10}\text{H}_5\text{NaO}_3\text{S} \quad 260.20]$

White crystals.
Freely soluble in water; slightly soluble in ethanol.

Sodium Nitrate $[\text{NaNO}_3 \quad 84.99]$

Colourless, transparent crystals or white granules; burns and detonates in contact, rubbed or bumped with organic substances.

Soluble in water; slightly soluble in ethanol.

Sodium Nitrite [NaNO_2 69.00]

White or pale yellow crystals or granules; hygroscopic; burns and detonates in contact with organic substances, evolving noxious and irritant gas of nitrogen oxide and nitrogen peroxide.

Soluble in water; slightly soluble in ethanol or ether.

Sodium Nitroprusside [$\text{Na}_2\text{Fe}(\text{NO})(\text{CN})_5 \cdot 2\text{H}_2\text{O}$ 297.95]

Transparent, dark red crystals; its aqueous solution decomposes gradually and turns to green.

Soluble in water; slightly soluble in ethanol.

Sodium 1-Nitroso-2-naphthol-3,6-disulfonate

[$\text{C}_{10}\text{H}_5\text{NNa}_2\text{O}_6\text{S}_2$ 377.26]

Golden yellow crystals or a crystalline powder.

Soluble in water; slightly soluble in ethanol.

Sodium Octanesulfonate [$\text{C}_8\text{H}_{17}\text{NaO}_3\text{S}$ 216.28]

Sodium Oxalate [$\text{Na}_2\text{C}_2\text{O}_4$ 134.00]

A white crystalline powder.

Soluble in water; insoluble in ethanol.

Sodium Pentanesulfonate [$\text{C}_5\text{H}_{11}\text{NaO}_3\text{S} \cdot \text{H}_2\text{O}$ 192.21]

White crystals.

Soluble in water.

Sodium Periodate [NaIO_4 213.89]

A white, crystalline powder.

Soluble in water, hydrochloric acid, nitric acid, sulfuric acid or acetic acid; insoluble in ethanol.

Sodium Phosphate [$\text{Na}_2\text{HPO}_4 \cdot 12\text{H}_2\text{O}$ 380.12]

Colourless or white granules.

Freely soluble in water; slightly soluble in ethanol.

Sodium Pyrosulfite [$\text{Na}_2\text{S}_2\text{O}_5$ 190.11]

White crystals or a powder with slight odour of sulfur dioxide; hygroscopic.

Soluble in water or glycerin; slightly soluble in ethanol.

Sodium Salicylate [$\text{C}_7\text{H}_5\text{NaO}_3$ 160.10]

White scales or powder; odourless, turns to pink on exposure to light for a long time.

Freely soluble in water and glycerin; soluble in ethanol; practically insoluble in chloroform, ether or benzene.

Sodium Selenite [Na_2SeO_3 172.94]

White crystals or a crystalline powder; efflorescent; readily reduced by reducing agent.

Freely soluble in water; insoluble in ethanol.

Sodium Sulfate, Anhydrous [Na_2SO_4 142.04]

A white crystalline powder; hygroscopic.

Soluble in water; insoluble in ethanol.

Sodium Sulfide [$\text{Na}_2\text{S} \cdot 9\text{H}_2\text{O}$ 240.18]

White crystals; its aqueous solution is alkaline.

Soluble in water; Slightly soluble in ethanol; insoluble in ether.

Sodium Sulfite [$\text{Na}_2\text{SO}_3 \cdot 7\text{H}_2\text{O}$ 252.15]

White, transparent crystals; odour, resembling sulfurous acid; efflorescent; oxidized to form sodium sulfate on exposure to air.

Soluble in water; very slightly soluble in ethanol.

Sodium Sulfite, Anhydrous [Na_2SO_3 126.04]

White small crystals or powder.

Soluble in water and glycerin; very slightly soluble in ethanol.

Sodium Taurocholate [$\text{C}_{26}\text{H}_{44}\text{NNaO}_7\text{S}$ 537.69]

White crystals; taste, sweet followed by bitter.

Freely soluble in water; soluble in ethanol.

Sodium Tellurite [Na_2TeO_3 221.58]

A white powder.

Freely soluble in hot water; slightly soluble in water.

Sodium Tetraphenylborate [$(\text{C}_6\text{H}_5)_4\text{BNa}$ 342.22]

White crystals; odourless.

Freely soluble in water, methanol, anhydrous ethanol or acetone.

Sodium Thioglycollate [$\text{CH}_2(\text{SH})\text{COONa}$ 114.10]

White crystals; odour, slight; hygroscopic.

Freely soluble in water; slightly soluble in ethanol.

Sodium Thiosulfate [$\text{Na}_2\text{S}_2\text{O}_3 \cdot 5\text{H}_2\text{O}$ 248.19]

Colourless, transparent crystals or white granules.

Soluble in water with endothermic reaction; slightly soluble in ethanol.

Sodium Tungstate [$\text{Na}_2\text{WO}_4 \cdot 2\text{H}_2\text{O}$ 329.86]

A white crystalline powder; efflorescent.

Soluble in water; insoluble in ethanol.

Soluble Starch

A white powder; odourless; tasteless.

Soluble in boiling water; insoluble in water, ethanol or ether.

Solvent Blue 19

It is a mixture of 1-amino-4-anilinoanthraquinone and 1-methylamino-4-anilinoanthraquinone.

Stannous Chloride [$\text{SnCl}_2 \cdot 2\text{H}_2\text{O}$ 225.65]

White crystals.

Soluble in water, ethanol or sodium hydroxide solution.

Strontium Chloride [$\text{SrCl}_2 \cdot 6\text{H}_2\text{O}$ 266.64]

Colourless crystals or granules; odourless; volatilizes on exposure to air; hygroscopic on exposure to moist air.

Freely soluble in water; soluble in ethanol.

Strontium Hydroxide [$\text{Sr}(\text{OH})_2 \cdot 8\text{H}_2\text{O}$ 265.76]

Colourless or white crystals; deliquescent; absorbs carbon dioxide from air to form carbonate. It loses seven molecules of water in dry air.

Soluble in hot water or acid; slightly soluble in water.

Succinic Acid [$\text{H}_2\text{C}_4\text{H}_4\text{O}_4$ 118.09]

White crystals.

Soluble in hot water; slightly soluble in ethanol, acetone or ether; insoluble in benzene, carbon disulfide, carbon tetrachloride or petroleum benzin.

Sudan IV [$\text{C}_{24}\text{H}_{20}\text{N}_4\text{O}$ 380.45]

A dark brown powder.

Soluble in ethanol, ether, chloroform, benzene or phenol; slightly soluble in acetone; insoluble in water.

Sulfamic Acid [$\text{NH}_2 \cdot \text{SO}_3\text{H}$ 97.09]

White crystals.

Soluble in water, hydrolyses easily with formation of ammonium bisulfate; slightly soluble in methanol or ethanol; insoluble in ether or acetone.

Sulfanilamide [$\text{C}_6\text{H}_5\text{N}_2\text{O}_2\text{S}$ 172.21]

White foliar or needle crystals or a powder.

Soluble in boiling water, ethanol, acetone, glycerin, hydrochloric acid or solution of caustic alkali; slightly soluble in water; insoluble in chloroform, ether or benzene.

Sulfanilic Acid [$\text{C}_6\text{H}_7\text{NO}_3\text{S}$ 173.19]

A white or almost white powder, discoloured on exposure to light.

Freely soluble in solution of ammonia, sodium hydroxide or sodium carbonate; soluble in hot water; slightly soluble in water.

Sulfosalicylic Acid [$C_7H_6O_5S \cdot 2H_2O$ 254.22]

White crystals or a crystalline powder; instantly turns to red with trace of iron; decompose to phenol or salicylic acid at high temperature.

Freely soluble in water or ethanol; soluble in ether.

Sulfuric Acid [H_2SO_4 98.08]

A clear, colourless, viscous liquid; generates much heat when mixed with water or alcohol. It contains 95%-98% (g/g) of H_2SO_4 .

Miscible with water or ethanol.

Relative density: about 1.84.

Sulfuric Acid, Nitrogen Free

Introduce sulfuric acid to a porcelain evaporating dish heated on a sand bath until the vapor of sulfur trioxide is evolved (about 2 hours), and continue to heat for more 15 minutes; then allow to cool in an empty desiccator.

Tannic Acid [$C_{76}H_{52}O_{46}$ 1701.22]

A pale yellow or pale brown loose powder; odour, characteristic; gradually darkens on exposure to air or light. Soluble in water or ethanol.

Tartaric Acid [$H_2C_4H_4O_6$ 150.09]

White, transparent crystals or a white crystalline powder. Soluble in water, methanol, ethanol, propanol or glycerin; slightly soluble in ether; insoluble in chloroform.

Tertiary Butanol [$(CH_3)_3COH$ 74.12]

White crystals; it is a liquid when containing a little of water; odour, camphor-like; hygroscopic; inflammable.

Miscible with ethanol or ether; soluble in water.

Boiling point: 82.4°C.

Tetrabromophenolphthalein Potassium Ethyl Ester

[$C_{22}H_{13}Br_4KO_4$ 700.06]

A dark green or bluish-violet crystalline powder.

Soluble in water, ethanol or ether.

Tetrabutylammonium Iodide [$(C_4H_9)_4NI$ 369.37]

A white or pale yellow powder.

Freely soluble in ethanol; soluble in water; slightly soluble in chloroform.

n-Tetradecane [$CH_3(CH_2)_{12}CH_3$ 198.39]

A clear, colourless liquid.

Miscible with ethanol or ether; insoluble in water.

Tetraethylammonium Hydroxide [$C_8H_{21}NO$ 147.26]

The free base only exists in solution or as a hydrate. Usually it is used as a solution of 10%, 25% or 60%. The aqueous solution is colourless, strongly corrosive; very strongly alkaline; freely absorbs carbon dioxide from air.

Tetraheptylammonium Bromide [$C_{28}H_{50}BrN$ 490.71]

Chromatographic pure.

melting point: 89-91°C.

Tetrahydrofuran [C_4H_8O 72.11]

A colourless liquid; odour, ether-like; inflammable; easily forms peroxide during storage.

Miscible with water, ethanol, acetone or ether.

Boiling point: 66°C.

Tetramethylammonium Hydroxide [$N(CH_3)_4OH$ 91.15]

A colourless, clear liquid; absorbs carbon dioxide easily; corrosive.

Soluble in water or ethanol.

Tetramethylethylenediamine [$C_6H_{16}N_2$ 116.21]

A clear, colourless liquid.

Miscible with water and ethanol.

Tetrazolium Blue [$C_{40}H_{32}Cl_2N_8O_2$ 727.65]

Colourless or yellow crystals.

Freely soluble in methanol, ethanol or chloroform; slightly soluble in water.

Thallous Chloride [Tld 239.85]

A white crystalline powder; poisonous.

Turns to purple on exposure to air or light.

Soluble in boiled water or 260 times cold water; insoluble in ethanol. Its solubility in water is decreased when mixed with hydrochloric acid.

Thallous Nitrate [$TiNO_3$ 266.40]

White or colourless crystals; poisonous; decompose at 450°C soluble in hot water; soluble in cold water; insoluble in alcohol.

Thioacetamide [CH_3CSNH_2 75.13]

Colourless or white flaky crystals.

Soluble in water, ethanol or benzene; slightly soluble in ether.

Thioglycollic Acid [$CH_2(SH)COOH$ 92.12]

A clear, colourless liquid; odour, irritant.

Miscible with water, ethanol, ether or benzene.

Thiourea [NH_2CSNH_2 76.12]

White rhombic crystals or needle crystals; taste, bitter.

Soluble in water or ethanol; slightly soluble in ether.

Thorin [$C_{15}H_{11}AsN_2Na_2O_{10}S_2$ 576.30]

Red crystals.

Freely soluble in water; insoluble in organic solvent.

Thymol [$C_{10}H_{14}O$ 150.22]

White crystals.

Very slightly soluble in water.

Thymol Blue [$C_{27}H_{30}O_5S$ 466.60]

A brownish-green crystalline powder.

Soluble in ethanol; insoluble in water.

Thymolphthalein [$C_{28}H_{30}O_4$ 430.54]

A white powder.

Soluble in ethanol; insoluble in water.

Titanium Dioxide [TiO_2 79.88]

A white powder.

Soluble in hydrofluoric acid or hot concentrated sulfuric acid; insoluble in water, hydrochloric acid, nitric acid or dilute sulfuric acid.

Titan Yellow [$C_{28}H_{19}N_5Na_2O_6S_4$ 695.73]

A pale yellow or brown powder.

Soluble in water, ethanol, sulfuric acid or sodium hydroxide solution.

Toluene [$C_6H_5CH_3$ 92.14]

A clear, colourless liquid; odour, benzene-like; inflammable.

Miscible with ethanol or ether.

Boiling point: 110.6°C.

p-Toluenesulfonic Acid [$CH_3C_6H_4SO_3H \cdot H_2O$ 190.22]

White crystals.

Freely soluble in water; soluble in ethanol or ether.

o-Toluidine [C_7H_9N 107.06]

A pale yellow liquid; turns to brownish-red gradually on exposure to light and air.

Soluble in ethanol, ether or dilute acid; slightly soluble in water.

Toluidine Blue [$C_{15}H_{16}ClN_3S$ 305.83]

A dark green powder, with bronze lustre.

Freely soluble in water; slightly soluble in ethanol; very slightly soluble in chloroform; practically insoluble in ether.

p-Tosyl-L-Arginine Methyl Ester Hydrochloride

[$C_{14}H_{22}N_4O_4S \cdot HCl$ 378.88]

White crystals.

Soluble in water or methanol.

Tragacanth

A white or faint yellow powder; odourless.

Soluble in alkali solution or hydrogen peroxide solution; insoluble in ethanol.

Trichloroacetic Acid [CCl_3COOH 163.39]

Colourless crystals; odour, characteristic; hygroscopic; corrosive; its aqueous solution is strongly acidic.

Freely soluble in ethanol or ether; soluble in water.

Triethanolamine [$\text{N}(\text{CH}_2\text{CH}_2\text{OH})_3$ 149.19]

A colourless or pale yellow, viscous liquid. Turns to brown on standing for a long time; absorbs water and carbon dioxide on exposure to air; it is strongly alkaline.

Miscible with water or ethanol.

Triethylamine [$(\text{C}_2\text{H}_5)_3\text{N}$ 101.19]

A colourless liquid; odour, strong ammonia.

Miscible with ethanol or ether; slightly soluble in water.

Boiling point: 89.5°C.

Triethylenediamine [$\text{C}_6\text{H}_{12}\text{N}_2 \cdot 6\text{H}_2\text{O}$ 220.27]

White or slightly yellow crystals; odour, characteristic; hygroscopic.

Freely soluble in water, methanol or ether.

Trifluoroacetic Acid [CF_3COOH 114.02]

A colourless, fuming liquid; hygroscopic; strongly corrosive.

Freely soluble in water, ethanol, acetone or ether.

Trimethylpentane [$(\text{CH}_3)_3\text{CCH}_2\text{CH}(\text{CH}_3)_2$ 114.23]

A clear, colourless liquid; inflammable. It can form explosive mixture with air.

Soluble in acetone, chloroform, ether or benzene; insoluble in water.

Boiling point: 99.2°C.

Trinitrophenol [$\text{C}_6\text{H}_3\text{N}_3\text{O}_7$ 229.11]

Pale yellow crystals; odourless; taste, bitter; violet explosion occurs at high temperature or when bumped or rubbed in dryness.

Soluble in hot water, ethanol or benzene.

Trioctyl Phosphate [$(\text{C}_8\text{H}_{17})_3 \cdot \text{PO}_4$ 434.64]

A colourless or pale yellow oily liquid.

Soluble in ethanol, acetone or ether.

Triphenyltetrazolium Chloride [$\text{C}_{19}\text{H}_{15}\text{ClN}_4$ 334.81]

White crystals; darkens gradually on exposure to light.

Soluble in water, ethanol or acetone; insoluble in ether.

Trometamol [$\text{C}_4\text{H}_{11}\text{NO}_3$ 121.14]

White crystals with strong alkalinity.

Soluble in water; insoluble in ether.

Trypsin

A white, almost white or pale yellow powder.

Soluble in water; insoluble in ethanol.

Tyrosine [$\text{C}_9\text{H}_9\text{NO}_3$ 181.19]

White crystals.

Soluble in water; insoluble in ethanol or ether.

Uranyl Acetate [$\text{UO}_2(\text{C}_2\text{H}_3\text{O}_2)_2 \cdot 2\text{H}_2\text{O}$ 424.15]

A yellow crystalline powder.

Soluble in water; slightly soluble in ethanol.

Urea [NH_2CONH_2 60.06]

White crystals or powder; odour, ammoniacal.

Soluble in water, ethanol or benzene; practically insoluble in chloroform or ether.

Urotropine [$\text{C}_6\text{H}_{12}\text{N}_4$ 140.19]

White crystals; odourless.

Soluble in water, ethanol or chloroform; slightly soluble in ether.

Valine [$\text{C}_6\text{H}_{11}\text{NO}_2$ 117.15]

White crystals; sublimable.

Soluble in water; insoluble in ethanol or ether.

Vanadium Pentoxide [V_2O_5 181.88]

An orange yellow crystalline powder or reddish-brown needle crystals.

Soluble in acid solution or alkali solution; slightly soluble in water; insoluble in ethanol.

Vanillin [$\text{CH}_3\text{O} \cdot \text{C}_6\text{H}_5(\text{OH})\text{CHO}$ 152.15]

White crystals; odour, fragrant.

Freely soluble in ethanol, chloroform, ether, glacial acetic acid or pyridine, soluble in oil or sodium hydroxide solution.

Water, Nitrate-free and Nitrite-free

Purified water, ammonia free, or deionized water.

Xanthidrol [$\text{C}_{13}\text{H}_{10}\text{O}_2$ 198.22]

A pale yellow crystalline powder.

Soluble in ethanol, chloroform or ether; insoluble in water.

Xylene [$\text{C}_6\text{H}_4(\text{CH}_3)_2$ 106.17]

A clear, colourless liquid; odour, characteristic; inflammable. It is a mixture of the three isomers of *o*-, *m*- and *p*-xylene.

Miscible with ethanol, chloroform or ether; insoluble in water.

Boiling point: 137-140°C.

Xylene Cyanol Blue FF [$\text{C}_{25}\text{H}_{27}\text{N}_2\text{NaO}_6\text{S}_2$ 538.62]

A brown or bluish-black powder.

Freely soluble in ethanol; soluble in water.

Xylenol Orange [$\text{C}_{31}\text{H}_{29}\text{N}_2\text{Na}_4\text{O}_{13}\text{S}$ 760.59]

A reddish-brown crystalline powder; hygroscopic.

Freely soluble in water; insoluble in ethanol.

Yeast Extract

A reddish-yellow to brown powder; odour, characteristic, but no rancid smell.

Soluble in water to yield a weak acidic reaction.

Chloride Not more than 5%, calculated as NaCl (Appendix VIII A).

Nitrogen 7.2%-9.5%, calculated on the dried basis (Appendix VII D).

Loss on drying Not more than 5.0% (Appendix VIII L).

Residue on ignition Not more than 15% (Appendix VIII N).

Coagulable Protein No sediment is produced when its aqueous solution (1→20) is filtered and boiled.

Yellow Mercuric Oxide [HgO 216.59]

A yellow or orange powder; heavy; darkens gradually on exposure to light.

Freely soluble in dilute sulfuric acid, dilute hydrochloric acid or dilute nitric acid; insoluble in water, ethanol, acetone or ether.

Zinc [Zn 65.39]

Greyish-white granules with metallic lustre.

Soluble in dilute acid with liberation of hydrogen; soluble slowly in ammonia solution or sodium hydroxide solution.

Zinc Acetate [$\text{Zn}(\text{C}_2\text{H}_3\text{O}_2)_2 \cdot 2\text{H}_2\text{O}$ 219.51]

White crystals.

Freely soluble in water or boiling ethanol; slightly soluble in ethanol.

Zinc Chloride [ZnCl_2 136.30]

A white crystalline powder or clinkers.

Freely soluble in water; soluble in ethanol, acetone or ether.

Zincon [$\text{C}_{20}\text{H}_{15}\text{N}_4\text{NaO}_6\text{S}$ 462.42]

A brown, crystalline powder.

Soluble in ethanol or sodium hydroxide solution; insoluble in water.

Zinc Oxide [ZnO 81.39]

A white or pale yellow powder.

Soluble in dilute acid, concentrated alkali solution or ammonia solution; insoluble in water or ethanol.

Zinc Sulfate [$\text{ZnSO}_4 \cdot 7\text{H}_2\text{O}$ 287.56]

White crystals, granules or powder.

Freely soluble in water; soluble in glycerin; slightly soluble in ethanol.

Zirconium Nitrate [$\text{Zr}(\text{NO}_3)_4 \cdot 5\text{H}_2\text{O}$ 429.32]

White crystals; hygroscopic; decomposes at 100°C.

Freely soluble in water; soluble in ethanol.

Zirconyl Chloride [$\text{ZrOCl}_2 \cdot 8\text{H}_2\text{O}$ 322.25]

White crystals.

Freely soluble in water or ethanol.

XV B Test Solutions

Acetic Acid, Dilute

Dilute 60 ml of glacial acetic acid with water to 1000 ml.

N-Acetyl-L-tyrosine Ethyl Ester TS

Dissolve 24.0 mg of N-Acetyl-L-tyrosine ethyl ester in 0.2 ml of ethanol, add 2 ml of phosphate buffer solution (mix 38.9 ml of 0.067 mol/L potassium dihydrogen phosphate with 61.6 ml of 0.067 mol/L sodium dihydrogen phosphate, pH=7.0) and 1 ml of the indicator solution (mix equal quantities of 0.1% alcoholic methyl red solution and 0.05% alcoholic methylene blue solution), dilute with water to 10 ml.

Acid Ferric Ammonium Sulfate TS

Dissolve 20 g of ferric ammonium sulfate in 9.4 ml of sulfuric acid, dilute with water to 100 ml.

Acid Stannous Chloride TS

Dissolve 20 g of stannous chloride in hydrochloric acid to make 50 ml and filter.

The solution should be used within three months.

Acid Zirconium Alizarin TS

Dissolve 70 mg of sodium alizarinsulfonate in 50 ml of water, and then add the solution slowly to 50 ml of 0.6% zirconyl chloride ($\text{ZrOCl}_2 \cdot 8\text{H}_2\text{O}$) solution. Dilute with a mixed acid solution which contains 123 ml of hydrochloric acid and 40 ml of sulfuric acid per 1000 ml to 1000 ml. Allow to stand for 1 hour.

Alizarin Fluoro Blue TS

Add 12.5 ml of sodium hydroxide solution (1.2→100) to 0.19 g of alizarin fluoro blue, add 800 ml of water and 0.25 g of sodium acetate crystals, adjust to about pH 5.4 with dilute hydrochloric acid and dilute with water to make 1000 ml, mix well.

Alkaline Cupric Citrate TS

(1) Dissolve 17.3 g of crystalline cupric sulfate and 115.0 g of citric acid in 200 ml of warm water.

(2) Dissolve 185.3 g of anhydrous sodium carbonate (dried at 180°C for 2 hours) in water to make 500 ml.

Add 50 ml of solution (2) to 20 ml of solution (1) with constant shaking before use, cool and then dilute with water to 100 ml.

Alkaline Cupric Tartrate TS

(1) Dissolve 6.93 g of crystalline cupric sulfate in water to make 100 ml.

(2) Dissolve 34.6 g of crystalline potassium sodium tartrate and 10 g of sodium hydroxide in water to make 100 ml.

Mix solution (1) with solution (2) before use.

Alkaline Mercuric Potassium Iodide TS

Dissolve 10 g of potassium iodide in 10 ml of water, add slowly with stirring a saturated solution of mercuric chloride until a red precipitate remains undissolved. Add 30 g of potassium hydroxide and allow to dissolve, then add 1 ml or more of the saturated solution of mercuric chloride. Dilute with water to 200 ml. Allow the precipitate to settle and use the supernatant liquid.

Add 2 ml of this solution to 50 ml of water which contains 0.05 mg of ammonia, a yellowish-brown colour is formed immediately.

Alkaline β-Naphthol TS

Dissolve 0.25 g of β-naphthol in 10 ml of sodium hydroxide solution (1→10). This solution should be freshly prepared.

Alkaline Pyrogallol TS

Dissolve 0.5 g of pyrogallol in 2 ml of water. Add 8 ml of water which contains 12 g of potassium hydroxide, mix well.

This solution should be freshly prepared.

Alkaline Sodium Hydrosulfite TS

Dissolve 50 g of sodium hydrosulfite in 250 ml of water. Dissolve 28.57 g of potassium hydroxide in water to make 40 ml. Mix these two solutions. This solution should be freshly prepared.

Alkaline Sodium Nitroprusside TS

Dissolve 1 g of sodium nitroprusside and 1 g of sodium carbonate in water to make 100 ml.

Alkaline Tetrazolium Blue TS

Mix 10 ml of 0.2% methanol solution of tetrazolium blue with 30 ml of 12% methanol solution of sodium hydroxide before use.

Alkaline Trinitrophenol TS

To 20 ml of 1% trinitrophenol solution, add 10 ml of 5% sodium hydroxide solution, then dilute with water to 100 ml.

This solution must be freshly prepared.

1-Amino-2-naphthol-4-sulfonic acid TS

Mix thoroughly 5 g of sodium sulfite anhydrous with 94.3 g of sodium bisulfite and 0.7 g of 1-amino-2-naphthol-4-sulfonic acid. Dissolve 1.5 g of the mixture in 10 ml of water before use, filter if necessary.

Ammonia TS

Dilute 400 ml of concentrated ammonia solution with water to make 1000 ml.

Ammonia Concentrated TS

Use concentrated ammonia solution directly.

Ammoniated Ammonium Chloride TS

Dilute concentrated ammonia TS with equal volume of water, add ammonium chloride to make a saturated solution.

Ammoniated Cupric Chloride TS

Dissolve 22.5 g of cupric chloride in 200 ml of water, add 100 ml of concentrated ammonia TS and mix well.

Ammoniated Cupric Sulfate TS

Add ammonia TS dropwise to cupric sulfate TS until the freshly formed precipitate is almost dissolved, allow to settle and decant the clear solution. The solution should be freshly prepared.

Ammoniated Nickel Nitrate TS

Dissolve 2.9 g of nickel nitrate in 100 ml of water, add 40 ml of ammonia TS, shake and then filter.

Ammoniated Silver Nitrate TS

Dissolve 1 g of silver nitrate in 20 ml of water, add ammonia TS dropwise with stirring until the precipitate is almost completely dissolved, filter.

Preserve the solution in amber coloured glass bottle, protected from light.

Ammoniated Sodium Ferricyanide TS

Dissolve 1 g of ammoniated sodium ferricyanide $[\text{Na}_2\text{Fe}(\text{CN})_5\text{NH}_3 \cdot \text{H}_2\text{O}]$ in water to make 100 ml.

Ammonium Acetate TS

Dissolve 10 g of ammonium acetate in water to make 100 ml.

Ammonium Carbonate TS

Dissolve 20 g of ammonium carbonate with 20 ml of ammonia TS in water to make 100 ml.

Ammonium Chloride TS

Dissolve 10.5 g of ammonium chloride in water to make 100 ml.

Ammonium Magnesium Chloride TS

Dissolve 5.5 g of magnesium chloride and 7 g of ammonium chloride in 65 ml of water and then add 35 ml of ammonia TS. Allow to stand in glass bottle for several days, filter. The solution should be filtered, if turbidity occurs.

Ammonium Mercuric Thiocyanate TS

Dissolve 5 g of ammonium thiocyanate and 4.5 g of mercuric chloride in water to make 100 ml.

Ammonium Molybdate TS

Dissolve 10 g of ammonium molybdate in water to make 100 ml.

Ammonium Molybdate in Sulfuric Acid TS

Dissolve 0.1 g of ammonium molybdate in 10 ml of sulfuric acid.

Ammonium Molybdate-Sulfuric Acid TS

Dissolve 2.5 g of ammonium molybdate in a mixture of 15 ml of sulfuric acid and water to make 100 ml. This solution should be used within two weeks.

Ammonium Oxalate

Dissolve 3.5 g of ammonium oxalate in water to make 100 ml.

Ammonium Polysulfide TS

Add sulfur to ammonium sulfide TS and make a saturated solution.

Ammonium Reineckate TS

Dissolve 0.5 g of ammonium reineckate in 20 ml of water, shake for 1 hour, filter. This solution should be freshly prepared and used within 48 hours.

Ammonium Sulfide TS

To a solution of 60 ml of ammonia TS saturated with hydrogen sulfide add 40 ml of ammonia TS. Preserve in amber coloured glass bottle, protected from light. This solution is unsuitable for use if a copious precipitate of sulfur is present.

Ammonium Thiocyanate TS

Dissolve 8 g of ammonium thiocyanate in water to make 100 ml.

Anthrone TS

Dissolve 0.7 g of anthrone in 50 ml of sulfuric acid and dilute with sulfuric acid solution (70→100) to 500 ml.

Auric Chloride TS

Dissolve 1 g of auric chloride in 35 ml of water.

Barium Chloride TS

Dissolve 5 g of fine powder of barium chloride in water to make 100 ml.

Barium Hydroxide TS

Dissolve barium hydroxide in freshly boiled and cooled water

to make a saturated solution. This solution should be freshly prepared.

Barium Nitrate TS

Dissolve 6.5 g of barium nitrate in water to make 100 ml.

Bromine TS

To 2-3 ml of bromine in a glass bottle which is stoppered and lubricated with vaseline add 100 ml of water to make a saturated solution by shaking. This solution should be protected from light.

Bromine-Potassium Bromide TS

Dissolve 30 g of bromine and 30 g of potassium bromide in water to make 100 ml.

Cadmium Iodide TS

Dissolve 5 g of cadmium iodide in water to make 100 ml.

Calcium Chloride TS

Dissolve 7.5 g of calcium chloride in water to make 100 ml.

Calcium Hydroxide TS

To 1000 ml of water in a stoppered glass bottle add 3 g of calcium hydroxide, allow to stand for 1 hour with frequent shaking vigorously, use the supernatant liquid as the test solution.

Calcium Sulfate TS

Use the saturated solution of calcium sulfate directly.

Ceric Ammonium Nitrate TS

Dissolve 25 g of ceric ammonium nitrate in dilute nitric acid to make 100 ml.

Cerous Nitrate TS

Dissolve 0.22 g of cerous nitrate in 50 ml of water, add 0.1 ml of nitric acid and 50 mg of hydroxylamine hydrochloride, dilute with water to make 1000 ml and mix well.

Chloral Hydrate TS

Dissolve 50 g of chloral hydrate in a mixture of 15 ml of water and 10 ml of glycerin.

Chlorine TS

Use the saturated solution of chlorine in water. This solution should be freshly prepared.

Chromotropic Acid TS

Dissolve 50 mg of sodium chromotropate in 100 ml of a cold mixture of sulfuric acid and water (9 : 4). This solution should be freshly prepared before use.

Citric-Acetic Anhydride TS

Dissolve 2 g of citric acid in 100 ml of acetic anhydride.

Cobaltous Acetate TS

Dissolve 0.1 g of cobaltous acetate in methanol to make 100 ml.

Cobaltous Chloride TS

Dissolve 2 g of cobaltous chloride in 1 ml of hydrochloric acid, add water to make 100 ml.

Copper-Pyridine TS

Dissolve 4 g of cupric sulfate in 90 ml of water and add 30 ml of pyridine. This solution should be freshly prepared.

Cupric Acetate TS

Dissolve 0.1 g of cupric acetate in 5 ml of water which contains a few drops of acetic acid. Dilute with water to 100 ml and filter.

Cupric Acetate Concentrated TS

Dissolve 13.3 g of cupric acetate in a mixture of 195 ml of water and 5 ml of acetic acid.

Cupric Sulfate TS

Dissolve 12.5 g of cupric sulfate in water to make 100 ml.

Cupric Iodotartrate TS

Dissolve successively 7.5 g of cupric sulfate, 25 g of potassium sodium tartrate, 25 g of anhydrous sodium carbonate, 20 g of sodium bicarbonate and 5 g of potassium iodide in 800 ml of water. Dissolve 0.535 g of potassium iodate in water and add this solution to the mixture mentioned above.

Dilute with water to 1000 ml.

Cyanogen Bromide TS

Add 0.1 mol/L ammonium thiocyanate solution dropwise to bromine TS until it is colourless.

This solution should be freshly prepared. It is poisonous.

Diaminonaphthylene TS

Dissolve 0.1 g of 2, 3-diaminonaphthylene and 0.5 g of hydroxylamine hydrochloride in 100 ml of 0.1 mol/L hydrochloric acid solution, heat if necessary, cool and filter. This solution should be freshly prepared and protected from light.

Diazotized Sulfanilic Acid TS

Dissolve 1.57 g of sulfanilic acid in 80 ml of water and 10 ml of dilute hydrochloric acid by heating on a water bath. Cool to 15°C and add 6.5 ml of sodium nitrite solution (1→10) with stirring and dilute with water to 100 ml.

This solution should be freshly prepared.

Diazotized Dinitroaniline TS

Dissolve 50 mg of 2,4-dinitroaniline in 1.5 ml of hydrochloric acid, add 1.5 ml of water, cool in ice bath, then add 5 ml of 10% sodium nitrite solution dropwise with shaking.

Diazotized *p*-Nitroaniline TS

Dissolve 0.4 g of *p*-nitroaniline in a mixture of 20 ml of dilute hydrochloric acid and 40 ml of water, cool to 15°C and add 10% sodium nitrite solution until 1 drop of the solution turns blue to starch potassium iodide TP.

This solution should be freshly prepared.

2,6-Dichlorophenol Indophenol Sodium TS

Dissolve 0.1 g of 2,6-dichlorophenol indophenol sodium in 100 ml of water and filter.

2,6-Dichloroquinone-Chlorimide TS

Dissolve 1 g of 2,6-dichloroquinone-chlorimide in 200 ml of ethanol.

***p*-Dimethylaminobenzaldehyde TS**

Dissolve 0.125 g of *p*-dimethylaminobenzaldehyde in a cooled mixture of 65 ml of nitrogen-free sulfuric acid and 35 ml of water, add 0.05 ml of ferric chloride TS and mix well.

This solution should be used within 7 days.

Dimethylglyoxime TS

Dissolve 1 g of 2, 3-dimethylglyoxime in 100 ml of ethanol.

Dinitrobenzene TS

Dissolve 2 g of *m*-dinitrobenzene in ethanol to make 100 ml.

Dinitrobenzoic Acid TS

Dissolve 1 g of 3,5-dinitrobenzoic acid in ethanol to make 100 ml.

Dinitrophenylhydrazine TS

Dissolve 1.5 g of 2,4-dinitrophenylhydrazine in 20 ml of sulfuric acid solution (1→2), dilute with water to 100 ml and filter.

Dinitrophenylhydrazine Dilute TS

Dissolve 0.15 g of 2,4-dinitrophenylhydrazine in 100 ml of aldehyde free ethanol which contains 0.15 ml of sulfuric acid.

Diethyl Sodium Sulfosuccinate TS

Dissolve 0.9 g of diethyl sodium sulfosuccinate in 50 ml of water with gentle heating. Cool to room temperature, dilute with water to 200 ml.

Diphenylamine TS

Dissolve 1 g of diphenylamine in 100 ml of sulfuric acid.

Dipyridyl TS

Dissolve 0.2 g of 2,2'-dipyridyl, 1 g of sodium acetate crystal and 5.5 ml of glacial acetic acid in water to make 100 ml.

Disodium Hydrogen Phosphate TS

Dissolve 12 g of crystalline disodium hydrogen phosphate in water to make 100 ml.

Ethanol, Dilute TS

Dilute 529 ml of ethanol with water to 1000 ml.

It contains 49.5%-50.5% (ml/ml) of C₂H₅OH at 20°C.

Ethanolic Ammonia TS

Add concentrated ammonia solution to dehydrated ethanol.

It contains 9-11 g of NH₃ per 100 ml.

Preserve in rubber stoppered bottle.

Ethanolic *p*-Dimethylaminobenzaldehyde TS

Dissolve 1 g of *p*-dimethylaminobenzaldehyde in 9.0 ml of ethanol and 2.3 ml of hydrochloric acid, dilute with ethanol to 100 ml.

Ethanolic Hydroxylamine Hydrochloride TS

Mix one portion of hydroxylamine hydrochloride solution (34.8 → 100), one portion of sodium acetate-sodium hydroxide TS with four portions of ethanol.

Ethanolic Mercuric Bromide TS

Dissolve 2.5 g of mercuric bromide in 50 ml of ethanol by gentle heat.

Preserve in glass-stoppered bottle, protected from light.

Ethanolic Potassium Hydroxide TS

Use alcoholic potassium hydroxide (0.5 mol/L) VS.

Ethanolic Silver Nitrate TS

Dissolve 4 g of silver nitrate in 10 ml of water, dilute with ethanol to 100 ml.

Ferric Chloride TS

Dissolve 9 g of ferric chloride in water to make 100 ml.

Ferric Salicylate TS

(1) Dissolve 0.1 g of ferric ammonium sulfate in 2 ml of dilute sulfuric acid and add water to make 100 ml;

(2) Dissolve 1.15 g of sodium salicylate in water to make 100 ml;

(3) Dissolve 13.6 g of sodium acetate in water to make 100 ml.

(4) Mix 1 ml of ferric ammonium sulfate solution, 0.5 ml of sodium salicylate solution, 0.8 ml of sodium acetate solution with 0.2 ml of dilute acetic acid before use, add water to make 5 ml and mix well.

Ferrous Sulfate TS

Dissolve 8 g of ferrous sulfate crystals in 100 ml of freshly boiled and cooled water.

This solution should be freshly prepared.

Folin TS

Heat 10 g of sodium tungstate under reflux, 2.5 g of sodium molybdate, 70 ml of water, 5 ml of 85% phosphoric acid solution and 10 ml of hydrochloric acid in a 200 ml flask gently for about 10 hours, cool, add 15 g of lithium sulfate, 5 ml of water and 1 drop of bromine VS. Boil the mixture for about 15 minutes, or until the excess bromine is expelled. Cool, dilute with water to 100 ml and filter. The filtrate is kept in amber coloured glass bottle in a refrigerator.

Dilute 2.5 ml of the stock solution with water to 10 ml before use, shake thoroughly.

Formaldehyde TS

Use "Formaldehyde Solution" directly.

Formaldehyde-Sulfuric Acid TS

Add 1 drop of formaldehyde TS to 1 ml of sulfuric acid and mix well.

This solution should be freshly prepared before use.

Fuchsin-Pyrogallol TS

Dissolve 0.1 g of fuchsin basic in 50 ml of boiling water, cool, add 2 ml of a saturated solution of sodium bisulfite, and allow to stand for 3 hours. Add 0.9 ml of hydrochloric acid and allow to stand overnight. Add 0.1 g of pyrogallol, shake until dissolution is effected, dilute with water to 100 ml.

Fuchsin-Sulfurous Acid TS

Dissolve 0.2 g of fuchsin basic in 100 ml of hot water, add 20 ml of sodium sulfite solution (1 → 10) and 2 ml of hydrochloric acid, then dilute with water to 200 ml, add 0.1 g of activated carbon, stir and filter promptly. Allow to stand for at least 1 hour.

This solution should be freshly prepared.

Furfural TS

Dilute 1 ml of furfural with water to 100 ml.

This solution should be freshly prepared.

Glycerin-acetic Acid TS

Mix 1 volume of glycerin, 1 volume of 50% acetic acid solution and 1 volume of water.

Hemoglobin TS

Dissolve 1 g of bovine hemoglobin in hydrochloric acid solution (dilute 65 ml of 1 mol/L hydrochloric acid solution with water to 1000 ml) to make 100 ml and mix.

Preserve in refrigerator and use within 2 days.

Hydrochloric Acid Dilute TS

Dilute 234 ml of hydrochloric acid with water to 1000 ml.

It contains 9.5%-10.5% of HCl.

Hydrogen Peroxide TS

Dilute 30% concentrated hydrogen peroxide solution with water to a 3% solution.

Hydrogen Sulfide TS

Use the saturated solution of hydrogen sulfide.

Preserve in amber coloured glass bottle and protected from the light. It is unsuitable to be used if it does not possess an odour of H_2S , or if it does not produce a copious precipitate of sulfur when added to an equal volume of ferric chloride TS.

p-Hydroxydiphenyl TS

Dissolve 1.5 g of p-hydroxydiphenyl in 10 ml of 5% sodium hydroxide solution and dilute with water to 100 ml.

This solution may be kept several months in amber coloured glass bottle.

Hydroxylamine Hydrochloride TS

Dissolve 3.5 g of hydroxylamine hydrochloride in 60% ethanol to make 100 ml.

Hydroxylamine Sodium Acetate TS

Dissolve 0.2 g of hydroxylamine hydrochloride and 0.2 g of anhydrous sodium acetate in 100 ml of methanol.

This solution should be freshly prepared.

Iodine Potassium Iodide TS

Dissolve 0.5 g of iodine and 1.5 g of potassium iodide in 25 ml of water.

Iodine TS

Use iodine (0.05 mol/L) VS directly.

Iodine Monochloride TS

Dissolve 0.14 g of potassium iodide and 90 mg of potassium iodate in 125 ml of water, add 125 ml of hydrochloric acid. Preserve in well-closed glass bottle and store in a cool place.

Indigo Carmine TS

Dissolve indigo carmine in a mixture of 12 ml of sulfuric acid and 80 ml of water to make a solution which contains 0.09-0.11 g of $\text{C}_{16}\text{H}_8\text{N}_2\text{O}_2(\text{SO}_3\text{Na})_2$ per 100 ml.

Isoniazid TS

Dissolve 0.25 g of isoniazid in 0.31 ml of hydrochloric acid and sufficient methanol (or dehydrated ethanol) to make 500 ml.

Lead Acetate TS

Dissolve 10 g of lead acetate in freshly boiled and cooled water, add acetic acid dropwise to make the solution clear, and then dilute with freshly boiled and cooled water to 100 ml.

Lead Subacetate TS

Add 14 ml of water to 14 g of lead monoxide, triturate until a paste is formed. Transfer it to a glass bottle with 10 ml of water, add 70 ml of a solution which contains 22 g of lead acetate, shake vigorously for 5 minutes. Allow the mixture to stand for 7 days with frequent shaking, filter, add freshly boiled and cooled water to make 100 ml.

Lead Subacetate, Dilute TS

Dilute 4 ml of lead subacetate TS with freshly boiled and cooled water to 100 ml.

Magnesium Sulfate TS

Dissolve 12 g of magnesium sulfate crystals ($\text{MgSO}_4 \cdot 7\text{H}_2\text{O}$) in water to make 100 ml.

Magnesium Sulfate, Dilute TS

Dissolve 2.3 g of magnesium sulfate in water to make 100 ml.

Mercuric Acetate TS

Dissolve 5 g of mercuric acetate, finely powdered, in warm glacial acetic acid to make 100 ml.

Preserve this solution in a well-closed amber coloured glass bottle.

Mercuric Chloride TS

Dissolve 6.5 g of mercuric chloride in water to make 100 ml.

Mercuric Nitrate TS

Dissolve 40 g of yellow mercuric oxide in a mixture of 32 ml of nitric acid and 15 ml of water.

Preserve in stoppered glass bottle and protected from light.

Mercuric Potassium Iodide TS

Dissolve 1.36 g of mercuric chloride in 60 ml of water and dissolve 5 g of potassium iodide in 10 ml of water, mix these two solutions and dilute with water to 100 ml.

Mercuric Sulfate TS

Mix 5 g of yellow mercuric oxide with 40 ml of water, add 20 ml of sulfuric acid slowly with stirring, then add another 40 ml of water and mix well.

Mercurous Nitrate TS

Dissolve 15 g of mercurous nitrate in a mixture of 90 ml of water and 10 ml of dilute nitric acid.

This solution should be kept in an amber coloured glass bottle with the addition of one drop of mercury.

p-Methylaminophenol TS

Dissolve 0.2 g of p-methylaminophenol sulfate in 100 ml of water. Add 20 g of sodium pyrosulfite and allow it to dissolve.

Preserve in a stoppered amber coloured glass bottle and use within two weeks.

Molybdenum Phosphotungstate TS

Boil 70 ml of water under reflux, 5 ml of phosphoric acid 10 g of sodium tungstate and 2.4 g of phosphomolybdic acid for 2 hours. Cool, dilute with water to 100 ml and shake thoroughly.

Preserve in a glass bottle, protected from light.

Ninhydrin TS

Dissolve 2 g of Ninhydrin in ethanol to make 100 ml.

Nitric Acid Dilute TS

Dilute 105 ml of nitric acid with water to 1000 ml.

It contains 9.5%-10.5% of HNO_3 .

Oxalic Acid TS

Dissolve 6.3 g of oxalic acid in water to make 100 ml.

Platinic Chloride TS

Dissolve 2.6 g of platinic chloride in water to make 20 ml.

Phenol Red TS

Dissolve 100 mg of phenol red in 100 ml of ethanol (filter if necessary).

Phenoldisulfonic Acid TS

To 3 g of freshly distilled phenol add 20 ml of sulfuric acid and heat in water bath for 6 hours. Transfer the product to a glass-stoppered bottle while it is not solidified. Before use heat gently in a water bath until it is molten.

Phenylhydrazine Sulfate TS

Dissolve 60 mg of phenylhydrazine hydrochloride in 100 ml of sulfuric acid solution (1→2).

Phloroglucinol TS

Dissolve 0.5 g of phloroglucinol in ethanol to make 25 ml.

Preserved in glass-stoppered bottle, protected from light.

Phosphotungstic Acid TS

Dissolve 1 g of phosphotungstic acid in water to make 100 ml.

Phthalaldehyde TS

Dissolve 1.0 g of phthalaldehyde in 5 ml of methanol and 95 ml of 0.4 mol/L boric acid solution (adjust to pH 10.4 with 45% sodium hydroxide solution) with shaking. Add 2 ml of thioglycolic acid and adjust to pH 10.4 with 45% sodium hydroxide solution.

Potassium Acetate TS

Dissolve 10 g of potassium acetate in water to make 100 ml.

Potassium Carbonate TS

Dissolve 7 g of anhydrous potassium carbonate in water to make 100 ml.

Potassium chromate TS

Dissolve 5 g of potassium chromate in water to make 100 ml.

Potassium Cyanide TS

Dissolve 10 g of potassium cyanide in water to make 100 ml.

Potassium Dichromate TS

Dissolve 7.5 g of potassium dichromate in water to make 100 ml.

Potassium Ferricyanide TS

Dissolve 1 g of potassium ferricyanide in 10 ml of water. This solution should be freshly prepared.

Potassium Ferrocyanide TS

Dissolve 1 g of potassium ferrocyanide in 10 ml of water. This solution should be freshly prepared.

Potassium Ferricyanide Dilute TS

To 10 ml of 1% potassium ferricyanide solution add 0.5 ml of 5% ferric chloride solution and 40 ml of water, shake thoroughly.

Potassium Hydroxide TS

Dissolve 6.5 g of potassium hydroxide in water to make 100 ml.

Potassium Iodide TS

Dissolve 16.5 g of potassium iodide in water to make 100 ml. This solution should be freshly prepared.

Potassium Iodobismuthate, Dilute TS

Dissolve 0.85 g of bismuth subnitrate in a mixture of 10 ml of glacial acetic acid and 40 ml of water. Before use, add 5 ml of potassium iodide solution (4→10) and 20 ml of glacial acetic acid to 5 ml of the solution mentioned above, dilute with water to 100 ml.

Potassium Iodobismuthate TS

Dissolve 0.85 g of bismuth subnitrate in a mixture of 10 ml of glacial acetic acid and 40 ml of water, and then add 20 ml of potassium iodide solution (4→10) and mix well.

Potassium Iodoplatinate TS

Dissolve 20 mg chloroplatinic in 2 ml of water, add 25 ml of 4% potassium iodide solution, shake to dissolve if a precipitate is produced, then add water to make 50 ml and shake thoroughly.

Potassium Iodoplatinate, Concentrated TS

Dissolve 0.15 g of chloroplatinic acid and 3 g of potassium iodide in water to make 60 ml.

Potassium permanganate TS

Use potassium permanganate (0.02 mol/L) VS directly.

Potassium Sulfate TS

Dissolve 1 g of potassium sulfate in water to make 100 ml.

Resorcinol TS

Dissolve 1 g of resorcinol in hydrochloric acid to make 100 ml.

Semicarbazide Hydrochloride TS

Triturate 2.5 g of semicarbazide hydrochloride with 3.3 g of sodium acetate, transfer the mixture to a conical flask with 30 ml of methanol, allow to stand for 30 minutes at a temperature below 4°C, filter and add methanol to make 100 ml.

Silicotungstic Acid TS

Dissolve 10 g of silicotungstic acid in water to make 100 ml.

Silver Diethyldithiocarbamate TS

To 0.25 g of silver diethyldithiocarbamate add a suitable amount of chloroform and 1.8 ml of triethylamine, dilute with chloroform to 100 ml and dissolve it by stirring. Allow the solution to stand overnight, and then filter with absorbent cotton wool.

Preserve in amber coloured glass bottle and store in a cool place.

Silver Nitrate TS

Use silver nitrate (0.1 mol/L) VS directly.

Sodium Acetate TS

Dissolve 13.6 g of crystalline sodium acetate in water to make 100 ml.

Sodium Acetate-Sodium Hydroxide TS

Dissolve 10.3 g of sodium acetate and 86.5 g of sodium hydroxide in water to make 1000 ml.

Sodium Bicarbonate TS

Dissolve 5 g of sodium bicarbonate in water to make 100 ml.

Sodium Bisulfite TS

Dissolve 10 g of sodium bisulfite in water to make 30 ml. This solution should be freshly prepared.

Sodium Bitartrate TS

Dissolve 1 g of sodium bitartrate in water to make 10 ml. This solution should be freshly prepared.

Sodium Carbonate TS

Dissolve 12.5 g of sodium carbonate monohydrate or 10.5 g of anhydrous sodium carbonate in water to make 100 ml.

Sodium Cobaltinitrite TS

Dissolve 10 g of sodium cobaltinitrite in water to make 50 ml.

and filter.

Sodium Diethyldithiocarbamate TS

Dissolve 0.1 g of sodium diethyldithiocarbamate in 100 ml of water and filter.

Sodium Fluoride TS

Dissolve 0.5 g of sodium fluoride in 100 ml of 0.1 mol/L hydrochloric acid solution.

This solution should be freshly prepared.

Sodium Hydroxide TS

Dissolve 4.3 g of sodium hydroxide in water to make 100 ml.

Sodium Hypobromite TS

Add 5 ml of bromine to a solution of 20 g of sodium hydroxide in 75 ml of water. Dilute with water to 100 ml and mix well.

This solution should be freshly prepared.

Sodium Hypochlorite TS

Prepare a homogeneous suspension by adding 100 ml of water to 20 g of chlorinated lime and add 100 ml of 14% sodium carbonate solution with stirring. Filter with wet filter paper and add a few drops of sodium carbonate TS to 5 ml of the filtrate. If a turbidity is produced, add sufficient 14% sodium carbonate solution to the bulk filtrate until the lime is completely precipitated, filter again, the final filtrate contains not less than 4% of NaClO.

Preserve in amber coloured glass bottle, protected from light.

Sodium Nitrite TS

Dissolve 1 g of sodium nitrite in water to make 100 ml.

Sodium Nitroprusside TS

Dissolve 1 g of sodium nitroprusside in water to make 20 ml.

This solution must be freshly prepared.

Sodium Nitroprusside Acetaldehyde TS

Mix 10 ml of 1% sodium nitroprusside solution with 1 ml of acetaldehyde.

Sodium Periodate TS

Dissolve 1.2 g of sodium periodate in 100 ml of water.

Sodium Sulfite TS

Dissolve 20 g of anhydrous sodium sulfite in 100 ml of water.

This solution should be freshly prepared.

Sodium Sulfide TS

Dissolve 1 g of sodium sulfide in water to make 10 ml.

This solution should be freshly prepared.

Sodium Thiosulfate TS

Use sodium thiosulfate (0.1 mol/L) VS directly.

Stannous Chloride TS

Dissolve 1.5 g of stannous chloride in 10 ml of water and a small amount of hydrochloric acid.

This solution should be freshly prepared.

Sulfanilamide TS

Dissolve 50 mg of sulfanilamide in 10 ml of 2 mol/L hydrochloric acid solution.

Sulfanilic- α -Naphthylamine TS

Dissolve 0.5 g of anhydrous sulfanilic acid in 150 ml of acetic acid. Dissolve 0.1 g of α -naphthylamine hydrochloride in 150 ml of acetic acid. Mix these two solutions.

This solution will show pink colour after standing for a long time, add zinc powder to decolourize it before use.

Sulfuric Acid, dilute, TS

Dilute 57 ml of sulfuric acid with water to 1000 ml.

It contains 9.5%-10.5% of H₂SO₄.

Tannic Acid TS

Dissolve 1 g of tannic acid in 1 ml of alcohol and dilute with

water to 100 ml.

This solution should be freshly prepared.

Tetramethylammonium hydroxide TS

Dilute 1 ml of 10% tetramethylammonium hydroxide solution with dehydrated ethanol to make 10 ml.

Thioacetamide TS

Dissolve 4 g of thioacetamide in water to make 100 ml. Store in refrigerator. Add 1.0 ml of thioacetamide solution to 5.0 ml of a mixture consisting of 15 ml of 1 mol/L sodium hydroxide solution, 5.0 ml of water and 20 ml of glycerin before use, heat for 20 seconds in a water bath, cool and use immediately.

Titanium Sulfate TS

Dissolve 0.1 g of titanium dioxide in 100 ml of sulfuric acid by heating, allow to cool.

***p*-Tosyl-L-Arginine Methyl Ester Hydrochloride TS**

Dissolve 98.5 mg of *p*-tosyl-L-arginine methyl ester hydrochloride in 5 ml of trometamol buffer solution (pH 8.1), add 0.25 ml of indicator solution (mix 0.1% alcoholic methyl red solution with an equal volume of 0.05% alcoholic methylene blue solution) and dilute with water to 25 ml.

Trichloroacetic Acid TS

Dissolve 6 g of trichloroacetic acid in 25 ml of chloroform, add 0.5 ml of 30% hydrogen peroxide solution and mix well.

Trinitrophenol TS

A saturated solution of trinitrophenol in water.

Trinitrophenol Lithium TS

Dissolve 0.25 g of lithium carbonate and 0.5 g of trinitrophenol in 80 ml of boiling water, cool and dilute with water to 100 ml.

Triphenyl Tetrazolium Chloride TS

Dissolve 1 g of triphenyl tetrazolium chloride in dehydrated ethanol to make 200 ml.

Vanadium Pentoxide TS

Dissolve vanadium pentoxide in phosphoric acid with shaking vigorously for 2 hours to produce a saturated solution. Filter with a sinter-glass funnel, dilute 1 volume of filtrate with 3 volume of water and mix well.

Vanillin TS

Dissolve 0.1 g of vanillin in 10 ml of hydrochloric acid.

Xanthidrol-Methanol TS

Dissolve 85% xanthidrol solution in 100 ml of methanol.

Zinc Chloride-Iodine TS

Dissolve 20 g of zinc chloride and 2 g of potassium iodide in 10 ml of water, then saturated with iodine.

Preserve in amber coloured glass bottle.

Zinc Uranyl Acetate TS

Dissolve 10 g of uranyl acetate in 5 ml of glacial acetic acid and 50 ml of water by heating. Dissolve 30 g of zinc acetate in 3 ml of glacial acetic acid and 30 ml of water with gentle heating. Mix the two solutions, cool and filter.

Zirconium Alizarin TS

Dissolve 5 mg of zirconium nitrate in a mixture of 5 ml of water and 1 ml of hydrochloric acid. Dissolve 1 mg of sodium alizarinsulfonate in 5 ml of water. Mix these two solutions.

XV C Test Papers

Ammoniated-Silver Nitrate TP

Immerse a strip of filter paper in ammoniated-silver nitrate TS until thoroughly wetted.

Benzidine-Cupric Acetate TP

To 9 ml of a saturated solution of benzidine acetate add 7 ml of water and 16 ml of 0.3% cupric acetate solution, immerse a strip of filter paper in the mixture until thoroughly wetted. Remove the paper and allow to dry.

Blue Litmus TP

Immerse a strip of filter paper in litmus IS until thoroughly wetted. Remove the paper and allow to dry.

Sensitivity Introduce 0.5 ml of 0.1 mol/L hydrochloric acid in a beaker. Add 100 ml of freshly boiled and cooled water and mix. Drop a strip of blue litmus TP 10-12 mm in width in the solution and stir continuously. The colour of the paper changes within 45 seconds.

Cadmium Acetate TP

Dissolve 3 g of cadmium acetate in 100 ml of ethanol, add ammonia TS until the majority of the precipitate is dissolved. Filter and immerse a strip of filter paper in the filtrate. Remove the paper before use and allow to dry.

Congo Red TP

Immerse a strip of filter paper in congo red IS until thoroughly wetted, remove the paper and allow to dry.

Curcuma TP (Turmeric TP)

Immerse a strip of filter paper in curcuma IS until thoroughly wetted. Lay the paper on a glass plate and dry at 100°C.

Lead Acetate TP

Immerse a strip of filter paper in lead acetate TS until thoroughly wetted. Remove the paper and allow to dry at 100°C.

Mercuric Bromide TP

Immerse a strip of filter paper in alcoholic mercuric bromide TS for 1 hour. Remove the paper and allow to dry in a dark place.

Mercuric Chloride TP

Immerse a strip of filter paper in a saturated solution of mercuric chloride for 1 hour, then remove the strip and allow to dry at 60°C in a dark place.

Mercuric Nitrate TP

To 45 ml of a saturated solution of mercuric nitrate add 1 ml of nitric acid. Immerse a strip of filter paper in the solution until thoroughly wetted. Remove the paper and allow to dry.

Red Litmus TP

Immerse a strip of filter paper in litmus IS, add a small amount of hydrochloric acid until a red colour is obtained. Remove the paper and allow to dry.

Sensitivity Introduce 0.5 ml of 0.1 mol/L sodium hydroxide solution to a beaker, add 100 ml of freshly boiled and cooled water and mix. Drop a strip of red litmus TP 10-12 mm in width in the solution and stir continuously. The colour of the paper changes within 30 seconds.

Starch-Iodide TP

Immerse a strip in 100 ml of freshly prepared starch IS, which contains 0.5 g of potassium iodide, until thoroughly wetted. Remove the paper and allow to dry.

XV D Buffer Solutions

Acetate BS (pH 3.5)

Dissolve 25 g of ammonium acetate in 25 ml of water, add 38 ml of 7 mol/L hydrochloric acid solution. Adopt the potentiometric method to adjust accurately to pH 3.5 with 2 mol/L hydrochloric acid solution or 5 mol/L ammonia solution and dilute with water to 100 ml.

Ammonium Acetate BS (pH 4.5)

Dissolve 7.7 g of ammonium acetate in 50 ml of water. Add 6 ml of glacial acetic acid and dilute with water to 100 ml.

Ammonium Acetate BS (pH 6.0)

Dissolve 100 g of ammonium acetate in 300 ml of water, add 7 ml of glacial acetic acid and mix well.

Ammonium Acetate-Ethanol BS (pH 3.7)

Mix 15.0 ml of 5 mol/L acetic acid solution with 60 ml of ethanol and 20 ml of water, and adjust to pH 3.7 with 10 mol/L ammonium hydroxide solution, dilute with water to 1000 ml.

Ammonia-Ammonium Chloride BS (pH 8.0)

Dissolve 1.07 g of ammonium chloride in water to make 100 ml. Add dilute ammonia solution (1→30) and adjust to pH 8.0.

Ammonia-Ammonium Chloride BS (pH 10.0)

Dissolve 5.4 g of ammonium chloride in 20 ml of water, add 35 ml of concentrated ammonia solution. Dilute with water to 100 ml.

Barbital BS (pH 7.4)

Dissolve 4.42 g of sodium barbital in 400 ml of water, adjust to pH 7.4 with 2 mol/L hydrochloric acid.

Barbital BS (pH 8.6)

Dissolve 5.52 g of barbital and 30.9 g of sodium barbital in water to make 2000 ml.

Barbital-Sodium Chloride BS (pH 7.8)

Dissolve 5.05 g of sodium barbital and 3.7 g of sodium chloride in water, heat to dissolve 0.5 g of gelatin in water, combine the two solution, adjust to pH 7.8 with 0.2 mol/L hydrochloric acid solution, make up to 500 ml with water.

Borate-Potassium Chloride BS (pH 9.0)

Dissolve 3.09 g of boric acid in 500 ml of 0.1 mol/L potassium chloride solution, and add 210 ml of 0.1 mol/L sodium hydroxide solution.

Borax-Calcium Chloride BS (pH 8.0)

Dissolve 0.572 g of borax and 2.94 g of calcium chloride in about 800 ml of water, and adjust to pH 8.0 with about 2.5 ml of 1 mol/L hydrochloric acid solution. Dilute with water to 1000 ml.

Borax-Sodium Carbonate BS (pH 10.8-11.2)

Dissolve 5.30 g of anhydrous sodium carbonate in water to make 1000 ml. Dissolve 1.91 g of borax in water to make 100 ml. Mix 973 ml of sodium carbonate solution with 27 ml of borax solution before use, shake thoroughly.

Citrate BS

Dissolve 4.2 g of citric acid in 40 ml of a solution of sodium hydroxide in 20% 1 mol/L ethanol solution. Dilute with 20% ethanol solution to 100 ml.

Citrate BS (pH 6.2)

Adjust the pH value of 2.1% citric acid solution to 6.2 with 50% sodium hydroxide solution.

Citrate-Disodium Hydrogen Phosphate BS (pH 4.0)

(a) Dissolve 21 g of citric acid or 19.2 g of anhydrous citric acid in water to make 1000 ml, preserve in a refrigerator.
 (b) Dissolve 71.63 g of disodium hydrogen phosphate in water to make 1000 ml.
 To 61.45 ml of solution (a) add 38.55 ml of solution (b) and mix well.

Lithium-Acetate BS (pH 3.0)

Add 800 ml of water to 50 ml of glacial acetic acid and mix. Adjust the pH value to 3.0 with lithium hydroxide, dilute with water to 1000 ml.

Phosphate BS

Dissolve 38.0 g of sodium dihydrogen phosphate and 5.04 g of disodium hydrogen phosphate in water to make 1000 ml.

Phosphate BS (pH 2.0)

(a) Dilute 16.6 ml of phosphoric acid with water to 1000 ml and mix well.
 (b) Dissolve 71.63 g of disodium hydrogen phosphate in water to make 1000 ml.
 To 72.5 ml of solution (a) add 27.5 ml of solution (b) and mix well.

Phosphate BS (pH 2.5)

Dissolve 100 g of potassium dihydrogen phosphate in 800 ml of water, adjust the pH value to 2.5 with hydrochloric acid, make up to 1000 ml with water.

Phosphate BS (pH 5.0)

Adjust the pH value of 0.2 mol/L sodium dihydrogen phosphate solution to 5.0 with sodium hydroxide TS.

Phosphate BS (pH 5.8)

Dissolve 8.34 g of potassium dihydrogen phosphate and 0.87 g of dipotassium hydrogen phosphate in water to make 1000 ml.

Phosphate BS (pH 6.5)

Dissolve 0.68 g of potassium dihydrogen phosphate in 15.2 ml of 0.1 mol/L sodium hydroxide solution, dilute with water to 100 ml.

Phosphate BS (pH 6.6)

Dissolve 1.74 g of sodium dihydrogen phosphate, 2.7 g of disodium hydrogen phosphate and 1.7 g of sodium chloride in water to make 400 ml.

Phosphate-Pancreatin BS (pH 6.8)

(a) Dissolve 6.8 g of potassium dihydrogen phosphate in 500 ml of water and adjust the pH value to 6.8 with 0.1 mol/L sodium hydroxide solution.
 (b) Dissolve 10 g of pancreatin in water.
 Mix the two solutions and dilute with water to 1000 ml.

Phosphate BS (pH 6.8)

Add 118 ml of 0.2 mol/L sodium hydroxide solution to 250 ml of 0.2 mol/L potassium dihydrogen phosphate solution, dilute with water to 1000 ml and shake thoroughly.

Phosphate BS (pH 7.0)

Dissolve 0.68 g of potassium dihydrogen phosphate in 29.1 ml of 0.1 mol/L sodium hydroxide solution and dilute with water to 100 ml.

Phosphate BS (pH 7.2)

Mix 50 ml of 0.2 mol/L potassium dihydrogen phosphate solution with 35 ml of 0.2 mol/L sodium hydroxide solution, dilute with freshly boiled and cooled water to 200 ml and mix well.

Phosphate BS (pH 7.3)

Dissolve 1.9734 g of disodium hydrogen phosphate and 0.2245 g of potassium dihydrogen phosphate in water to make 1000 ml. Adjust the pH value to 7.3.

Phosphate BS (pH 7.4)

Dissolve 1.36 g of potassium dihydrogen phosphate in 79 ml of 0.1 mol/L sodium hydroxide solution, dilute with water to 200 ml.

Phosphate BS (pH 7.6)

Dissolve 27.22 g of potassium dihydrogen phosphate in water to make 1000 ml.
 Mix 50 ml of this solution with 42.4 ml of 0.2 mol/L sodium hydroxide solution, dilute with water to 200 ml.

Phosphate BS (pH 7.8)

(a) Dissolve 35.9 g of disodium hydrogen phosphate in water to make 500 ml.
 (b) Dissolve 2.76 g of sodium dihydrogen phosphate in water to make 100 ml.
 To 91.5 ml of solution (a) add 8.5 ml of solution (b), mix well.

Phosphate BS (pH 7.8-8.0)

Dissolve 5.59 g of dipotassium hydrogen phosphate and 0.41 g of potassium dihydrogen phosphate in water to make 1000 ml.

Phosphate-Triethylamine BS

Mix about 4 ml of phosphoric acid with about 7 ml of triethylamine, dilute with 50% methanol to 1000 ml, adjust the pH value to 3.2 with phosphoric acid.

Phthalate BS (pH 5.6)

Dissolve 10 g of potassium biphthalate in 900 ml of water with stirring. Adjust to pH 5.6 with sodium hydroxide TS (or dilute hydrochloric acid). Dilute with water to 1000 ml and mix well.

Potassium Acetate BS (pH 4.3)

Dissolve 14 g of potassium acetate in 20.5 ml of glacial acetic acid, and dilute with water to 1000 ml.

Sodium Acetate BS (pH 3.6)

Dissolve 5.1 g of sodium acetate in 20 ml of glacial acetic acid, dilute with water to 250 ml.

Sodium Acetate BS (pH 3.7)

Dissolve 20 g of anhydrous sodium acetate in 300 ml of water, add 1 ml of bromophenol blue IS and 60-80 ml of glacial acetic acid until the colour changes from blue to pure green, and then dilute with water to 1000 ml.

Sodium Acetate BS (pH 3.8)

Mix 13 ml of 2 mol/L sodium acetate solution with 87 ml of 2 mol/L acetic acid solution. Add 0.5 ml of cupric sulfate solution which contains 1 mg of Cu per ml.
 Dilute with water to 1000 ml.

Sodium Acetate BS (pH 4.5)

Dissolve 18 g of sodium acetate in 9.8 ml of glacial acetic acid, and dilute with water to 1000 ml.

Sodium Acetate BS (pH 4.6)

Dissolve 5.4 g of sodium acetate in 50 ml of water, adjust to pH 4.6 with glacial acetic acid, dilute with water to 100 ml.

Sodium Acetate BS (pH 6.0)

Dissolve 54.6 g of sodium acetate in 20 ml of 1 mol/L acetic acid solution. Dilute with water to 500 ml.

Sodium Formate BS (pH 3.3)

To 25 ml of 2 mol/L formic acid solution add 1 drop of phenolphthalein IS, neutralize with 2 mol/L sodium hydroxide solution, and then add 75 ml of 2 mol/L formic acid solution. Dilute with water to 200 ml. The pH value of the solution is 3.25-3.30.

Trometamol BS (pH 8.0)

Dissolve 12.14 g of trometamol in 800 ml of water with stirring, dilute with water to 1000 ml. Adjust to pH 8.0 with 6 mol/L hydrochloric acid solution.

Trometamol BS (pH 8.1)

Dissolve 0.294 g of calcium chloride in 40 ml of 0.2 mol/L trometamol solution. Adjust to pH 8.1 with 1 mol/L hydrochloric acid solution, and then dilute with water to 100 ml.

Trometamol BS (pH 9.0)

Dissolve 6.06 g of trometamol, 3.65 g of lysine hydrochloride, 5.8 g of sodium chloride and 0.37 g of disodium edetate in 1000 ml of water, adjust to pH 9.0.

Urotropine BS

Dissolve 75 g of urotropine in water, add 4.2 ml of concentrated ammonia solution, and then dilute with water to 250 ml.

XV E Indicator Solutions

Azo Violet IS

Dissolve 0.1 g of azo violet in 100 ml of dimethylformamide.

Brilliant Green IS

Dissolve 0.5 g of brilliant green in 100 ml of glacial acetic acid.

Colour changes from yellow to green (pH 0.0-2.6).

Bromocresol Green IS

Dissolve 0.1 g of bromocresol green in 2.8 ml of sodium hydroxide solution (0.05 mol/L), and dilute with water to 200 ml.

Colour changes from yellow to blue (pH 3.6-5.2).

Bromocresol Purple IS

Dissolve 0.1 g of bromocresol purple in 20 ml of 0.02 mol/L sodium hydroxide solution, and dilute with water to 100 ml. Colour changes from yellow to violet (pH 5.2-6.8).

Bromophenol Blue IS

Dissolve 0.1 g of bromophenol blue in 3.0 ml of 0.05 mol/L sodium hydroxide solution, and dilute with water to 200 ml. Colour changes from yellow to bluish green (pH 2.8-4.6).

Bromothymol Blue IS

Dissolve 0.1 g of bromothymol blue in 3.2 ml of 0.05 mol/L sodium hydroxide solution, and dilute with water to 200 ml. Colour changes from yellow to blue (pH 6.0-7.6).

Calcein Indicator Mixture

Mix uniformly 0.1 g of calcein with 10 g of potassium chloride by grinding.

Calcon Indicator Mixture

Mix uniformly 0.1 g of calcon with 10 g of anhydrous sodium sulfate by grinding.

Catechol Violet IS

Dissolve 0.1 g of catechol violet in 100 ml of water. Colour changes from yellow to violet and then to purplish-red (pH 6.0-7.0-9.0).

Congo Red IS

Dissolve 0.5 g of congo red in 100 ml of 10% ethanol. Colour changes from blue to red (pH 3.0-5.0).

Cresol Red IS

Dissolve 0.1 g of cresol red in 5.3 ml of 0.05 mol/L sodium hydroxide solution, and dilute with water to 100 ml. Colour changes from yellow to red (pH 7.2-8.8).

m-Cresol Purple IS

Dissolve 0.1 g of m-cresol purple in 10 ml of 0.01 mol/L sodium hydroxide solution, and dilute with water to 100 ml.

Colour changes from yellow to purple (pH 7.5-9.2).

Cresol Red-Thymol blue IS

Mix 1 volume of cresol red IS with 3 volume of a 0.1% thymol blue solution.

Crystal Violet IS

Dissolve 0.5 g of crystal violet in 100 ml of glacial acetic acid.

Curcuma IS (Turmeric IS)

Extract 20 g of curcuma powder with 4 quantities of each of 100 ml of water to remove water soluble matter and dry the residue at 100°C. Macerate with 100 ml of ethanol for a few days and filter.

Dimethyl Yellow IS

Dissolve 0.1 g of dimethyl yellow in 100 ml of ethanol. Colour changes from red to yellow (pH 2.9-4.0).

Dimethyl Yellow-methylene Blue IS

Dissolve 15 mg of dimethyl yellow and 15 mg of methylene blue in 100 ml of chloroform with shake (heat gently if necessary), and filter.

Dimethyl Yellow-solvent blue 19 IS

Dissolve 15 mg of dimethyl yellow and 15 mg of solvent blue 19 in 100 ml of chloroform.

Diphenylcarbazide IS

Dissolve 1 g of diphenylcarbazide in 100 ml of ethanol.

Eriochrome Black T Indicator Mixture

Mix uniformly 0.1 g of eriochrome black T with 10 g of sodium chloride by grinding.

Ethoxychrysoidine IS

Dissolve 0.1 g of ethoxychrysoidine in 100 ml of ethanol. Colour changes from red to yellow (pH 3.5-5.5).

Eosin Sodium IS

Dissolve 0.5 g of eosin sodium in 100 ml of water.

Ferric Ammonium Sulfate IS

Dissolve 8 g of ferric ammonium sulfate in 100 ml of water.

Fluorescein IS

Dissolve 0.1 g of fluorescein in 100 ml of ethanol.

Litmus IS

Add 40 ml of ethanol to 10 g of litmus powder, heat under reflux for 1 hour. Allow to settle and decant off the supernatant liquid. Repeat the operation twice using 30 ml of ethanol each time. Wash the residue with 10 ml of water and decant off the washing liquid. Boil the residue with 50 ml of water, allow to cool and filter. Colour changes from red to blue (pH 4.5-8.0).

Malachite Green IS

Dissolve 0.3 g of malachite green in 100 ml of glacial acetic acid. Colour changes from yellow to green (pH 0.0-2.0); from green to colourless (pH 11.0-13.5).

Metaphthalein IS

Dissolve 1 g of metaphthalein and small amount of ammonia TS in 100 ml of water.

Methyl Orange IS

Dissolve 0.1 g of methyl orange in 100 ml of water. Colour changes from red to yellow (pH 3.2-4.4).

Methyl Orange-Methylene Blue IS

To 20 ml of methyl orange IS add 8 ml of 0.2% solution of methylene blue, and mix well.

Methyl orange-Xylene Cyanol blue FF IS

Dissolve 0.1 g of methyl orange and 0.1 g of xylene cyanol blue FF in 100 ml of ethanol.

Methyl Red IS

Dissolve 0.1 g of methyl red in 7.4 ml of 0.05 mol/L sodium hydroxide solution and dilute with water to 200 ml. Colour changes from red to yellow (pH 4.2-6.3).

Methyl Red-Bromocresol Green IS

To 20 ml of 0.1% alcoholic solution of methyl red add 30 ml of 0.2% ethanol solution of bromocresol green, and mix well.

Methyl Red-Methylene blue IS

To 20 ml of 0.1% alcoholic solution of methyl red add 8 ml of 0.2% solution of methylene blue, and mix well.

Naphtholbenzein IS

Dissolve 0.5 g of α -naphtholbenzein in 100 ml of glacial acetic acid.

Colour changes from yellow to green (pH 8.5-9.8).

Neutral Red IS

Dissolve 0.5 g of neutral red in 100 ml of water and filter. Colour changes from red to yellow (pH 6.8-8.0).

Nile Blue IS

Dissolve 1 g of nile blue in 100 ml of glacial acetic acid. Colour changes from blue to red (pH 10.1-11.1).

p-Nitrophenol IS

Dissolve 0.25 g of p-nitrophenol in 100 ml of water.

Orange IV IS

Dissolve 0.5 g of orange IV in 100 ml of glacial acetic acid. Colour changes from red to yellow (pH 1.4-3.2).

o-Phenanthroline IS

Dissolve 0.5 g of ferrous sulfate in 100 ml of water, add 2 drops of sulfuric acid and 0.5 g of o-phenanthroline. Shake thoroughly.

This solution should be freshly prepared.

Phenol Red IS

Dissolve 100 mg phenol red in 100 ml of ethanol (Filter if necessary).

Phenol sulfonphthalein IS

Dissolve 0.1 g of phenol sulfonphthalein in 5.7 ml of 0.05 mol/L sodium hydroxide solution, and dilute with water to 200 ml.

Colour changes from yellow to red (pH 6.8-8.4).

Phenolphthalein IS

Dissolve 1 g of phenolphthalein in 100 ml of ethanol. Colour changes from colourless to red (pH 8.3-10.0).

Phthalein purple IS

Adjust to pH of 10 ml of water to 11 with ammonia solution, and then add 10 mg of phthalein purple and dissolve.

Potassium Chromate IS

Dissolve 10 g of potassium chromate in 100 ml of water.

Quinaldine Red IS

Dissolve 0.1 g of quinaldine red in 100 ml of methanol. Colour changes from colourless to red (pH 1.4-3.2).

Quinaldine Red-Methylene Blue IS

Dissolve 0.3 g of quinaldine red and 0.1 g of methylene blue in 100 ml of anhydrous methanol.

Sodium Alizarinsulfonate IS

Dissolve 0.1 g of sodium alizarinsulfonate in 100 ml of water.

Colour changes from yellow to purple (pH 3.7-5.2).

Solvent Blue 19 IS

Dissolve 0.5 g of solvent blue 19 in 100 ml of glacial acetic acid.

Starch IS

Add 5 ml of water to 0.5 g of soluble starch and mix well,

then pour the suspension slowly into 100 ml of boiling water with stirring. Boil for 2 minutes, cool and decant the supernatant liquid.

This solution should be freshly prepared.

Starch Iodide IS

Dissolve 0.2 g of potassium iodide in 100 ml of freshly prepared starch IS.

Sudan IV IS

Dissolve 0.5 g of sudan IV in 100 ml of chloroform.

Tetrabromophenolphthalein Potassium Ethyl Ester IS

Dissolve 0.1 g of tetrabromophenolphthalein potassium ethyl ester in 100 ml of glacial acetic acid.

Thymol Blue IS

Dissolve 0.1 g of thymol blue in 4.3 ml of 0.05 mol/L sodium hydroxide solution, and dilute with water to 200 ml.

Colour changes from red to yellow (pH 1.2-2.8); from yellow to bluish-violet (pH 8.0-9.6).

Thymolphthalein IS

Dissolve 0.1 g of thymolphthalein in 100 ml of ethanol.

Colour changes from colourless to blue (pH 9.3-10.5).

Xylenol Orange IS

Dissolve 0.2 g of xylenol orange in 100 ml of water.

Zinc-Starch Iodide IS

Mix 100 ml of water, 5 ml of potassium iodide solution (3→20) with 10 ml of zinc chloride solution (1→5), boil and add starch suspension (to 5 g of soluble starch add 30 ml of water and mix well) with stirring, and continue to boil for 2 minutes, allow to cool.

Preserve in a well-closed bottle, stored in a cool place.

XV F Volumetric Solutions

Ammonium Ferrous Sulfate (0.1 mol/L) VS

[$\text{Fe}(\text{NH}_4)_2(\text{SO}_4)_2 \cdot 6\text{H}_2\text{O}$ 392.13] 39.21 g→1000 ml
Preparation Dissolve 40 g of ammonium ferrous sulfate in a previously cooled mixture of 40 ml of sulfuric acid and 200 ml of water, make up to 1000 ml with water and mix well.

Standardization To 25 ml of ammonium ferrous sulfate solution, accurately measured, add two drops of o-phenanthroline IS and titrate with ceric sulfate (0.1 mol/L) VS until the colour turns from pale red to pale green. Calculate the concentration of ammonium ferrous sulfate VS according to the volume consumed.

This solution should be standardized before use.

Ammonium Thiocyanate (0.1 mol/L) VS

[NH_4SCN 76.12] 7.612 g→1000 ml
Preparation Dissolve 8.0 g of ammonium thiocyanate in water to make 1000 ml, and mix well.

Standardization To 25 ml of silver nitrate (0.1 mol/L) VS, accurately measured, add 50 ml of water, 2 ml of nitric acid and 2 ml of ferric ammonium sulfate IS; titrate with ammonium thiocyanate solution to the appearance of pale reddish-brown colour which persists on shake vigorously. Calculate the concentration of the ammonium thiocyanate VS according to the volume consumed. Sodium thiocyanate (0.1 mol/L) VS or potassium thiocyanate (0.1 mol/L) VS can be used in place of the Ammonium Thiocyanate (0.1 mol/L) VS.

Barium Perchlorate (0.05 mol/L) VS

[$\text{Ba}(\text{ClO}_4)_2 \cdot 3\text{H}_2\text{O}$ 390.32] 19.52 g→1000 ml
Preparation To 15.8 g of barium hydroxide add 75 ml of water and 7.5 ml of perchloric acid, adjust to pH 3.0 with

perchloric acid and filter if necessary. Add 150 ml of ethanol and dilute to 250 ml with water. Make up to 1000 ml with acetate buffer solution (dissolve 10 g of anhydrous sodium acetate in 300 ml of water, adjust to pH 3.7 with glacial acetic acid and make up to 1000 ml with water).

Standardization To 5 ml of sulfuric acid (0.05 mol/L) VS, accurately measured, add 5 ml of water, 60 ml of ethanol, 0.5 ml of 0.1% alizarin red solution as the indicator solution and 50 ml of acetate buffer solution described above. Titrate with barium perchlorate (0.05 mol/L) VS until the colour changes to orange red and calculate the concentration of barium perchlorate VS according to the volume consumed.

Benzalkonium Chloride (0.01 mol/L) VS

Preparation Dissolve 3.8 g of benzalkonium chloride in water, add 10 ml of sodium acetate BS (pH 3.7) and dilute with water to 1000 ml. Mix well.

Standardization Dissolve about 0.18 g of analytical pure potassium chloride, accurately weighed, previously dried for 1 hour at 150°C, in sodium acetate BS (pH 3.7) to make 250 ml. Mix well. Transfer accurately 20 ml to a 50 ml volumetric flask, add accurately 25 ml of sodium tetraphenylborate (0.02 mol/L) VS, dilute with water to 50 ml and mix well. Filter with dry filter paper, discard the initial filtrate. Transfer accurately 25 ml of the successive filtrate to a 150 ml conical flask, add 0.5 ml of bromophenol blue IS. Titrate with benzalkonium chloride (0.01 mol/L) VS to a blue colour. Each ml of benzalkonium chloride (0.01 mol/L) VS is equivalent to 0.7445 mg of potassium chloride.

Bromine (0.05 mol/L) VS

[Br₂ 159.81] 7.990 g→1000 ml
Preparation Dissolve 3.0 g of potassium bromate and 15 g of potassium bromide in water to make 1000 ml, and mix well.

Standardization To 25 ml of bromine VS, accurately measured, in an iodine flask add 100 ml of water and 2.0 g of potassium iodide, shake thoroughly. Add 5 ml of hydrochloric acid, stopper the flask and allow to stand in the dark for 5 minutes. Titrate with sodium thiosulfate (0.1 mol/L) VS, add 2 ml of starch IS towards the end point of titration, continue to titrate until the blue colour disappears. Calculate the concentration of the bromine VS according to the volume consumed.

When the room temperature is above 25°C, the reacting liquid must be cooled to about 20°C. Bromine VS should be standardized immediately before use.

If bromine (0.005 mol/L) VS is needed, dilute bromine (0.05 mol/L) VS with water and standardize accordingly.

Storage Preserve in well-closed amber coloured glass bottle, stored at a cool place.

Ceric Sulfate (0.1 mol/L) VS

[Ce (SO₄)₂ · 4H₂O 404.30] 40.43 g→1000 ml

Preparation Dissolve 42 g of ceric sulfate (or 70 g of ceric ammonium sulfate) in 500 ml of water and 28 ml of sulfuric acid by heat, cool, add water to make 1000 ml.

Standardization Dissolve about 0.15 g, accurately weighed, of arsenic trioxide, previously dried to constant weight at 105°C, in 10 ml of sodium hydroxide (1 mol/L) VS, by warm, add 50 ml of water, 25 ml of hydrochloric acid, 5 ml of iodine monochloride TS and 2 drops of α -phenanthroline IS, then titrate with ceric sulfate (0.1 mol/L) VS towards the end point of titration, heat it to 50°C and continue to titrate until the colour turns from pale red to pale green. Each ml of ceric sulfate (0.1 mol/L) VS is equivalent to 4.946 mg of arsenic trioxide.

If ceric sulfate (0.01 mol/L) VS is needed, dilute ceric sulfate (0.1 mol/L) VS with water containing 2.8%

(ml/ml) of sulfuric acid.

Disodium Edetate (0.05 mol/L) VS

[C₁₀H₁₄N₂Na₂O₈ · 2H₂O 372.24] 18.61 g→1000 ml

Preparation Dissolve 19 g of disodium edetate in water to make 1000 ml and mix well.

Standardization Dissolve 0.12 g of zinc oxide primary standard, previously ignited to constant weight at about 800°C and accurately weighed, in 3 ml of dilute hydrochloric acid. Add 25 ml of water and 1 drop of 0.025% ethanolic solution of methyl red, and add ammonia TS until a slight yellow colour is obtained. Add 25 ml of water, 10 ml of ammonium chloride BS (pH 10.0) and a small amount of eriochrome black T indicator. Titrate with disodium edetate VS until the colour changes from violet to pure blue. Perform a blank determination and make any necessary correction. Each ml of disodium edetate (0.05 mol/L) VS is equivalent to 4.069 mg of ZnO.

Storage Preserve in a glass stoppered bottle, avoid to contact with rubber.

Ethanolic Potassium Hydroxide (0.5 mol/L) VS

[KOH 56.11] 28.06 g→1000 ml

Preparation Dissolve 35 g of potassium hydroxide in a conical flask, in aldehyde-free ethanol to make 1000 ml, well close with a rubber stopper and allow to settle for 24 hours. Decant the supernatant liquid immediately and transfer into a rubber stoppered amber coloured glass bottle.

Standardization Dilute 25 ml of hydrochloric acid (0.5 mol/L) VS with 50 ml of water, add a few drops of phenolphthalein IS. Titrate with ethanolic potassium hydroxide (0.5 mol/L) VS. Calculate the concentration of the ethanolic potassium hydroxide VS according to the volume consumed.

This solution should be standardized before use.

Storage Preserve in well closed a rubber stoppered amber coloured glass bottle.

Hydrochloric Acid (1, 0.5, 0.2 or 0.1 mol/L) VS

[HCl 36.46] 36.46 g→1000 ml

18.23 g→1000 ml

7.292 g→1000 ml

3.646 g→1000 ml

Preparation (1) Hydrochloric Acid (1 mol/L) VS Dilute 90 ml of hydrochloric acid with water to 1000 ml and mix well.

(2) Hydrochloric Acid (0.5, 0.2 or 0.1 mol/L) VS Dilute 45 ml, 18 ml or 9.0 ml of hydrochloric acid respectively with water to 1000 ml and mix well.

Standardization (1) Hydrochloric Acid (1 mol/L) VS Weigh accurately about 1.5 g of anhydrous sodium carbonate primary standard, previously dried to constant weight at 270-300°C, and dissolve it in 50 ml of water. Add 10 drops of methyl red-bromocresol green IS, titrate with hydrochloric acid (1 mol/L) VS until the colour turns from green to purplish-red. Boil for 2 minutes, cool to room temperature and continue the titration until the colour turns from green to dark purple. Each ml of hydrochloric acid (1 mol/L) VS is equivalent to 53.00 mg of anhydrous sodium carbonate.

(2) Hydrochloric Acid (0.5 mol/L) VS Weigh accurately about 0.8 g of anhydrous sodium carbonate primary standard titrate as directed above. Each ml of hydrochloric acid (0.5 mol/L) VS is equivalent to 26.50 mg of anhydrous sodium carbonate.

(3) Hydrochloric Acid (0.2 mol/L) VS Weigh accurately about 0.3 g of anhydrous sodium carbonate primary standard titrate as directed above. Each ml of hydrochloric acid (0.2 mol/L) VS is equivalent to 10.60 mg of anhydrous sodium carbonate.

(4) Hydrochloric Acid (0.1 mol/L) VS Weigh accurately about 0.15 g of anhydrous sodium carbonate primary

standard titrate as directed above. Each ml of hydrochloric acid (0.1 mol/L) VS is equivalent to 5.30 mg of anhydrous sodium carbonate.

If hydrochloric acid (0.05, 0.02 or 0.01 mol/L) VS is needed, dilute hydrochloric acid (1 or 0.1 mol/L) VS with water, standardize if necessary.

Iodine (0.05 mol/L) VS

[I₂ 253.81] 12.69 g→1000 ml

Preparation Dissolve 13.0 g of iodine and 36 g of potassium iodine in 50 ml of water, add 3 drops of hydrochloric acid and dilute with water to 1000 ml, mix well and filter with a sintered glass filter.

Standardization Weigh accurately about 0.15 g of arsenic trioxide primary standard, previously dried to constant weight at 105°C, and dissolve it in 10 ml of sodium hydroxide (1 mol/L) VS by heating gently. Add 20 ml of water, 1 drop of methyl orange IS, and add sulfuric acid (0.5 mol/L) VS until the colour turns from yellow to pink. Then add 2 g of sodium bicarbonate, 50 ml of water and 2 ml of starch IS, titrate with iodine VS until the solution is bluish-violet in colour. Each ml of iodine (0.05 mol/L) VS is equivalent to 4.946 mg of arsenic trioxide.

If iodine (0.025 mol/L) VS is needed, dilute the iodine (0.05 mol/L) VS with water.

Storage Preserve in well-closed, amber glass bottle, store at a cool place.

Lithium Methoxide (0.1 mol/L) VS

[CH₃OLi 37.97] 3.797 g→1000 ml

Comply with the preparation, the standardization and the storage described under sodium methoxide (0.1 mol/L) VS, use 0.694 g of freshly cut metallic lithium.

Mercuric Nitrate (0.02 mol/L or 0.05 mol/L) VS

[Hg(NO₃)₂ · H₂O 342.62] 6.85 g→1000 ml

17.13 g→1000 ml

Preparation (1) Mercuric Nitrate (0.02 mol/L) VS Dissolve 6.85 g of mercuric nitrate in 20 ml of 1 mol/L nitric acid solution, make up to 1000 ml with water and mix well.

(2) Mercuric Nitrate (0.05 mol/L) VS Dissolve 17.2 g of mercuric nitrate in 400 ml of water and 5 ml of nitric acid, filter, dilute with water to 1000 ml and mix well.

Standardization (1) Mercuric Nitrate (0.02 mol/L) VS Dissolve about 15 mg of sodium chloride primary standard, weigh accurately, previously dried to constant weight at 110°C, in 50 ml of water, carry out the method for potentiometric titration (Appendix VII A), titrate with mercuric nitrate (0.02 mol/L) VS with stirring, using platinum electrode as an indicator electrode and mercury-mercurous sulfate as a reference electrode. Each ml of mercuric nitrate (0.02 mol/L) VS is equivalent to 2.338 mg of sodium chloride.

(2) Mercuric Nitrate (0.05 mol/L) VS Weigh accurately about 0.15 g of sodium chloride primary standard previously dried to constant weight at 110°C, and dissolve it in 100 ml of water, add 1 ml of diphenylcarbazide IS and titrate with mercuric nitrate VS, shake vigorously until a pale rose violet colour appears. Each ml of mercuric nitrate (0.05 mol/L) VS is equivalent to 5.844 mg of sodium chloride.

Methanolic Potassium Hydroxide (0.1 mol/L) VS

[KOH 56.11] 5.611 g→1000 ml

Preparation Dissolve 6.8 g of potassium hydroxide in 4 ml of water, add methanol to 1000 ml, well close with a rubber stopper and allow to settle 24 hours. Decant the supernatant liquid immediately and transfer into a rubber stoppered amber coloured glass bottle.

Standardization Comply with standardization described under ethanolic potassium hydroxide (0.5 mol/L) VS.

Storage Preserve in well closed a rubber stoppered amber coloured glass bottle.

Oxalic Acid (0.05 mol/L) VS

[C₂H₂O₄ · 2H₂O 126.07] 6.304 g→1000 ml

Preparation Dissolve 6.4 g of oxalic acid in water to make 1000 ml and shake thoroughly.

Standardization Add 200 ml of water and 10 ml of sulfuric acid to 25 ml of oxalic acid VS, accurately measured. Titrate with potassium permanganate (0.02 mol/L) VS towards the end point of titration, heat the solution to 65°C and continue the titration until the pale red colour persists for 30 seconds. The temperature of the solution should not be lower than 55°C at the end of titration. Calculate the concentration of oxalic acid VS according to the volume consumed.

If oxalic acid (0.25 mol/L) VS is needed, weigh about 32 g of oxalic acid, prepare and standardize as directed above but titrate with potassium permanganate (0.1 mol/L) VS.

Storage Preserve in well-closed stoppered amber coloured glass bottle.

Perchloric Acid (0.1 mol/L) VS

[HClO₄ 100.46] 10.05 g→1000 ml

Preparation To 750 ml of anhydrous glacial acetic acid add an amount of acetic anhydride equivalent to 5.22 ml per g of water present, add 8.5 ml of perchloric acid (70%-72%) and mix well. Add 23 ml of acetic anhydride dropwise with shake, cool and dilute with anhydrous glacial acetic acid to 1000 ml, mix well and allow to stand for 24 hours. If the reactant is susceptible to acetylation, the water content of perchloric acid VS should be determined (Appendix VIII M, method 1), and adjusted to 0.01%-0.2% by the addition of water or acetic anhydride.

Standardization Weigh accurately about 0.16 g of potassium biphthalate primary standard, previously dried to constant weight at 105°C, and dissolve in 20 ml of anhydrous glacial acetic acid. Add 1 drop of crystal violet IS and titrate slowly with perchloric acid (0.1 mol/L) VS to a blue end point. Perform a blank determination and make any necessary correction.

Each ml of perchloric acid (0.1 mol/L) VS is equivalent to 20.42 mg of potassium biphthalate.

If perchloric acid (0.05 or 0.02 mol/L) VS is needed, dilute perchloric acid (0.1 mol/L) VS with anhydrous glacial acetic acid and standardize, if necessary.

Perchloric Acid in dioxane (0.1 mol/L) VS Dissolve 8.5 ml of perchloric acid (70%-72%) in 100 ml of isopropanol and dilute with dioxane to 1000 ml.

Weigh accurately about 0.16 g of potassium biphthalate primary standard, previously dried to constant weight at 105°C, and dissolve it in 25 ml of propylene glycol and 5 ml of isopropanol by warming. Cool, add 30 ml of dioxane and a few drops of methyl orange-xylene cyanol blue IS, titrate with perchloric acid in dioxane VS until the colour turns from green to bluish-grey. Perform a blank determination and make any necessary correction.

Storage Preserve in well-closed amber coloured glass bottle.

Potassium Bromate (0.01667 mol/L) VS

[KBrO₃ 167.00] 2.784 g→1000 ml

Preparation Dissolve 2.8 g of potassium bromate in water to make 1000 ml and mix well.

Standardization To 25 ml of potassium bromate VS, accurately measured, in an iodine flask add 2.0 g of potassium iodide and 5 ml of dilute sulfuric acid, stopper the flask and mix well. Allow to stand in the dark for 5 minutes, dilute with 100 ml of water, titrate with sodium thiosulfate (0.1 mol/L) VS towards the end point of titration, add 2 ml of starch IS, continue to titrate until the blue colour disappears. Calculate the concentration of the potassium bromate VS according to the volume consumed.

If the room temperature is above 25°C, the reacting liquid and the water of dilution must be cooled to about 20°C.

Potassium Dichromate (0.01667 mol/L) VS

[K₂Cr₂O₇ 294.18] 4.903 g→1000 ml

Preparation Weigh accurately about 4.903 g of potassium dichromate primary standard, previously dried to constant weight at 120°C, and dissolve in water to make 1000 ml and mix well.

Potassium Iodate (0.05 or 0.01667 mol/L) VS

[KIO₃ 214.00] 10.700 g→1000 ml

Preparation Potassium Iodate (0.05 mol/L) VS Weigh accurately 10.700 g of potassium iodate primary standard, previously dried to constant weight at 105°C, and dissolve it in water to make 1000 ml, mix well.

Potassium Iodate (0.01667 mol/L) VS Weigh accurately 3.5667 g of potassium iodate primary standard, previously dried to constant weight at 105°C, and dissolve it in water to make 1000 ml, mix well.

Potassium Permanganate (0.02 mol/L) VS

[KMnO₄ 158.03] 3.161 g→1000 ml

Preparation Boil about 3.2 g of potassium permanganate with 1000 ml of water for 15 minutes, allow to stand in a well closed vessel for 2 days, filter with a sintered glass filter and mix well.

Standardization Weigh accurately about 0.2 g of sodium oxalate primary standard, previously dried to constant weight at 105°C, and dissolve it in 250 ml of freshly boiled and cooled water and 10 ml of sulfuric acid with stirring. Add quickly from a burette about 25 ml of potassium permanganate (0.02 mol/L) VS with shaking to avoid the production of precipitate, after the fading of its colour, heat the solution to 65°C and continue to titrate until the red colour persists for 30 seconds. The temperature of the solution should not be lower than 55°C at the end of titration. Each ml of potassium permanganate (0.02 mol/L) VS is equivalent to 6.70 mg of sodium oxalate.

If potassium permanganate (0.002 mol/L) VS is needed, dilute potassium permanganate (0.02 mol/L) VS with water, boil and cool. Filter and standardize, if necessary.

Storage Preserve in well-closed amber coloured glass bottle.

Silver Nitrate (0.1 mol/L) VS

[AgNO₃ 169.87] 16.99 g→1000 ml

Preparation Dissolve 17.5 g of silver nitrate in water to make 1000 ml and mix well.

Standardization Weigh accurately about 0.2 g of sodium chloride primary standard, previously dried to constant weight at 110°C, and dissolve it in 50 ml of water. Add 5 ml of dextrin solution (1→50), 0.1 g of calcium carbonate and 8 drops of fluorescein IS, titrate with silver nitrate (0.1 mol/L) VS until the colour of the opalescent liquid turns from yellowish-green to red. Each ml of silver nitrate (0.1 mol/L) VS is equivalent to 5.844 mg of sodium chloride.

If silver nitrate (0.01 mol/L) VS is needed, dilute silver nitrate (0.1 mol/L) VS with water immediately before use.

Storage Preserve in a well-closed amber coloured glass bottle.

Sodium Acetate (0.1 mol/L) VS

[C₂H₃NaO₂ 82.04] 8.204 g→1000 ml

Preparation Dissolve 5.3 g of anhydrous sodium carbonate in 100 ml of anhydrous glacial acetic acid (5.22 ml of acetic anhydride per g of water) with stirring, add anhydrous glacial acetic acid to 1000 ml and mix well.

Standardization To 15 ml of perchloric acid (0.1 mol/L) VS, accurately measured add a few drops of crystal violet

IS, titrate with sodium acetate (0.1 mol/L) VS until the colour turns to green. Calculate the concentration of sodium acetate VS according to the volume consumed.

Sodium Hydroxide (1, 0.5 or 0.1 mol/L) VS

[NaOH 40.00] 40.00 g→1000 ml

20.00 g→1000 ml

4.000 g→1000 ml

Preparation Shake sodium hydroxide with water to make a saturated solution, cool, transfer to a polyvinyl plastic bottle and allow to stand for several days.

Dilute 56, 28 or 5.6 ml respectively of the saturated and clarified sodium hydroxide solution with freshly boiled and cooled water to 1000 ml, and mix well.

Standardization (1) Sodium Hydroxide (1 mol/L) VS Weigh accurately about 6 g of potassium biphthalate primary standard, previously dried to constant weight at 105°C, add 50 ml of freshly boiled and cooled water and shake thoroughly. Add 2 drops of phenolphthalein IS and titrate with sodium hydroxide (1 mol/L) VS to a pink end point. Potassium biphthalate should have been completely dissolved towards the end point of titration.

Each ml of sodium hydroxide (1 mol/L) VS is equivalent to 204.2 mg of potassium biphthalate.

(2) Sodium Hydroxide (0.5 mol/L) VS Weigh accurately about 3 g of potassium biphthalate primary standard, previously dried to constant weight at 105°C. Standardize as directed above. Each ml of sodium hydroxide (0.5 mol/L) VS is equivalent to 102.1 mg of potassium biphthalate.

(3) Sodium Hydroxide (0.1 mol/L) VS Weigh accurately about 0.6 g of potassium biphthalate primary standard, previously dried to constant weight at 105°C. Standardize as directed above. Each ml of sodium hydroxide (0.1 mol/L) VS is equivalent to 20.42 mg of potassium biphthalate.

If sodium hydroxide (0.05, 0.02 or 0.01 mol/L) VS is needed, dilute sodium hydroxide (0.1 mol/L) VS with freshly boiled and cooled water. Standardize against hydrochloric acid (0.05, 0.02 or 0.01 mol/L) VS, if necessary.

Storage Preserve in a tightly closed polyvinyl plastic bottle, insert 2 glass tubes through the stopper, connect one of the tubes to a soda lime tube, use the other tube for the outlet of the volumetric solution.

Sodium Methoxide (0.1 mol/L) VS

[CH₃ONa 54.02] 5.402 g→1000 ml

Preparation Place 150 ml of dehydrated methanol (it contains water less than 0.2%) in a vessel cooled with ice water, add 2.5 g of freshly cut metallic sodium in portions, add dehydrated benzene (it contains water less than 0.02%) to make 1000 ml and mix well.

Standardization Weigh accurately about 0.4 g of benzoic acid primary standard, previously dried to constant weight in a vacuum desiccator over phosphorus pentoxide, and dissolve it in 15 ml of dehydrated methanol. Add 5 ml of dehydrated benzene and 1 drop of a 1% solution of thymol blue in dehydrated methanol, titrate with sodium methoxide VS to a blue end point. Perform a blank determination and make any necessary correction.

Each ml of sodium methoxide (0.1 mol/L) VS is equivalent to 12.21 mg of benzoic acid.

Sodium methoxide VS must be standardized immediately before use, protected from carbon dioxide and avoid volatilization of solvent.

Storage Preserve in a well-closed container of a titrating assembly, protected from carbon dioxide and moisture.

Sodium Nitrite (0.1 mol/L) VS

[NaNO₂ 69.00] 6.900 g→1000 ml

Preparation Dissolve 7.2 g of sodium nitrite and 0.10 g of anhydrous sodium carbonate in water to make 1000 ml and mix well.

Standardization Weigh accurately about 0.5 g of sulfanilic acid primary standard, previously dried to constant weight at 120°C, and dissolve it in 30 ml of water and 3 ml of concentrated ammonia TS. Add 20 ml of hydrochloric acid solution (1→2) with stirring, plunge the burette into the solution so that about 2/3 of the tip is under the liquid surface, titrate with sodium nitrite VS quickly with stirring at a temperature below 30°C. Withdraw the burette tip towards the end point of titration, rinse it with water and add the washings to the solution, continue the titration slowly, adopt the dead-stop method for end point determination. Each ml of sodium nitrite (0.1 mol/L) VS is equivalent to 17.32 mg of sulfanilic acid.

When sodium nitrite (0.05 mol/L) VS is needed, dilute sodium nitrite (0.1 mol/L) VS with water and standardize, if necessary.

Storage Preserve in well-closed amber coloured glass bottle.

Sodium Tetraphenylborate (0.02 mol/L) VS

$[(C_6H_5)_4BNa]$ 342.22] 6.845 g→1000 ml

Preparation Dissolve 7.0 g of sodium tetraphenylborate in 50 ml of water with shake. Add freshly prepared aluminum hydroxide gel (dissolve 1.0 g of aluminum chloride in 25 ml of water, add sodium hydroxide TS dropwise with stirring until the pH is 8-9), 16.6 g of sodium chloride and stir thoroughly. Add 250 ml of water and shake for 15 minutes, allow to stand for 10 minutes and filter. Add sodium hydroxide TS dropwise to the filtrate until the pH is 8-9, and then dilute with water to 1000 ml, mix well.

Standardization To 10 ml of sodium tetraphenylborate VS add 10 ml of sodium acetate BS (pH 3.7) and 0.5 ml of bromophenol blue IS, and then titrate with benzalkonium chloride (0.01 mol/L) VS until the colour changes to blue. Perform a blank determination and make any necessary correction. Calculate the concentration of sodium tetraphenylborate (0.02 mol/L) VS according to the volume consumed.

This solution should be standardized before use.

Dilute this solution with water before use, if sodium tetraphenylborate (0.01 mol/L) VS is needed, and standardize, if necessary.

Storage Preserve in well-closed amber coloured glass bottle.

Sodium Thiosulfate (0.1 mol/L) VS

$[Na_2S_2O_3 \cdot 5H_2O]$ 248.19] 24.82 g→1000 ml

Preparation Dissolve 26 g of sodium thiosulfate and 0.20 g of anhydrous sodium carbonate in freshly boiled and cooled water to make 1000 ml, shake thoroughly, allow to stand for 1 month and filter.

Standardization Weigh accurately about 0.15 g of potassium dichromate primary standard, previously dried to constant weight at 120°C, and dissolve it in 50 ml of water in an iodine flask. Add 2.0 g of potassium iodide and dissolve with gentle shake, add 40 ml of dilute sulfuric acid. Stopper the flask and shake thoroughly, allow to stand in the dark for 10 minutes, Dilute with 250 ml of water and titrate with sodium thiosulfate (0.1 mol/L) VS until the end point is nearly reached, add 3 ml of starch IS and continue to titrate until the colour turns from blue to brilliant green.

Perform a blank determination and make any necessary correction. Each ml of sodium thiosulfate (0.1 mol/L) VS is equivalent to 4.903 mg of potassium dichromate. When the room temperature is above 25°C, the reacting liquid and water of dilution must be cooled to about 20°C.

If sodium thiosulfate (0.01 or 0.005 mol/L) VS is needed, dilute sodium thiosulfate (0.1 mol/L) VS with freshly boiled and cooled water immediately before use.

Sulfuric Acid (0.5, 0.25, 0.1 or 0.05 mol/L) VS

$[H_2SO_4]$ 98.08] 49.04 g→1000 ml

24.52 g→1000 ml

9.81 g→1000 ml

4.904 g→1000 ml

Preparation Sulfuric acid (0.5 mol/L) VS Add slowly 30 ml of sulfuric acid to water with stirring, cool to room temperature, dilute with water to 1000 ml, mix well.

Sulfuric acid (0.25, 0.1 or 0.05 mol/L) VS Add slowly 15 ml, 6.0 ml or 3.0 ml of sulfuric acid to water with stirring, dilute with water to 1000 ml, mix well.

Standardization Standardize as described under hydrochloric acid (1, 0.5, 0.2 or 0.1 mol/L) VS.

If sulfuric acid (0.01 mol/L) VS is needed, dilute sulfuric acid (0.5, 0.1 or 0.05 mol/L) VS with water and standardize, if necessary.

Tetrabutylammonium Hydroxide (0.1 mol/L) VS

$[(C_4H_9)_4NOH]$ 259.48] 25.95 g→1000 ml

Preparation Dissolve 40 g of tetrabutylammonium iodide in 90 ml of dehydrated methanol in a stoppered glass conical flask. Place in an ice bath, add 20 g of finely powdered silver oxide, stopper the flask and shake vigorously for 60 minutes. Centrifuge a few ml and test the supernatant liquid for iodide. If the test is positive, add an additional 2 g of silver oxide to the above mixture and shake vigorously for 30 minutes. When all of the iodide has reacted, filter through a sintered glass funnel, rinse the flask and the funnel with three portions of 50 ml of dehydrated toluene, add the rinsings to the filtrate. Dilute with a mixture of dehydrated toluene and dehydrated methanol (3 : 1) to 1000 ml and mix well. Flush the solution for 10 minutes with dry nitrogen which is free from carbon dioxide. If the solution is not clear, add a few ml of dehydrated methanol.

Standardization Weigh accurately about 90 mg of benzoic acid primary standard, previously dried to constant weight in a vacuum desiccator over phosphorous pentoxide, and dissolve in 10 ml of dimethylformamide. Add 3 drops of a 0.3% solution of thymol blue in dehydrated methanol, and titrate to a blue end point with tetrabutylammonium hydroxide VS (adopt potentiometric method to indicate the end point). Perform a blank determination and make any necessary correction. Each ml of tetrabutylammonium hydroxide (0.1 mol/L) VS is equivalent to 12.21 mg of benzoic acid.

Storage Preserve in well-closed container, keep away from the carbon dioxide and moisture in air.

Zinc (0.05 mol/L) VS

$[Zn]$ 65.39] 3.270 g→1000 ml

Preparation Dissolve 15 g of zinc sulfate (equivalent to 3.3 g of Zn) in 10 ml of dilute hydrochloric acid and sufficient water to make 1000 ml, mix well.

Standardization To 25 ml of zinc (0.05 mol/L) VS, accurately measured, add 1 drop of a 0.025% solution of methyl red in ethanol, add ammonia TS dropwise until a slight yellow colour appears. Add 25 ml of water, 10 ml of ammonium chloride BS (pH 10.0) and a small amount of eriochrome black T indicator, titrate with disodium edetate (0.05 mol/L) VS until the colour changes from purple to pure blue.

Perform a blank determination and make any necessary correction. Calculate the concentration of zinc VS according to the volume consumed.

XV G Reference Standards

Acetaminophenol
Acetanilide

Acetazolamide	Casein
Acetylspiramycin	Cefadroxil
Aciclovir	Cefaclor
Adipiodone	Cefaclor δ -3-Isomer
Adrenaline	Cefalexin
β -Alanine	Cefalotin
Alarelin Acetate	Cefathiamidine
Alfacalcidol	Cefazolin
Alprostadil	Cefdinir
Almitrine Bismesylate	Cefoperazone
Altretamine	Cefoperazone Impurity A
Amikacin Impurity A	Cefoperazone S-isomer
Aminobenzoic Acid	Cefotaxime
(+)- α -Amino-butanol	Cefradine
2-Amino-2'-chloro-5-nitrodiphenyl Ketone	Ceftazole
Amiodarone Hydrochloride	Ceftriaxone
Amiloride Hydrochloride	Cefuroxime
Aminoglutethimide	Cefuroxime Axetil
Amoxicillin	Chlorambucil
Amphotericin B	Chloramphenicol
Ampicillin	Chloramphenicol A Crystal Form
Amrinone	Chloramphenicol B Crystal Form
Anhydrous 4-demethyl Metamizole Sodium	Chlorhexidine Acetate
Anhydrous Glucose	Chlormadinone Acetate
Anhydrous Morphine	Chlortetracycline Hydrochloride
Anisodamine Hydrobromide	4-[2-(5-Chloro-2-methoxybenzamide) ethyl] benzene Sulfonamide
Antazoline Hydrochloride	<i>o</i> -Chlorobenzylpenicillin Sodium
Arginine	2-Chloro-4-nitroaniline
Artemether	Chloroquine Phosphate
Artemisinin	Chlorphenamine Maleate
Artesunate	Chlorprothixene
Asparaginase	Chlortalidone
Aspartate	Chlortetracycline Hydrochloride
Atenolol	Cholic Acid
Atropine Sulfate	Choline Chloride
Azathioprine	Chorionic Gonadotrophin
Azithromycin	Ciclopirox Olamine
Bacitracin	Ciclosporin
Beclometasone Dipropionate	Cilostazol
Bendazac Lysine	Cimetidine
Bendrofluazide	Cinchonidine
Benorilate	Ciprofloxacin
Benproperine Phosphate	Ciprofloxacin Lactate
Benserazide Hydrochloride	Citicoline Sodium
Benzaldehyde	<i>cis</i> -Tranexamic Acid
Benzathine Benzylpenicillin	Clavulanic Acid
Benzhexol Hydrochloride	Clemastine Fumarate
1-Benzoyl-3-methyl-5-aminopyrazole	Clenbuterol Hydrochloride
Benzoyl Peroxide	Clindamycin
1-Benzyl-3-hydroxy-indazole	Clioquinol
Benzylpenicillin	Clobetasol Propionate
Betacyclodextrin	Clofibrate
Betamethasone	Clomifene Citrate
Bifendate	Clomipramine Hydrochloride
Bifonazole	Clonazepam
Bisacodyl	Clonidine Hydrochloride
Bulleyaconitine A	Clorprenaline Hydrochloride
Buprenorphine Hydrochloride	Clotrimazole
Caffeine	Cloxacillin
Calcium Folate	Clozapine
Capreomycin	Codeine Phosphate
Captopril	Coenzyme Q ₁₀
Captopril Disulfide	Colistin
Carbachol	Cortisone Acetate
Carbamazepine	Crotamiton
Carbocysteine	Curcumenol
Carboplatin	Cyclohexylamine
Carmofur	Cyclophosphamide
Carteolol Hydrochloride	Cysteine

Cystine	Fenfluramine Hydrochloride
Danazol	Fentanyl Citrate
Dapsone	Ferulic acid
Daunorubicin	Fleroxacin
Declozine Hydrochloride	Fluconazole
Deslanoside C	Flucytosine
Desoxycortone Acetate	Fludrocortisone Acetate
Dexamethasone	Flunarizine Hydrochloride
Dexamethasone Acetate	Fluocin
Dexamethasone Sodium Phosphate	Fluocinonide
Dialcoholate Chloramphenicol	Fluorouracil
Diatrizoic Acid	Fluphenazine Hydrochloride
Diazepam	Flurazepam Hydrochloride
Diclofenac Sodium	Folic Acid
Diethylene Glycol	Formylated Recombinant Human Insulin
Diethylstilbestrol	Fosfomycin
Difenidol Hydrochloride	Fructose
Digitalis	Ftibamzone
Digitoxin	Furosemide
Digoxin	Gadopentetate Meglumine
Dihydroartemisinin	Galactose
3,4-Dihydroxy-2'-methylamino acetophenone-3,4-Dineopentanoic Perchlorate	Galanthamine Hydrobromide
2,3-Dihydro-6-phenyl-imidazo [2,1-b] thiazole	Gemfibrozil
Diltiazem Hydrochloride	Gentamycin
Dimenhydrinate	Gentamycin C ₁
Dimercaptosuccinic Acid	Glibenclamide
Dimer of Human Insulin	Gliclazide
Dimer of Human Somatropin	Glipizide
Dioxane	Gliquidone
Diphenhydramine Hydrochloride	Glutamic Acid
Diphenoxylate Hydrochloride	Glycopyrrolate
Diphenyl-(2-chlorophenyl) methanol	Granisetron Hydrochloride
Dipivefrin Hydrochloride	Griseofulvin
Dipotassium Glycyrrhizinate	Halcinonide
Dithranol	Haloperidol
Dopamine Hydrochloride	Heparin
Doxapram Hydrochloride	Histamine Phosphate
Doxepin Hydrochloride	Histidine
Doxorubicin Hydrochloride	Huperzine A
Doxycycline	Hyaluronidase
β -Doxycycline	Hydrazine Sulfate
Doxycycline Hydrochloride	Hydrochlorothiazide
Econazole Nitrate	Hydrocortisone
Emetine Hydrochloride	Hydrocortisone Acetate
Enalaprilat	Hydrocortisone Butyrate
Enalapril Diketone	Hydrocortisone Sodium Succinate
Enalapril Maleate	Hydroquinone
Enflurane	<i>p</i> -Hydroxylacetylaminobenzene
Enoxacin	α -Hydroxyphenylglycine
Ephedrine Hydrochloride	1-(4-Hydroxy-3-methylbenzyl)-2-(tertiary butylamino)ethanol
Epirubicin	Hydroxyprogesterone Caproate
Ergometrine Maleate	Hydroxyzine Hydrochloride
Erythromycin	Hymecromone
Erythromycin Ethylsuccinate	Ibuprofen
Estazolam	Imidazole
Estradiol	Imipramine Hydrochloride
Estradiol Benzoate	Indapamide
Etamsylate	Indometacin
Ethambutol Hydrochloride	Inosine
1,2-Ethanediol	Iotalamic Acid
Ethinylestradiol	Isocarboxazid
Ethyl acrylate	Isoprenaline Hydrochloride
Ethylene oxide	Isoquinoline Compound [1,2,3,4-Tetrahydro-2-(4-sulfonylamido-phenyl)-4,4-dimethyl-7-methoxy-1,3-isoquinoline Diketone
Etimicin	Isosorbide Dinitrate C
Etomidate	Isotretinoin
Famciclovir	Jateorrhizine
Famciclovir Hydrochloride	Kanamycin
Farrotidine	

Kanamycin B	Netilmicin
Ketoconazole	Nifedipine
Ketoprofen	Nilestriol
Ketotifen Fumarate	Noradrenaline Bitartrate
Kitasamycin	Norethisterone
Lactose	Norfloxacin
Lactulose	Norgestrel
Levamisole Hydrochloride	Norvancomycin
Levodopa	Noscapine
Levonorgestrel	Ofloxacin
Lidocaine	Omeprazole
Ligustrazine Phosphate	Omeprazole Sulfonyl Compound
Lincomycin	Ondansetron Hydrochloride
Lindane	Oxacillin Sodium
Lithium Carbonate	Oxaprozin
Lofexidine Hydrochloride	Oxazepam
Loperamide Hydrochloride	Oxytetracycline
Lysine Hydrochloride	Papaverine Hydrochloride
Malaridine Phosphate	Paracetamol
Maprotiline Hydrochloride	Parachlorophenol
Mebendazole	Paromomycin
Meclofenoxate Hydrochloride	Paroxetine Hydrochloride
Medroxyprogesterone Acetate	Pefloxacin
Mefenamic Acid	Penicillamine
Meloxicam	Perphenazine
Meleumycin	Pethidine Hydrochloride
Menadione	Phenoxybenzamine Hydrochloride
Menadione Sodium Bisulfite	Phenprobamate
Menotropins	Phenylglycine
6-Mercaptopurine	Phenytoin
Meropenem	Pilocarpine Nitrate
Metacycline	Pipemidic Acid
Metamizole Sodium	Piperacetanile
Methacrylic Acid	Piperacillin
Methacrylic Acid Copolymer I	Piperazine
Methacrylic Acid Copolymer II	Piperazine Ferulate
Methionine	Piroxicam
Methotrexate	Pizotifen
6-Methoxy-2-acetylnaphthalene	Poloxamer
<i>p</i> -Methylbenzene Sulfonamide	Polymycin B
<i>o</i> -Methylphenol	Posterior Pituitary
<i>N</i> -Methylpiperazine	Potassium Dehydroandrographolide Succinate
α -Methylpyridine	Potassium Iodide
4 [2-(5-methylpyrazine-2-carboxamido)ethyl] phenyl sulfonamid	Praziquantel
Methyl 3,5-diamino-6-chloropyrazine-2-carboxylate	Prazosin Hydrochloride
Methyl methacrylate	Prasterone Sulfate
Methyl 5-methyl-3-isoxazolecarboxylate	Prednisolone
2-methyl-5-nitro Imidazole	Prednisolone Acetate
Metildigoxin	Prednisone Acetate
Metoclopramide	Primidone
Metronidazole	Procaccerol Hydrochloride
Mezlocillin	Progesterone
Miconazole Nitrate	Proglumide
Micronomicin	Propranolol Hydrochloride
Minocycline	Propylthiouracil
Minoxidil	Pseudoephedrine Hydrochloride
Mitomycin	Puerarin
Moclobemide	Qunidine
Morphine	Quinestrol
Naloxone Hydrochloride	Ranitidine Hydrochloride
Nandrolone Phenylpropionate	Raubasine
Naphazoline Hydrochloride	Recombinant Human Insulin
Naproxen	Recombinant Human Somatropin
Naproxen Sodium	Reserpine
Nefopam Hydrochloride	Ribavirin
Neomycamine	Ribostamycin
Neomycin	Rifampicin
Neomycin Sulfate	Rotundine Hydrochloride
Neostigmine Methylsulfate	

Roxithromycin	Thiamphenicol
Salbutamol	Thiopental
Salbutamol Sulfate	Thioridazine Hydrochloride
Salcatonin	Thrombin
Salicylic Acid	Ticlopidine Hydrochloride
Sarcosine	Tioguanine
Scopolamine Butylbromide	Tobramycin
Scopolamine Hydrobromide	Tolazoline Hydrochloride
Serazide Hydrochloride	Tramadol Hydrochloride
Sisomicin	<i>cis</i> -Tramadol Hydrochloride
Sodium Cromoglicate	Tranexamic Acid
Sodium Fluoride	<i>cis</i> -Tranexamic Acid
Sodium Houttuyfonate	Tretinoin
Sodium Selenite	Triamcinolone
Sodium Stibogluconate	Triamcinolone Acetonide
Sparfloxacin	Triamterene
Spirolactone	Triazolam
Spectinomycin	Trihydrate Ampicillin
Stanozolol	Trihydroxyl Benzyl Benserazide Hydrochloride
Streptomycin	Trimethoprim
Strophanthin G	Trypsin
Sulbactam	Tryptophan
Sulbenicillin	Tyrosine
Sulfamethazine	Ubenimex
Sulfamethoxazole	Urokinase
Sulfanilamide	Verapamil Hydrochloride
Sulfaoxazole	Vincristine Sulfate
Sulindac	Vindesine Sulfate
Sulpiride	Vinorelbine Tartrate
Sultamicillin	Vitamin B ₆
Suxamethonium Chloride	Vitamin B ₁₂
E-Tamoxifen Citrate	Vitamin D ₂
Tegafur	Vitamin D ₃
Testosterone Undecanoate	Vitamin E
Testosterone Propionate	Vitamin K ₁
Tetracycline Hydrochloride	Xanthinol Nicotinate
Thebaine	
Theophylline	

Appendix XVI Infrared Reference Spectra

Infrared reference spectra used for identification or purity test of drugs can be found in the "Atlas of Infrared Spectra of Drugs", a companion volume to the Chinese Pharmacopoeia. The instruments used for recording the spectra, procedure for preparation of samples, requirements for the spectrum recording and some information are described under the Notice section of the Atlas.

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(The monograph title is followed by spectrum number)

Name	Spectrum No.
Acedapsone	541
Acenocoumarol	543
Acetazolamide	9
Acetylcysteine	7
Aciclovir	213
Adenosine Disodium Triphosphate	903
Alanine	68
Albendazol	212
Allopurinol	194
Almitrine Bismesylate	900
Alprazolam	215
Amantadine	369
Ambroxol Hydrochloride	1102
Amiloride Hydrochloride	828
Aminoglutethimide	417
Aminomethylbenzoic Acid	410
Amiodarone Hydrochloride	382
Amitriptylin Hydrochloride	360
Amobarbital	163
Amobarbital Sodium	164
Amoxicillin	441
Amphotericin B	176
Ampicillin	658
Amrinone	809
Anisodamine Hydrobromide	287
Antazoline Hydrochloride	348
Apomorphine Hydrochloride	359
Arginine	1075
Arginine Hydrochloride	406
Artemether	519
Artemisinin	220
Aspartame	768
Aspartic Acid	27
Aspirin	5
Atenolol	214
Atropine Sulfate	487

continue

Name	Spectrum No.
Azathioprine	478
Beclometasone Dipropionate	71
Benflumetol	76
Benorilate	42
Benproperine Phosphate	579
Benzhexol Hydrochloride	366
Benzocaine	237
Benzoic Acid	233
Benzyl Alcohol	236
Benzylpenicillin Potassium	223
Benzylpenicillin Sodium	222
Berberine Hydrochloride	320
Betamethasone	418
Betamethasone Sodium Phosphate	659
Bifendate	461
Bifonazole	666
Bisacodyl	35
Bromhexine Hydrochloride	402
Bucinnazine Hydrochloride	315
Bumetanide	86
Bupivacaine Hydrochloride	324
Caffeine	250
Calcium Gluconate	465
Calcium Lactate	254
Calcium Pantothenate	208
Camphor	535
Captopril	96
Carbamazepine	94
Carbenoxolone Sodium	80
Carbidopa	97
Carmorfur	713
Carteolol Hydrochloride	817
Cefadroxil	596
Cefalexin	128
Cefalotin Sodium	129
Cefathiamidine	924
Cefotaxime Sodium	130
Cefradine	722
Cefuroxime Sodium	721
Chenodeoxycholic Acid	493
Chlorambucil	226
Chloramphenicol	507

continue		continue	
Name	Spectrum No.	Name	Spectrum No.
Chloramphenicol Palmitate(Type A)	37	Diclofenamide	54
Chloramphenicol Palmitate(Type B)	38	Diethylcarbamazine citrate	264
Chloramphenicol Succinate	460	Diethylstilbestrol	28
Chlormadinone Acetate	555	Difenidol Hydrochloride	338
Chlormethine Hydrochloride	390	Diffunisal	901
Chlorotrianisene	501	Digoxin	139
Chlorphenamine Maleate	61	Dihydroartemisinin	696
Chlorpromazine Hydrochloride	391	Diltiazem Hydrochloride	337
Chlorprothixene	304	Dimenhydrinate	271
Chlortalidone	673	Dimercaprol	15
Cimetidine	142	Dimethicone	10
Cinnarizine	306	Dioxopromethazine Hydrochloride	322
Ciprofloxacin	979	Diphenhydramine Hydrochloride	365
Ciprofloxacin Hydrochloride	647	Diphenoxylate Hydrochloride	339
Cisplatin	297	Dipivefrin Hydrochloride	335
Citicoline Sodium	1000	Diprophylline	12
Citric Acid	263	Dipyridamole	557
Clemastine Fumarate	514	Dithranol	140
Clenbuterol Hydrochloride	351	Dobutamine Hydrochloride	346
Clioquinol	506	Dopamine Hydrochloride	345
Clindamycin Hydrochloride	352	Doxepin Hydrochloride	347
Clobetasol Propionate	592	Doxorubicin Hydrochloride	1015
Clofazimine	671	Econazole Nitrate	475
Clofibrate	494	Enalapril Maleate	587
Clomifene Citrate	268	Enflurane	807
Clonazepam	502	Enoxacin	282
Clonidine Hydrochloride	327	Ephedrine Hydrochloride	387
Clorprenaline Hydrochloride	655	Ergometrine Maleate	32
Clotrimazole	169	Ergotamine Tartrate	424
Cloxacillin Sodium	200	Erythromycin	167
Clozapine	504	Erythromycin Estolate	36
Cocaine Hydrochloride	326	Erythromycin Lactobionate	257
Codeine Phosphate	577	Erythromycin Stearate	468
Colchicine	277	Estazolam	63
Cortisone Acetate	544	Estradiol	681
Cyclandelate	217	Estradiol Benzoate	235
Cyclophosphamide	218	Estradiol Valerate	30
Cyproheptadine Hydrochloride	404	Etacrynic Acid	196
Cystine	419	Etamsylate	430
L-Cysteine Hydrochloride	816	Ethambutol Hydrochloride	311
Cytarabine Hydrochloride	361	Ethinylestradiol	259
Dactinomycin	177	Ethisterone	617
Danazol	147	Ethosuximide	4
Dapsone	412	Ethylmorphine Hydrochloride	312
Daunorubicin Hydrochloride	323	Etofylline Clofibrate	426
Dexamethasone Acetate	546	Etoposide	615
Dexamethasone Sodium Phosphate	141	Famciclovir	956
Diatrizoic Acid	209	Famotidine	781
Diazepam	138	Febuprol	246
Diclofenac Sodium	53	Felodipine	794

continue	
Name	Spectrum No.
Ferrous Fumarate	513
Eleroxacin	799
Flunarizine Hydrochloride	379
Fluocinonide	550
Fluorescein Sodium	273
Fluorouracil	280
Fluphenazine Decanoate	279
Fluphenazine Hydrochloride	378
Flurazepam Hydrochloride	377
Folic Acid	93
Formylmerphalan	118
Fosfomycin Calcium	1080
Etibamzone	427
Furosemide	184
Gemfibrozil	601
Glibenclamide	307
Glipizide	808
Gliquidone	1097
Glucose	464
Glucurrolactone	467
Glutamic Acid	202
Glycerol	77
Glycine	81
Glycopyrrolate	308
Glyfosin	83
Granisetron Hydrochloride	1027
Griseofulvin	146
Halcinonide	498
Haloperidol	281
Histidine	785
Histidine Hydrochloride	372
Homoharringtonine	420
Huperzine A	936
Hydralazine Hydrochloride	371
Hydrocortisone	283
Hydrocortisone Acetate	552
Hydrocortisone Butyrate	585
Hydrocortisone Sodium Succinate	994
Hydroxycarbamide	663
Hydroxyprogesterone Caproate	30
Hymecromone	438
Ibuprofen	85
Indapamide	192
Indocyanine Green	611
Indometacin	193
Inosine	605
Iopanoic Acid	522
Iotalamic Acid	678
Isoleucine	165

continue	
Name	Spectrum No.
Isoniazid	166
Isoprenaline Hydrochloride	349
Isosorbide Dinitrate	473
Ketamine Hydrochloride	393
Ketoconazole	677
Ketoprofen	517
Ketotifen Fumarate	515
Lactose	256
Laurocapram	48
Leucine	298
Levamisole Hydrochloride	325
Levodopa	87
Lidocaine Hydrochloride	357
Lofexidine Hydrochloride	1025
Lomustine	300
Loperamide Hydrochloride	649
Lysine Acetate	890
Lysine Hydrochloride	399
Mafenide Acetate	556
Malaridine Phosphate	684
Mannitol	84
Maprotiline Hydrochloride	634
Mebendazole	101
Medofenoxate Hydrochloride	331
Medroxyprogesterone Acetate	160
Megestrol Acetate	545
Meglumine	463
Meloxicam	998
Menadiol Diacetate	458
Menadione Sodium Bisulfite	457
Mephentermine Sulfate	489
Meprobamate	99
Mercaptopurine	516
Meropenem	997
Metamizole Sodium	159
Metaraminol Bitartrate	294
Metformin Hydrochloride	631
Methenamine	45
Methionine	444
Methotrexate	108
Methoxamine Hydrochloride	329
Methylphenidate Hydrochloride	374
Methyltestosterone	120
Methylthionium Chloride	143
Metoclopramide	107
Metoprolol Tartrate	425
Metronidazole	112
Mexiletine Hydrochloride	381
Miconazole Nitrate	474

continue		continue	
Name	Spectrum No.	Name	Spectrum No.
Mifepristone	162	Phenytoin Sodium	238
Minocycline Hydrochloride	825	Pholcodine	531
Minoxidil	608	Phthalylsulfathiazole	428
Mitoxantrone Hydrochloride	824	Pilocarpine Nitrate	472
Moclobemide	740	Pindolol	610
Moracizine Hydrochloride	651	Pipemidic Acid	189
Morphine Hydrochloride	344	Piperacillin	621
Morphine Sulfate	873	Piperaquine Phosphate	580
		Piperazine Ferulate	969
Naloxone Hydrochloride	646	Piperazine Phosphate	581
Nandrolone Phenylpropionate	231	Piracetam	185
Naphazoline Hydrochloride	385	Piroxicam	188
Naproxen	432	Pizotifen	242
Nefopam Hydrochloride	367	Pralidoxime Iodide	523
Neostigmine Bromide	526	Praziquantel	190
Neostigmine Methylsulfate	110	Prazosin Hydrochloride	375
Nicardipine Hydrochloride	334	Prednisolone	284
Niclosamide	503	Prednisolone Acetate	553
Nicotinamide	421	Prednisone	612
Nicotinic Acid	422	Prednisone Acetate	549
Nifedipine	469	Primaquine Phosphate	578
Nikethamide	135	Primidone	62
Nilestriol	136	Probenecid	73
Nimodipine	599	Probucol	1054
Nitrazepam	470	Procainamide Hydrochloride	398
Nitrendipine	600	Procaine Benzylpenicillin	511
Nitrofurantoin	181	Procaine Hydrochloride	397
Norethisterone	258	Procaterol Hydrochloride	637
Norgestrel	109	Progesterone	434
Noscapine	609	Proglumide	67
		Proline	436
Omeprazole	675	Prolonium Iodide	512
Ondansetron Hydrochloride	832	Promethazine Hydrochloride	350
Oxazepam	75	Propafenone Hydrochloride	395
		Propranolol Hydrochloride	396
Papaverine Hydrochloride	405	Propylthiouracil	70
Pantoprazole Sodium	1083	Protionamide	69
Pefloxacin Mesylate	933	Pseudoephedrine Hydrochloride	642
Penfluridol	41	Puerarin	878
Pentoxifylline	29	Pyrantel Pamoate	51
Pentoxyverine Citrate	267	Pyrazinamide	191
Perphenazine	243	Pyridostigmine Bromide	527
Pethidine Hydrochloride	376	Pyritinol Hydrochloride	356
Phenformin Hydrochloride	363		
Phenobarbital	227	Quinine Dihydrochloride	11
Phenol	240	Quinine Sulfate	488
Phenolphthalein	429		
Phenoxybenzamine Hydrochloride	384	Ranitidine Hydrochloride	401
Phenoxymethylpenicillin Potassium	792	Raubasine	1044
Phenprobamate	229	Reserpine	195
Phenylalanine	230	Resorcinol	206
Phenylpropanol	232	Ribavirin	22

continue	
Name	Spectrum No.
Riboflavin Sodium Phosphate	628
Rifampicin	198
Rotundine	251
Rotundine Hydrochloride	834
Saccharin Sodium	576
Salbutamol Sulfate	486
Salicylic Acid	57
Scopolamine Butylbromide	21
Scopolamine Hydrobromide	288
Secobarbital Sodium	137
Serine	133
Sodium Aminosalicylate	132
Sodium Benzoate	234
Sodium Cromoglicate	155
Sodium Cyclamate	669
Sodium Etacrylate	197
Sodium Ferulate	775
Sodium Houttuyfonate	153
Sodium Hydroxybutyrate	437
Sodium Prasterone Sulfate	874
Sodium Valproate	65
Sorbic Acid	25
Sorbitol	26
Sparfloxacin	921
Spironolactone	582
Stanozolol	597
Sulbactam Sodium	509
Sulfadiazine	570
Sulfadiazine Silver	572
Sulfadiazine Zinc	573
Sulfadimidine	562
Sulfadoxine	567
Sulfafurazole	561
Sulfalene	563
Sulfamethoxazole	565
Sulfamethoxydiazine	566
Sulfamonomethoxine	568
Sulfobromophthalein Sodium	575
Sulindac	877
Sulpiride	510
Sulfasalazine	620
Suxamethonium Chloride	496

continue	
Name	Spectrum No.
Tamoxifen Citrate	265
Taurine	44
Testosterone Undecanoate	584
Testosterone Propionate	72
Tetracaine Hydrochloride	314
Theophylline	272
Thiamazole	117
Thiamine Nitrate	476
Thiamphenicol	594
Thiotepa	530
Threonine	175
Ticlopidine Hydrochloride	640
Timolol Maleate	33
Tioguanine	477
Tolbutamide	102
Tretinoin	445
Triamcinolone	747
Triamcinolone Acetonide	603
Triamcinolone Acetonide Acetate	547
Triazolam	586
Trifluoperazine Hydrochloride	317
Trimethoprim	103
Tryptophan	156
Tyrosine	518
Ubenimex	911
Urea	210
Ursodeoxycholic Acid	534
Valacyclovir Hydrochloride	1013
Valine	559
Verapamil Hydrochloride	389
Vinblastine Sulfate	481
Vincristine Sulfate	480
Vitamin B ₂	447
Vitamin B ₆	448
Vitamin B ₁₂	449
Vitamin C	450
Vitamin D ₂	452
Vitamin D ₃	453
Xanthinol Nicotinate	660
Xylitol	1088
Zinc Acexamate	1103

Pharmaceutical Purposes

nonsterile preparations. It may also be used as extraction of medicinal materials for nonsterile. Purified water should not be used for injections or as their diluent.

It can be produced by various methods. Every production should be monitored to prevent from contamination. It should generally be prepared and used as the solvent, diluent or water for

Water for Injection Water for Injection is water prepared by purified water. It complies with the requirements of the test of bacterial endotoxins. Bacterial contamination should be prevented during the production process, distribution. The quality of water for injection should meet the requirements of the monograph of water for injection in Volume II.

preparation process, storage, distribution and use.

The system for water preparation should be verified, systems of daily monitoring, analysis and report should be established, and complete original data should be kept for reference. Storage tank and pipes should be cleaned and sterilized periodically by suitable methods (illumination with ultra-violet lamps, heat sterilization, etc.).

Drinking Water Drinking Water may be used for washing crude drugs before purification and for preliminarily washing pharmaceutical appliances. Unless otherwise specified, drinking water may also be used as the solvent for extraction of crude drugs.

Purified Water Purified water is prepared from drinking water by distillation, ion exchange, reverse osmosis or by means of any other appropriate methods. It contains no additives and its quality complies with the requirements of the monograph of purified water in Volume II.

Purified water may be used as the solvent for preparation of ordinary pharmaceutical preparations, or as a reagent in the test, or as the solvent for extraction of crude drugs for preparation of sterile preparations such as injections or eye drops of traditional Chinese drugs, or as the solvent or diluent for preparation of oral preparations or preparations for external use, or as the water for precisely washing

Water for injection may be used as the solvent or diluent for preparation of injections, or for precisely washing their containers. It may be used as the solvent for preparation of eye drops if necessary.

In order to guarantee the quality of water for injection, every step of the production process of preparation of water for injection by distillation should be monitored at all time, and the appliances for preparation and transportation be washed and sterilized periodically to strictly prevent from bacterial endotoxins. Water for injection should generally be kept at a temperature exceeding 80°C, kept circulating at 65°C or preserved on sterile condition below 4°C, and be used not exceeding 12 hours after preparation.

Sterile Water for Injection Sterile Water for Injection is prepared from water for injection according to the technological conditions under which injections are prepared. It is mainly used as the solvent for sterile powders for injection or as diluent for injections. Its quality complies with the requirements of the monograph of sterile water for injection.

The specification of filling for sterile water for injection should meet the clinical requirements. Contamination due to large dimension or multi-use must be avoided.

Appendix XVIII Methods of Sterilisation

Sterilisation is the process to inactivate or remove any viable micro-organisms of a product by physical or chemical means. The methods described in this chapter may be used for the sterilisation of preparations, raw materials, excipients and medical devices.

Sterility is the absence of any viable micro-organisms. Absolute sterility of a product can not be guaranteed nor can it be demonstrated by testing to any batch of sterilized product. In practice, a product is sterilized to decrease the survival probability of micro-organisms to a specified level, and is designated as sterility assurance level (SAL). The survival probability of micro-organisms of a product treated by terminal sterilization is not more than 10^{-6} . The SAL of a process for a given product is established by appropriate validation studies.

The sterility assurance of a sterile product can not be guaranteed by testing, but depends on the use of the validated sterilisation process, good manufacturing practice (GMP), and good quality assurance system. It is essential that the following factors are fully considered in choosing a suitable sterilisation procedure, including nature of the product to be sterilized, effectiveness and economy of the procedure, and integrity and stability of the product after sterilisation.

It is essential to validate the process before being applied to practice. The validated items include:

- (1) Establish the validation protocols and the evaluation standard.
- (2) Ensure that the equipments are suitable and running effectively.
- (3) Demonstrate that the key equipment and instrumentation are capable of operating within the prescribed parameter criteria.
- (4) Perform replicate cycles by employing actual or simulated product and demonstrate the effectiveness of the process.
- (5) Summarize the records and complete the documents above, to form a validation report.

In manufacture practice, the process of sterilisation should be monitored, and the key parameters of the procedure (such as temperature, pressure, duration, humidity, concentration of the gas and the dose of radiation etc.) should be within the validated limits. The Validation of sterilisation process should be repeated at suitable interval. Revalidation is carried out whenever major changes in the procedure, including changes in the load, take place.

The sterility assurance is related with the degree of microbial contamination of the product before sterilisation and the resistance of the contaminating micro-organisms. Therefore, it is essential to control the level of viable micro-organisms contamination of a product prior to sterilisation and the resistance of the contaminating micro-organisms, to choose adequate precautions to minimize the contamination within the prescribed limits in the manufacturing process.

It is necessary to avoid re-contamination of the product after sterilisation. In all cases, the container and closure are required to maintain the sterility of the product throughout its shelf-life.

Methods of Sterilisation

The frequently-used methods include steam, dry heat, ionization radiation, gas and filtration. One or combinations of the above methods may be used, depending on the nature of the product. Wherever possible, the terminal sterilization should be chosen. If terminal sterilization is not possible, filtration or aseptic processing is used. Wherever possible, appropriate additional treatment (for example, steam) of a non-final product is applied.

1. Steam sterilisation

In this method, the products are placed in a chamber, and sterilized by saturated steam under pressure or overheated water flow which leads to denaturation of protein and nucleic acid to achieve the inactivation of micro-organisms. Steam is the most effective and most widely used method, and may be used for pharmaceutical preparations, containers, culture media, sterile coats, plastic plugs, and other materials resistant to high temperature and moisture. Steam sterilization does not guarantee the complete inactivation of bacterial spores, and is often used as an complementary sterile technique for thermo-labile products.

The process is usually carried out by the following conditions:

121°C	15 min
121°C	30 min
116°C	40 min

Other combinations of time and temperature may be used provided that they could give an SAL of 10^{-6} or less. For thermo-stable product, deep sterilisation is used, the SAL should be less than 10^{-12} . For thermo-labile products, the standard time of sterilisation (F_0) (means the standard duration in the condition of 121.1°C of sterile temperature, one minute of D-value, and 10.0°C of Z-value) usually is not less than eight minutes. If F_0 is less than eight, the contamination of micro-organisms should be monitored in the whole manufacturing process, all the measures should be taken to minimize the level of contamination of micro-organisms and to ensure that products being sterilized meet the requirements of sterility assurance.

For steam sterilisation, the products to be sterilized should be loaded in the sterilizing chamber perfectly, no tightness, to ensure that they are all effectively and equally sterilized. Knowledge of the coolest part of the chamber is obtained before this method is applied. Put the biological indicator at the coolest part to ensure SAL of the products has been achieved. Spores of *Bacillus stearothermophilus* are usually used as the indicator for this method.

2. Dry heat sterilisation

Dry heat sterilisation is carried out in an oven or tunnel equipment for sterilisation with forced air circulation, where micro-organisms and pyrogens are inactivated by high temperature. This method is suitable for products where steam sterilisation is inappropriate, such as glass utensils, metal containers, fibre products, solid drugs, and liquid paraffin wax.

The process is usually carried out by heating the product at 160-170°C for 120 minutes or longer, 170-180°C for 60 minutes or longer, or 250°C for 45 minutes or longer. Other

combinations of time and temperature may be used provided that they could give an SAL of 10^{-6} or less. For thermo-stable product, sterilize it until the SAL is $\leq 10^{-12}$ wherever possible. In the latter case, sterility test for these products prior to sterilisation is not necessary. Dry heat at 250°C for 45 minutes can also remove the pyrogens of containers and other equipments.

Put the products in suitable containers to ensure that they are all effectively and equally sterilized.

Knowledge of the coolest part of the chamber is obtained before this method is applied. Spores of *Bacillus subtilis* are usually used as the indicator for this method. Put the biological indicator at the coolest part to ensure SAL of the products has been achieved. Endotoxin inactivation test can verify the effectiveness of depyrogenation. Generally not less than 1000 EU of endotoxin which is derived from *Escherichia coli* may be added into the items prior to depyrogenation, in this case the reduction of the endotoxin is at least 3-log.

3. Ionising radiation sterilisation

Sterilisation by this method is achieved by exposure of the product to ionizing radiation in the form of gamma radiation from a suitable radioisotopic source (such as cobalt 60) or of a beam of electrons energized by a suitable electron accelerator. This method may be used for medical devices, containers, manufacturing equipments, and other raw materials and preparations resistant to radiation.

The SAL of the product is not more than 10^{-6} after ionising radiation sterilisation. The key parameter of ionising radiation sterilisation is mainly absorbed radiation dose. The radiation dose absorbed by the material being irradiated should be identified according to the suitability of the products and the maximum amount of the contaminated micro-organisms and the maximum resistance to radiation. It should be validated before the performance that the safety, efficiency and stability of a product should not be changed by the radiation dose. A reference absorbed dose is 25 kGy. Use the lowest possible radiation dose for the final product, raw materials and medical devices. Before irradiation, test the number of contaminated microorganisms and the resistance to the irradiation of the product to evaluate the SAL of the procedure.

During the procedure, the radiation absorbed by the product should be monitored regularly by means of suitable chemical or physical methods to ensure that the dose is appropriate. If dosimeters radiated along with sterilized products are adopted, place them at specific positions. Calibrate against a standard source at suitable intervals.

Spores of *Bacillus pumilus* are usually used as the indicator for this method.

4. Gas sterilisation

In this method, micro-organisms are inactivated in a high-pressure chamber filled with gas of disinfectors, for example, ethylene oxide, hydrogen peroxide, formaldehyde and ozone (O_3). This method is suitable for the products which are stable in these gases. Inflammability, teratogenesis and residue toxicity of the gases should be considered in the process of sterilisation.

The most generally used gas in this method which is carried out in a high pressure chamber filled with sterilized gas is ethylene oxide, usually mixed with 80%-90% inert gases. This method is applicable to medical devices and plastic products that are not durable by using high temperature methods. This method is not applicable to products which contain chlorine or can absorb ethylene oxide.

Temperature, humidity and gas concentration in the chamber, as well as the duration could affect the effectiveness of sterilisation by using ethylene oxide. The following conditions are recommended:

Temperature: $(54 \pm 10)^{\circ}\text{C}$.

Pressure: $8 \times 10^5 \text{ Pa}$

Relative humidity: $(60 \pm 10)\%$

Duration: 90 minutes

The process of sterilisation is validated before application. During the procedure, the chamber is vacuumized first, then filled with vapor to the specified humidity and temperature. Fill in the filtered and pre-heated ethylene oxide. During the process, seriously monitor the temperature, humidity, pressure, concentration of ethylene oxide and time. Use biological indicators to monitor the effectiveness of sterilisation, if necessary. The process should be supervised by skilled technicians. After the material to be sterilized is exposed either to ethylene oxide or to a mixture of ethylene oxide with a suitable inert gas, adequate time should be left to allow dispersal of residual ethylene oxide and other volatile residues. It should be monitored that the residues are within the prescribed limits. Eliminate the remaining gas in the product to a degree free of toxicity to human.

Leaking test should be carried out to ensure obturation of the chamber. Package materials and alignment of the products can affect the gas penetration and diffusion. Spores of *Bacillus subtilis* are usually used as the indicator for this method.

5. Filtration

In this method, micro-organisms in the gas or liquid products are removed by filtering through a certain type of filter material. It is usually used for thermo-labile solutions of drugs and raw materials. Sterilisation filter units use microporous filter membranes (hydrophilic or lipophilic) as the filter material. The pore size is usually less than $0.22 \mu\text{m}$. Avoid loss of solute by absorption on to the filter and to avoid the release of contaminants from the filter. Avoid use of membranes containing asbestos. The filter unit and membranes are sterilized before use. The filter units is cleaned first and then new membranes are used for a new batch of products.

The sterility assurance level in this method is related with bioburden of a product prior to sterilisation and the log reduction value (LRV) of the filter unit. Calculate LRV with the following expression:

$$\text{LRV} = \lg N_0 - \lg N$$

Where N_0 represents the number of micro-organisms before filtration, and N is the number after filtration.

LRV is used to express the efficiency of filtration. The LRV per cm^2 of active filter surface is not less than 7 for $0.22 \mu\text{m}$ -pore-size membranes. Two filters may be linked to increase the efficiency.

Key factors, such as pore size, membrane integrity and LRV cannot be monitored in the filtration process. Therefore, The integrity and effectiveness of the membranes should be validated before use. Validate the filter unit for at least once in a working day.

The products sterilized by this method should be operated in a cleaned area with rigorous monitoring and a sterile area is recommended. Relative facility, package container, stopper and other materials should be sterilized by appropriate methods, and recontamination should be avoided.

Pseudomonas diminuta are usually used as the indicator for this method.

6. Aseptic preparation

Aseptic preparation denotes the manufacturing of sterile preparations under sterile condition. It may include aseptic filling of products into containers and aseptic lyophilization. Filtration is usually used in the latter process.

It is necessary to monitor the environmental of aseptic preparation, and the filtration should be carried out under sterile conditions. The equipments, containers, plugs and other materials should be used suitable sterilization methods

and recolonisation should be avoided.

Sterility assurance of this process is carried out by simulating test for sterility by aseptic filling culture media. Sterility of the circumstance, personnel and materials should be monitored in the whole process.

The aseptic preparation should be validated at intervals, including periodic environmental filter examination and simulating test for sterility by aseptic filling culture media.

Biological indicators

Biological indicators are preparations of viable micro-organisms used to assess the performance of sterilisation equipments, to validate and monitor the effectiveness of sterilisation process. They usually consist of bacterial spores.

1. The Requirements for micro-organisms used as biological indicators

Different biological indicators are used for different sterilisation methods. The micro-organisms used as biological indicators comply with the following requirements:

- (1) The test strain is more resistant than any possible contaminating micro-organisms in the product to be examined.
- (2) The test strain is non-pathogenic.
- (3) The test strain is resistant to mutation and easy to store.
- (4) The test strain is easy to culture. If resting spores are used, they should be more than 90% of the indicator.

2. Preparation of biological indicators

The biological indicators are prepared using a specified procedure. Characteristics of the micro-organisms are determined before use, for example, D-value, which is the duration (expressed in minutes) with which the number of viable organisms are reduced to 10% of the original number at a definite temperature. Use suitable culture media for the incubation. Suspend the cultures, which mainly consist of spores. Store the spores as suspensions in nutrient liquids. Biological indicators consist of a definite number of one of more types of spores. They are usually placed on an inert carrier, for example a strip of filter paper, a glass slide, stainless or plastic materials. Spore suspensions may be presented in sealed ampoules. Biological indicators are packed with suitable materials, and an expiry date is set. The carriers and package materials protect the biological indicators from any deterioration or contamination, while allowing the sterilizing agent to enter into and contact with the micro-organisms. The packages are designed to facilitate storage, transportation, sampling and subculture. Some biological indicators may be inoculated directly into a liquid product to be sterilized or into a liquid product similar to that to be sterilized. In the latter case, the equivalence of the liquid products are demonstrated.

3. Application of biological indicators

In validation of sterilisation process, though some parameter can be used, the effectiveness of a sterilisation process is most easily assessed by the degree to which biological indicators are inactivated. Commercial biological indicators, or spores prepared from resistant micro-organisms isolated from contaminants are used as biological indicators. The resistance, purity and number of spores are validated for the

biological indicators. The quantity and resistance of spore of the biological indicators used should be more or greater than the contamination of the product to ensure the effectiveness of the process. Put the biological indicators at different position of the chamber for the terminal sterilisation. Avoid direct contact of the indicator with the product to be sterilized. Incubate the indicators after specified sterilisation on suitable culture media to guarantee inactivation of all the spores.

Commercial biological indicators may be used for validation test of deep sterilisation. For susceptible products, select suitable strains and spores as the biological indicator and design the process depending on the degree that the products are contaminated. Sterility assurance of these products are assessed by monitoring the number and resistance of contaminating micro-organisms and the validation test.

4. Common biological indicators

(1) **Steam sterilisation** Spores of *Bacillus stearothermophilus* (for example, NCTC 10007, NCIMB 8157, ATCC 7953) are recommended as the indicator for steam sterilisation. The D-value is 1.5-3.0 minutes, the number of viable spores in each tablet (or ampul) is 5×10^5 - 5×10^6 , and all the micro-organisms are inactivated at 121°C for 19 minutes. Spores of *Clostridium sporogenes* (for example, NCTC 8594, NCIMB 8053, ATCC 7955) may also be used, with D-value of 0.4-0.8 minutes.

(2) **Dry-heat sterilisation** Spores of *Bacillus subtilis* (for example, NCIMB 8058, ATCC 9372) are recommended as the indicator for dry-heat sterilisation. The D-value is more than 1.5 minutes, the number of viable spores in each tablet is 5×10^5 - 5×10^6 . Use *Escherichia coli* endotoxin for validation of depyrogenation, the amount added is not less than 1000 EU.

(3) **Ionising radiation sterilisation** Spores of *Bacillus pumilus* (for example, NCTC 10327, NCIMB 10692, ATCC 27142) are recommended as the indicator for ionising radiation sterilisation. The number of viable spores in each tablet is 10^7 - 10^8 . The D-value is around 3 kGy when a 25 kGy radiation dose is applied. Contaminated micro-organisms in the product may be more resistant to radiation than *B. pumilus*. Therefore, the latter can only be used to monitor the process, and cannot be used to establish the radiation dose.

(4) **Gas sterilisation** Spores of *Bacillus subtilis* (for example, NCTC 10073, ATCC 9372) are recommended as the indicator for gas sterilisation with ethylene oxide. The number of viable spores in each tablet is 1×10^6 - 5×10^6 . The D-value is more than 2.5 minutes, and the concentration of ethylene oxide is 600 mg/L. The relative humidity is 60%. The microorganisms are inactivated at 54°C for 60 minutes. Spores of *Bacillus stearothermophilus* (for example, NCTC 10007, NCIMB 8157, ATCC 7953) are recommended as the indicator for gas sterilisation with hydrogen peroxide.

(5) **Filtration** *Pseudomonas diminuta* (for example ATCC 19146) is recommended as the indicator when 0.22 µm-pore-size membranes are used for filtration. *Serratia marcescens* (for example, ATCC 14756) is recommended when 0.45 µm-pore-size membranes are used.

Appendix XIX Names, Symbols and Atomic Weights of Elements

C=12.00

Element	Symbol	Atomic weight	Element	Symbol	Atomic weight
Aluminium	Al	26.981538(2)	Magnesium	Mg	24.3050(6)
Antimony(Stibium)	Sb	121.760(1)	Manganese	Mn	54.938049(9)
Argon	Ar	39.948(1)	Mercury(Hydrargyrum)	Hg	200.59(2)
Arsenic	As	74.92160(2)	Molybdenum	Mo	95.94(2)
Barium	Ba	137.327(7)	Nickel	Ni	58.6934(2)
Bismuth	Bi	208.98038(2)	Nitrogen	N	14.0067(2)
Boron	B	10.811(7)	Oxygen	O	15.9994(3)
Bromine	Br	79.904(1)	Palladium	Pd	106.42(1)
Cadmium	Cd	112.411(8)	Phosphorus	P	30.973761(2)
Calcium	Ca	40.078(4)	Platinum	Pt	195.078(2)
Carbon	C	12.0107(8)	Potassium(Kalium)	K	39.0983(1)
Cerium	Ce	140.116(1)	Selenium	Se	78.96(3)
Chlorine	Cl	35.453(2)	Silicon	Si	28.0855(3)
Chromium	Cr	51.9961(6)	Silver(Argentum)	Ag	107.8682(2)
Cobalt	Co	58.933200(9)	Sodium(Natrium)	Na	22.989770(2)
Copper(Cuprum)	Cu	63.546(3)	Strontium	Sr	87.62(1)
Fluorine	F	18.998403 2(5)	Sulfur	S	32.065(5)
Gallium	Ga	69.723(1)	Technetium	Tc	[99]
Germanium	Ge	72.64(1)	Tellurium	Te	127.60(3)
Gold(Aurum)	Au	196.96655(2)	Thorium	Th	232.0381(1)
Helium	He	4.002602(2)	Tin(Stannum)	Sn	118.710(7)
Holmium	Ho	164.93032(2)	Titanium	Ti	47.867(1)
Hydrogen	H	1.00794(7)	Tungsten(Wolfram)	W	183.84(1)
Indium	In	114.818(3)	Uranium	U	238.02891(3)
Iodine	I	126.90447(3)	Vanadium	V	50.9415(1)
Iron(Ferrum)	Fe	55.845(2)	Xenon	Xe	131.293(6)
Lanthanum	La	138.9055(2)	Ytterbium	Yb	173.04(3)
Lead(Plumbum)	Pb	207.2(1)	Zinc	Zn	65.409(4)
Lithium	Li	6.941(2)	Zirconium	Zr	91.224(2)

- Notes
1. The last digit of an atomic mass is shown in parentheses.
 2. The figure in square brackets is the atomic mass of an isotope which exists with the longest half-life.

Appendix XX

XX A Guidelines for Validation of Analytical Method Adopted in Pharmaceutical Quality Specification

The purpose of validation of analytical method is to ensure that the adopted method meets the requirements for the intended analytical applications. In the course of drafting of the drug quality specification the analytical method must be verified. In case of changing of pharmaceutical synthetic processes or the components of preparation, or revising of the original analytical method, the analytical method of the specification must also be validated. Both process and result of the method validation must be recorded in the description of draft and revision of pharmaceutical quality specification.

The analytical items that must be verified include identification, quantification or limit test of impurities, content determination of the active ingredient in drug substance or preparation and that of other components in the preparation, such as degradation products, antiseptic etc. In the dissolution and release test of pharmaceuticals, the analytical method of dissolution amount must also be validated.

The parameters of validation characteristics include accuracy, precision (including repeatability, intermediate-precision and reproducibility), specificity, limit of detection, limit of quantitation, linearity, range and ruggedness. The parameters to be validated depend on the purpose for which the procedure is required. The analytical items and the corresponding parameters to be validated are listed in the attached table, which can be used for reference.

The parameters of analytical method to be validated are as follow.

Accuracy The accuracy of an analytical method is the closeness of test results obtained by that method to the true value or the reference value. Accuracy is often expressed as percent recovery and should be in the specified range.

1. Accuracy of the method for content determination

The accuracy for drug substance may be determined with a reference substance or a sample with known purity, or by comparing the result obtained by this method with the result obtained by another method of which the accuracy has been established. The accuracy for drug preparation may be determined with the mixture of components, to which known amounts of analyte have been added. If it is not possible to obtain all the components, the accuracy may be determined by adding known amounts of analyte to the preparation, or by comparing the result obtained by this method with the result obtained by another method which accuracy has been known. When the precision, linearity and specificity of a method have been developed, then it is not necessary to determine the accuracy because the accuracy can be calculated.

2. Accuracy of quantitative determination of impurity

The accuracy may be determined by adding known amounts of impurity to the drug substance or preparation. When the

impurity or degradation product is not available, the accuracy may be determined by comparing the result obtained by this method with the result obtained by another method which accuracy has been known, such as pharmacopoeial method or validated method. The response factor of the drug substance may be used if the response factor or the relative response factor of the impurity or degradation product to the drug substance can not be determined. The percent ratio of weight or area of a single impurity and total impurities to that of the active ingredient should be testified definitely.

3. Requirement for the data

In specified range, the accuracy should be evaluated using at least 9 testing results of the sample, for example, 3 different concentration levels are selected, 3 testing solutions of each level are prepared and measured. The percent recovery of the added amount, or the difference between the average value of testing results and the actual value and its confidential limit should be reported.

Precision The precision of an analytical method is the degree of agreement among individual test results when the procedure is applied repeatedly to multiple samplings of a homogeneous sample. The precision of an analytical method is usually expressed as deviation, standard deviation or relative standard deviation.

Repeatability is the precision obtained by the same analyst within a laboratory over a short period of time with the same equipment. Intermediate-precision is the precision obtained by different analysts within the same laboratory on different days with different equipment. Reproducibility is the precision obtained by different analysts in different laboratories using the same analytical procedure.

Precision of the method should be considered when the content of the active ingredient or impurity is determined.

1. **Repeatability** In specified range, repeatability should be evaluated with at least 9 measurement results, for example, 3 different concentration levels are selected, 3 testing solutions of each level are prepared and measured. Repeatability can also be evaluated with at least 6 measurement results when the concentration level of the analyte at 100%.

2. **Intermediate-precision** Scheme should be designed to inspect the effect of random variable factors on the precision. The variable factors include different dates, different analysts and different equipment.

3. **Reproducibility** Reproducibility should be done when an analytical method is adopted as the legal standard. For example, reproducibility should be inspected by collaborative study when pharmacopoeial method will be developed. Both the process of the collaborative study and result of the reproducibility should be recorded in the description of draft file. Where a reproducibility testing is to be conducted, the sample should be uniform, properly stored and transported to obtain reliable result.

4. **Requirement for data** Standard deviation, relative standard deviation and confidential limit should be reported.

Specificity The specificity of an analytical method is its ability to measure accurately and specifically the analyte in

the presence of components that may be expected to be present in the sample matrix, such as impurity, degradation product and excipients. Specificity should be inspected when identification, impurity test and content determination will be done. If the specificity of the method is not enough, other methods should be adopted for supplementation.

1. **Identification** The compounds that may coexist or have close related structures should be distinguished from the active ingredient. The sample without the tested ingredient, compound with close related structures and related chemical compound should all offer negative response.

2. **Assay and test for impurity** The representative graphs should be recorded for verifying specificity when chromatography or other separation methods are used. The position of each component should be marked in the graph. The resolution of the chromatographic method should meet the requirements. If available, the impurities or excipients may be added to the sample for assay to inspect whether the result is interfered, and the result can be compared with that from the sample without adding impurities or excipients. As to test for impurity, a certain amount of the impurity may be added to the sample to inspect whether the impurity can be separated from other ingredients.

If the impurities or degradation products are not available, the sample with impurities or degradation products may be used for determination, and the result may be compared with that obtained by the pharmacopoeial method or other validated method. Accelerating decomposition may be done for studying degradation products, such as irradiation with strong light, high temperature, high humidity, acidic or alkaline hydrolysis, oxidation etc. The results of two methods should be compared for content determination and the number of impurities should be compared with that obtained in test for impurity. Diode array detector and mass spectrometer may be used for purity test when necessary.

Limit of Detection The limit of detection is the lowest concentration of the analyte in a sample that can be detected. The methods in common use are as follows.

1. **Noninstrumental method** The limit of detection is generally determined by the analysis of samples with known concentrations of analyte and by establishing the minimum level at which the analyte can be reliably detected.

2. **Signal-to-noise ratio method** The method for the instrumental method which can record the noise of the baseline, the minimum level at which the analyte can be reliably detected, can be established by comparing the test results from samples with known concentrations of analyte with those of blank samples. The concentration or the amount injected into the instrument corresponding to the signal-to-noise ratio of 2 : 1 or 3 : 1 is generally accepted.

3. **Requirement for data** The test graphs should be attached, the test process and the results should be declared.

Limit of Quantitation Limit of quantitation is the lowest concentration of the analyte in a sample that can be determined with acceptable precision and accuracy under the stated experimental conditions. The limit of quantitation should be determined when the quantitative determination for impurities and degradation products are developed.

Signal-to-noise ratio method is a common approach to determine the limit of quantitation. The concentration or the amount injected into the instrument corresponding to the signal-to-noise ratio of 10 : 1 is generally accepted.

Linearity The linearity of an analytical method is its ability to elicit test results that are directly proportional to the concentration of analyte in samples within a given range. Linearity relationship should be determined over the claimed range of the method. The samples with varying concentrations of analyte for linearity determination are prepared by diluting accurately a stock solution, or by measuring accurately an amount of analyte separately. Five portions of samples should be prepared at least. The treatment is normally a calculation of a regression line by the method of least squares of test results versus analyte concentrations. In some cases, the test data may have to be subjected to mathematical transformation prior to the linearity regression analysis. Requirement for data: regression equation, correlation coefficient and the linear graph should be given.

Range The range of an analytical method is the concentration or quantity interval between the upper and lower levels of analyte (including these levels) that have been demonstrated to be determined with precision, accuracy, and linearity using the method as written.

The range should be determined according to practical application and the results and requirement of linearity, accuracy and precision. The range should be 80% to 120% of the test concentration for content determination of drug substance and preparation. The range should be 70% to 130% of the test concentration for content uniformity of preparation, and may be widened appropriately according to the dosage forms, such as aerosol, sprays. For test of dissolution or release, the range should be $\pm 20\%$ of the limit. If the range of limit is provided, it should be -20% of lower limit to $+20\%$ of upper limit. For study of impurity determination, the range should be stipulated from -20% to $+20\%$ of the provided limit on the basis of preliminary actual determination. If the content determination and impurities test are to be done with normalization method simultaneously, the linear range should be -20% of the provided limit of impurity to $+20\%$ of the provided limit of content (or upper limit).

Ruggedness Ruggedness of an analytical method is the degree of tolerance that the determining result is not affected when there is small change in the operational condition. The ruggedness of the method should be taken into account at the beginning to develop an analytical method. If the requirement for test condition is hard, it should be recorded clearly in the method. The typical variable factors are stability of the test solution, times and duration of sample extraction, and so on. The variable factors of liquid chromatography are composition and pH value of the mobile phase, same type of chromatographic column but from different manufacturers or different batches, column temperature, flow rate, etc. The variable factors of GC are column and stationary phase with different brand or different batches, different type of support, column temperature, sample inlet and detector temperature, etc. It should be illustrated whether the testing conditions with slight change meet the requirements for system suitability test to validate the method.

Tab. List of validation characteristics required to be evaluated in tests of each type

Parameters	Identification	Impurity test		Determination of content or release
		Quantitation	Limit of test	
Accuracy	—	+	—	+
Precision				

continue

Parameters	Identification	Impurity test		Determination of content or release
		Quantitation	Limit of test	
Repeatability	—	+	—	+
Intermediate precision	—	+ ^①	—	+ ^①
Specificity ^②	+	+	+	+
Limit of detection	—	— ^③	+	—
Limit of quantification	—	+	—	—
Linearity	—	+	—	+
Range	—	+	—	+
Ruggedness	+	+	+	+

① It is not necessary to validate the intermediate precision when the reproducibility has been developed.

② The lack of the specificity of an analytical method may be compensated by other relevant analytical methods.

③ It depends on the specific condition.

XX B Guidances in vivo Bioavailability and Bioequivalence Studies for Drug Preparations

Bioavailability means the rate and extent of the active ingredient absorbed into bloodstream from a drug preparation. Bioequivalence means no significant statistical difference in the main pharmacokinetic parameters reflecting rate and extent of the absorbed active ingredient in different preparations when administered at the same dose and under similar test conditions.

The extent of absorption of active ingredient in preparations for oral or other *non-vascular* administration can be affected by many factors. Among them, the factors affecting absorption are production processes, powder particle size, crystal forms or polymorphism, and the excipients such as binders, disintegrants, lubricants, coating materials, solvents, suspending agents and etc. The bioavailability is an important index which assures the inherent quality of the products, and the bioequivalence is the main basis to guarantee the quality consistency of identical active ingredient in different preparations. Although the concepts of them are not completely identical, the experiment method is almost the same. This guidance is especially for the purpose to ensure the effectiveness, safety of pharmaceutical products and to control the quality. Whether bioequivalence or bioavailability study is needed for pharmaceutical products depends on the regulations enacted by the authority.

The clinical institutes and analytical laboratories performing bioavailability and bioequivalence studies should be identified along with the name of unit as well as names, titles and curriculum vitae of the medical, scientific or analytical directors.

The Basic Requirements for Analytical Methods of Biological Specimen The specificity and the sensitivity of quantitative analytical methods for active ingredient and metabolites in biological specimen are the key points for performing successful bioavailability and bioequivalence studies. The chromatography, such as HPLC, GC and the combination techniques, e. g., GC-MS, LC-MS, LC-MS-MS, are best recommended, and internal standard method is normally used for quantitative analysis. Biological or biochemical methods also can be used if necessary.

Because there are various factors, which can affect biological specimen analysis, e. g., less specimen, low concentration of active ingredient, endogenous substances (such as inorganic

salt, lipid, protein and metabolite) and individual difference, analytical methods of biological specimen must be established on the basis of the structure of the substance being examined, biological matrix and predicted concentration range and the methods must be validated to assure the reliability of the methods.

1. *Specificity* It should be demonstrated that the measured analyte is an unchanged active ingredient or special active metabolite. The sample analysis should not be interfered by endogenous substances and relevant metabolite. It is necessary to submit the chromatograms of blank biological matrix, standard substance (indicated with its concentration) combined with blank biological matrix and the biological sample taken after administration. Specificity study should be enforced for the compound preparations to exclude the possible interference.

2. *Standard curve and linear range* Standard curve should be obtained by the method of regression analysis on the basis of the relationship between responses and concentrations of measured analyte. Linear range is the interval between the upper and lower concentration in a standard curve. In this range, the precision and accuracy of the measured results required by the study can be achieved.

A standard curve should consist of at least 6 concentrations made of the same biological matrix as samples. Linear range should cover the entire range of concentrations of the unknown samples. Estimation of unknown concentrations by extrapolations of linear range is not recommended. The zero point is not included in the standard curve.

3. *Precision and accuracy* It is required that precision and accuracy should be determined using 3 concentrations of the quality control sample at the same time, one approach the lower limit of quantitation (LLOQ) and must be within 3-fold of LLOQ; one approach the upper boundary of the standard curve; and one near the center. At least 5 samples per concentration should be measured.

The precision can be interpreted as the relative standard deviation (RSD) within-day and between-day, by determining the quality control sample. In general, RSD should not exceed 15%, except for near the lower limit of quantitation where it should not exceed 20%.

Accuracy refers to the closeness of the concentration of biological specimen to the true value determined by a special method. It should be within 85% to 115%, but within 80% to 120% for near the lower limit of quantitation.

4. *Lower limit of quantitation* The lower limit of quantitation is the lowest concentration on the standard curve. At least, it should meet analysis of the concentration of specimen at the time of three to five times the half-life or

one tenth to one twentieth of the C_{max} of the active ingredient concentration. Its accuracy should be within 80% to 120% of the true concentration. RSD should be less than 20%, and signal-to-noise ratio should be more than 5.

5. *Stability of the specimen* According to the concrete conditions, the stability of the biological specimen which contains the active ingredient should be evaluated under the room temperature, freezing and thawing condition, and different storage period, for the purpose of determining the storage condition and period of the biological specimen.

6. *Recovery of extraction* The recovery of extraction should be evaluated using upper, middle and lower concentrations of a sample. All results should be identical, precise, and reproducible.

7. *Quality control samples* The quality control samples, which are used to quality control, are biological matrix spiked with known quantities of the drug substance to be analysed.

8. *Quality control* The unknown biological specimen is determined after the analytical method is validated. Analysis of unknown samples can be done by single determination, or replicate analysis if necessary. A new standard curve should be generated for analysis of each batch of biological specimen and the duplicate quality control samples at three concentrations (upper, middle and lower) should be incorporated into each run. In general, the deviation from the results of the quality control samples is not more than 15%, and the deviation from the low concentration is not more than 20%. Not more than two quality control samples in different concentrations, whose results exceed the limit, are allowed. If not, the test results that day are invalid.

9. *Test results* The analytical methods in detail, published references, every standard curves, and the calculating process of results of quality control samples and unknown samples should be included in the test results. The chromatograms of all unknown samples, including the chromatograms of all associated standard curve and quality control samples should be available for regulatory authorities.

Ordinary Preparations

1. *Selection of Subjects* The requirements for the subjects who will be selected for the studies of the bioavailability and bioequivalence are:

(1) Conditions of subjects In general cases, healthy male is selected. In special cases the reason should be explained, i. e., drug for the gynecological usage. Adult subjects should be selected for the drug that is for children use. The detail is as following.

a. Sex distinction; Male.

b. Age: Generally the ages of 18-40 years are required. In the same study group, the difference in age should be controlled in a range of 10 years.

c. Body weight: Standard body weight $\pm 10\%$, body weights should be similar for subjects in the same study group, the unit of body weight is kilogram.

d. Subjects should be healthy, without any history of heart, hepatic, digestive disease, abnormal metabolism and nervous system diseases etc. A health examination should be taken which includes: ECG, blood pressure, heart rate, hepatic, renal, pulmonary function and blood test etc, all results should be normal. Related examinations are needed for special drugs, e. g., the examination of blood sugar level should be taken for drug that can reduce blood sugar level.

e. Subjects should be without any history of allergy and posture hypotension.

f. Any other drugs should not be taken within the past two weeks and during the whole study period. During the study period, tobacco, alcohol and any drinks containing caffeine

are prohibited.

g. Both investigators and subjects should sign informed consent form.

(2) The number of subjects Enough number of subjects are necessary, 18-24 subjects are required according to the related regulation. If necessary, the number could be increased.

2. *Reference Preparations* Reference preparations should be used in the studies of bioavailability and bioequivalence as a control. Reference preparations should be safe and effective. The selective principles of the reference preparations are as follows.

In the study of absolute bioavailability, the commercial dosage form of intravenous injection should be selected as a reference preparation. In the study of relative bioavailability or bioequivalence, reference preparations should be selected among the same type dominant product, which is commercially supplied domestically or abroad.

3. *Test Preparations* Test preparations should be magnified pilot product, which complies with the requirements of quality standards for clinical practice. The data of in vitro dissolution, stability, content or potency etc. should be presented. For particular products, documents about their polymorphism and optical isomers should be presented.

4. *Study design* When comparing two products, i. e., the test product and reference product, two-period and two-product crossover study is usually adopted. In order to erase influence of test period and individual difference on the study results, the subjects are randomly assigned into two groups. One group is administered with test sample first and then with reference sample; the other is administered with reference sample first and then with test sample. Between these two periods of the study, an interval is taken as wash out period, which is typically one or two weeks and should not be less than 10 half-life of the active ingredient.

For comparing among three products: two test products and one reference product, it is better to adopt three-product three periods double 3×3 Latin square study. The wash out periods between each study period are typically one or two weeks.

Sampling time points is important for a reliable test. The pre-dose sample should be collected, a perfect plasma concentration-time curve should include absorption phase, distribution phase and elimination phase. In general, at least four sampling time points are taken in front of the peak of plasma concentration-time curve, six or more sampling time points should be taken after the peak, there should be enough points around the peak time, the total sampling time points should not be less than 12. In general, sampling should be lasted till 3-5 elimination half-lives of the active ingredient, or the plasma concentration lower than $\frac{1}{10} \sim \frac{1}{20} C_{max}$.

When plasma concentration can not be analyzed, the analysis can be performed by adopting other biological samples, e. g. urine, but the test drug and study method should be in agreement with the requirements for measurement of bioavailability.

5. *The determination of administration dose* In study of bioavailability and bioequivalence, the dose is usually in agreement with clinical administration dose. It is better to administer the same dose of test preparation as that of reference preparation. In the case where the use of different doses is needed, the reason should be explained and if the test drug accords with linear pharmacokinetic in this dose range, the doses should be adjusted for the calculation of bioavailability.

6. *Study procedure* Following an overnight fasting (at least 10 hours), the subjects should be administered a single

dose of test or reference preparation with 250 ml warm water in the next morning. Subjects can have water after 2 hours and have standard meal after 4 hours of administration. According to the requirements, at different sampling time point the venous blood samples are collected. On the basis of requirement, the blood samples (whole blood, plasma or serum) are collected and frozen for analysis. After administration the subjects should avoid strenuous exercise. The blood sample should be collected in clinical monitoring room. If some adverse event happened, the effective treatment should be taken immediately. The study could be stopped if necessary.

7. Pharmacokinetic analysis Make tables and diagrams to show the data of plasma concentration of samples, and their mean value and standard deviation, at different time obtained from each subject. Then the relative pharmacokinetic parameters for each subject, and their mean values and standard deviations are calculated respectively. The main pharmacokinetic parameters are the half-life ($T_{1/2}$) of elimination, the peak drug concentration (C_{max}), the time for peak concentration (T_{max}) and the area under the plasma concentration-time curve (AUC). C_{max} and T_{max} are expressed directly by the values obtained from experiment without interpolation. AUC_{0-t_n} (area under the plasma concentration-time curve from time zero to time t) are calculated by trapezoidal rule or logarithmic trapezoidal rule, where t_n is the sampling time of the last measurable concentration. $AUC_{0-\infty}$ (area under the plasma concentration-time curve from time zero to time infinity) is calculated using the formula: $AUC_{0-\infty} = AUC_{0-t_n} + C_{t_n}/\lambda_z$, where C_{t_n} is the drug concentration of last sample point, and λ_z is the constant of terminal elimination rate. $T_{1/2}$ can be obtained using the formula of $T_{1/2} = 0.693/\lambda_z$, where λ_z is calculated from the slope of terminal linear part of log-plasma concentration-time curve.

Concerning to human bioavailability test, the AUC_{0-t_n} from time zero to the time for last sampling point should satisfy: $(AUC_{0-t_n}/AUC_{0-\infty}) \times 100\% > 80\%$.

8. Calculation of bioavailability (1) Single dose Bioavailability F should be calculated respectively by using AUC_{0-t_n} and $AUC_{0-\infty}$ of each subject, and the mean value and standard deviation are also calculated. When the dose of test preparation (T) is the same as that of reference preparation (R).

$$F = (AUC_{0-t_n})_T / (AUC_{0-t_n})_R \times 100\%$$

$$F = (AUC_{0-\infty})_T / (AUC_{0-\infty})_R \times 100\%$$

If the test drug being of the characteristic of linear pharmacokinetic, the dose of test preparation can be different from reference preparation, and the F can be modified and expressed in the following:

$$F = [(AUC_{0-t_n})_T \times D_R / (AUC_{0-t_n})_R \times D_T] \times 100\%$$

$$F = [(AUC_{0-\infty})_T \times D_R / (AUC_{0-\infty})_R \times D_T] \times 100\%$$

where, D_R is the administration dose of reference preparation and D_T is the administration dose of test preparation. The dose of test and reference preparation should be calculated according to actual content.

Data of metabolites: Prototype drug in blood may not be measured because of pro-drugs or because drugs are metabolized very quickly in the body. In this case, the bioavailability of these drugs can be studied using appropriate corresponding active metabolites.

The calculation of bioavailability is made mainly on the basis of AUC_{0-t_n} and the $AUC_{0-\infty}$ is used as a reference.

(2) Multiple Dose In the cases mentioned below, when steady state is reached after multiple dose administration,

the bioavailability can be estimated by means of the plasma drug concentration at steady state.

a. Extent of absorption of drug is similar, but the absorption rate of drug is quite different.

b. The difference of bioavailability among different individuals is large.

c. Extended, controlled release preparation.

d. After administration of single dose, the concentration of prototype drug or its metabolite is very low, which can not be measured by appropriate analytic method.

After multiple dose administration with an equal interval time τ a steady state is reached, then blood samples are collected multiply during the administration interval. The drug concentration is analyzed, and the area under the plasma concentration-time curve from time zero to time τ (AUC^*) in the dosing interval at steady state is calculated. When the dose of test preparation is equal to that of reference preparation, the relative bioavailability can be calculated in the following:

$$F = AUC_T^* / AUC_R^* \times 100\%$$

where AUC_T^* and AUC_R^* represent AUC at steady states for test and reference preparations respectively.

9. The evaluation of bioequivalence (statistical analysis of pharmacokinetic data) The statistical analysis should be focused on main pharmacokinetic parameters (e. g., AUC , C_{max}), and the bioequivalence is evaluated. After the data of AUC and C_{max} are converted by a log-metric scale, the statistical analysis is performed by means of the variance analysis and the two-tailed confidence interval method. If the 90% fiducial limits of the parameter AUC of test preparation is located within a range of 80%-125% of reference preparation and if C_{max} is within 70%-143% of reference preparation, the bioequivalence between the test and reference preparations is recognized. T_{max} can be tested by non-parameter method.

To facilitate bioequivalence comparisons, pharmacokinetic parameters (AUC and C_{max}) for each subject should be displayed in a parallel table for the preparations tested. Ratio (T/R) and log ratio between the test and reference values should be tabulated side by side for all subjects. In addition to the arithmetic mean for the test and reference products, the geometric means should be calculated. All means are to be included in the report.

10. Clinical report, side effects, and adverse reactions

Medical histories, physical examination and laboratory reports of subjects, and all incidents of possible side effects and adverse reactions related to the study should be reported.

Extended, Controlled Release Preparations In vivo bioavailability and bioequivalence studies of extended, controlled release preparations should be determined under the conditions of single and multiple dose.

1. Single dose, two-period crossover study The objective of this study is to compare the rate and extent of absorption of the test preparation and reference preparation under fasting conditions of subjects and to determine whether extended, controlled release preparation are bioequivalent with the reference preparation, and have the extended, controlled release character.

(1) The requirements for subjects and the criteria of selection are the same as described under Ordinary Preparations.

(2) Reference preparations In general, the reference preparations should be selected among the same type dominant product, which is commercially supplied domestically or abroad. If the products are new created extended, controlled release preparations, the dominant ordinary preparations, which are commercially supplied domestically

parameter C_{\max} is reduced, t_{\max} is extended, and at least one parameter in the results does not comply with the requirements of bioequivalence by statistic analysis according to part 9 described under ordinary preparations.

2. *Multiple dose, two-period crossover study* The objective of this study is to investigate the rate and extent of absorption, and fluctuation of blood concentration at the steady state when multiple doses of test and reference extended, controlled release preparations are given.

(1) The requirements and selection criteria for subjects The selection of subjects is similar as described under Single dose study and the subjects used in Single dose study can be continuously selected. 18 to 24 subjects are required. If necessary, the number can be increased. Reference preparations are similar as described under Single dose study.

(2) Study design and procedure A randomized crossover study design and multiple doses administration of test and reference preparations are recommended. For test preparation, the studied out scheme of dosage and administration is used. The preparations, which are administrated once a day, should be dosed in the morning following a fast of at least 10 hours; subjects should continue fasting for 2 to 4 hours after dosing. For preparations which are dosed twice a day, the first dose should be given following a fast of 10 hours, and subjects should continue fasting 2-4 hours after dosing; the second dose should be administrated before or after the meal of 2 hours and subjects should continue fasting for 2 hours post-dose. Each dose should be administered with 250 ml of warm water. In general, subjects can drink water after 1-2 hours of dosing. When reference is ordinary preparation, the routine clinical dosage and administration is used, but the overall dosage should be equal to the dosage per day of test extended, controlled release preparations.

(3) Blood-sampling design After multiple doses are given for a period of at least 7 elimination half-lives, three trough concentrations (C_{\min}) on three consecutive days should be determined to ascertain that the blood concentrations are at steady state. Blood sampling should be collected at the same time (normally in the morning) of different days in order to offset an interference of time to pharmacokinetics and be comparable. After reaching steady state and in a dosing interval of the last dose administration, adequate blood samples should be collected according to blood-sampling design of Single dose study. Then the blood concentration-

data during that interval will be measured and needed parameters of pharmacokinetics, e. g., the concentration, the time for peak concentration, trough concentration at steady state (C_{av}) and AUC^{ss} be calculated.

pharmacokinetics data processing a. Make tablet and o show the data of plasma concentration of and their mean value and standard deviation at ne obtained from each subject.

total C_{\max} , C_{\min} , T_{\max} , C_{av} , AUC^{ss} , and mean standard deviation of each parameter should be C_{\max} and T_{\max} are obtained directly from data interpolation. In general, C_{\min} is obtained from the two trough concentrations. One is sampled before ring an interval of the last dose administration, r is sampled at the τ . AUC^{ss} is calculated by the rule.

g concentration at steady state (C_{av}) which can be calculated as following:

$$C_{av} = (AUC^{ss}) / \tau$$

is area under the blood concentration-time curve from zero to time τ over a dosing interval at steady state is the dosing interval.

ability at steady state can be calculated as follows:

$$F = (AUC^{ss})_T / (AUC^{ss})_R \times 100\%$$

$$F = (AUC^{ss})_T \times D_R / (AUC^{ss})_R \times D_T \times 100\%$$

d. Percent degree of fluctuation ($DF\%$) of blood concentration, which can be calculated as following.

$$DF = 100\% \times (C_{\max} - C_{\min}) / C_{av}$$

where C_{\max} is peak drug concentration, obtained directly from the data, after the last dose is administrated at steady state and C_{\min} is a trough concentration at the end of last dosing interval during steady state. If reference preparation is the same extended release preparation, D_F/τ of test preparation should not be more than 143% of reference preparation. If reference preparation is ordinary preparation, D_F/τ of test preparation should be significantly less than that of ordinary preparation.

e. Statistical analysis and bioequivalence evaluation The methods and requirements for statistical analysis and bioequivalence evaluation are similar as described under Single dose study of extended, controlled release preparations.

f. Clinical report, side effects, and adverse reactions The requirements are the same as that for ordinary preparations.

XX C Guidelines for the Stability Testing of Drug Substances and Preparations

The purpose of stability testing is to provide information on the quality variation of a drug substance or drug preparation with time under the influence of a variety of environmental factors, such as temperature, humidity and light, to substantiate the recommended manufacture, package, storage, transportation and shipment conditions, and to establish shelf lives of the drug concerned.

The basic requirements for stability testing include: (1) Affecting factors testing, accelerated testing and long-term testing. One batch of drug substance is required for affecting factors testing. Three batches of substance/drug preparation are required for accelerated and long-term testing. (2) Drug substances used for stability testing should be from pilot

scale, and the amount required for testing should be equivalent to that for stability testing of their preparations. The manufacturing process should be the same as those for full scale production. The drug preparations used for stability testing should be from extended pilot scale (e.g., about 10000 tablets or capsules for Tablets or Capsules, at least about 10 times the amount needed for tests of each item for large volume preparations, such as intravenous infusion, oral solution, etc., the amount of particular preparation or dosage form can be varied depending on specific conditions.), and the formulation and manufacturing process should be the same as those of full scale manufacturing. (3) The quality specification of the drug for stability testing should be identical to that for pre-clinical and clinical studies. (4) The container, packaging materials and final package of the drug for accelerated and long-term testing should be the same as those for marketing. (5) The testing methods for assessment of drug stability testing must be accurate, precise and specific for the drug substance or preparation as well as for related substances (including degradation products and other substances introduced under various environmental or product related factors), and these analytical parameters should be validated to ensure the reliability of the results of the stability testing. The determination of degradation products and related products is important in the stability testing. (6) Because the quantity of the pilot production is less than that of full scale manufacturing, the applicant shall promise that the accelerated and long-term testings are also to be conducted for the first three batches of the validated full scale manufacturing. This guideline consists of two parts; the first is for drug substance, and the second is for drug preparation.

Drug substance The following tests for drug substance should be carried out.

1. Affecting factors testing This testing is normally carried out under more severe conditions than those used for accelerated testing. The purpose is to investigate the intrinsic stability of the drug substance in order to identify the factors that affecting stability, and the likely degradation pathways and degradation products, so that provide the rational scientific evidence for manufacturing, package, storage of the drug preparation and establishment of the analytical method for degradation products. This testing may be carried out on sample of a single batch. The substance being examined is usually distributed evenly in a suitable container (e.g., weighing bottle or petri dish) to form a thin layer with a thickness of not more than 5 mm, or not more than 10 mm for loose substance. Where significant change in degradation products is found according to the testing result, qualitative and quantitative analysis should be conducted for the degradation products due to the potential safety problem when necessary.

(1) **High temperature testing** Open the loaded container and place it in a suitable clean and tightly closed facility at 60°C for ten days. Sampling at the fifth and the tenth day and examine the specified items of stability testing. Where the substance changes significantly (e.g., a 5% potency loses from the initial assay value), the additional testing at 40°C should be conducted.

(2) **High humidity testing** Open the loaded container and place it in a closed facility with constant humidity at 25°C/90% ± 5% RH for ten days. Sampling at the fifth and the tenth day and examine the specified items of stability testing. The weight of the substance before and after testing is weighed accurately to evaluate the hygroscopic properties of the substance. Where increase is more than 5% of its weight, additional testing at 25°C/75% ± 5% RH should be conducted. Conditions of constant humidity are made up by

placing a saturated salt solution in the lower part of the closed container, such as a desiccator. According to the requirements for relative humidity, saturated solutions of NaCl (75% ± 1% RH at 15.5°C to 60°C) and KNO₃ (92.5% RH at 25°C) may be used appropriately.

(3) **Photostability testing by strong light** Open the loaded container and place it in a light cabinet or other suitable light device. The substance being examined should be exposed to light of 4500 lx ± 500 lx for 10 days and sampling at the fifth and the tenth day and examine the specified items for stability testing. Any changes in appearance of the substance should be noticed.

As to the light emitting device, It is recommended to use the device of the tunable exposure box. A light cabinet may also be used, in which several daylight lamps are placed to achieve the defined exposure, and the height of the sample platform may be adjusted. An aspirator is installed at the upper part of the cabinet to eliminate the heat possibly produced. An illuminometer is fixed on the cabinet to monitor the illumination of the cabinet at any moment. The light cabinet should not be interfered by natural light and keep the illumination intensity constant. Note should be prevented in light cabinet.

According to the chemical, physical and microbiological properties of the drug, experiment can be designed when necessary for exploring the affect of pH, oxygen and other factors on stability of the drug, and analytical method of related substances should be developed. For innovative or new drugs, it is necessary to study the properties of their decomposition products.

2. Accelerated testing This testing is carried out under extraordinary conditions. The purpose is to study and predict the drug stability by accelerating the chemical or physical change of the drug to provide the necessary data for evaluation, manufacturing, transportation and storage of drug. Three batches of samples, with the package as same as the market package, are required for accelerated testing, being placed at 40°C ± 2°C/75% ± 5% RH for 6 months. The equipment must be capable of controlling the temperature within a range of ± 2°C and relative humidity of ± 5% RH and monitoring the actual temperature and humidity. The drug substance should be examined respectively at the first, second, third and sixth month during the testing periods according to the specific items for stability testing. If the examined substance does not conform to the quality standard in 6 months duration under conditions of accelerated testing at 40°C ± 2°C/75% ± 5% RH, additional testing at an intermediate condition, such as 30°C ± 2°C/65% ± 5% RH (saturated solution of NaCrO₄ may be used, the relative humidity is 64.8%-61.5% at 30°C), should be conducted for six months. It is recommended that a water-separating type of electric heating constant temperature culture box (20-60°C) be used for the accelerated testing. A desiccator containing a saturated salt solution with a definite relative humidity is put at the lower part of the box, the temperature should be even controllable as required and suitable for long-term use. A constant humidity and temperature box or other suitable device can also be used. For temperature sensitive or less stable drug substance, suppose to be stored only in a refrigerator (4-8°C), the six months accelerated testing may be carried out at 25°C ± 2°C/60% ± 5% RH.

3. Long-term testing Long-term testing is carried out under the conditions close to the actual storage conditions for the drug. The purpose is to provide data for the shelf life of the drug. Three batches of drug substance, with the package as same as market package are placed for 12 months under the defined long-term conditions (25°C ± 2°C/60% ± 10% RH). The stability testing on specified items will be carried out at

the 0, 3rd, 6th, 9th, 12th month. Thereafter, the examinations at the 18th, 24th and 36th month are still required. Shelf life of the drug is fixed by comparing the results at different duration with those at 0 month. Statistical analysis is generally conducted using 95% confidence limit because of the variation of the experimental data. If the variation of the statistical analytical results of the 3 batches is small, the average is taken as the shelf life, if the variation is significant, the value obtained in shortest duration is taken as the shelf life. If the variation of the results of stability testing is so small, the drug is taken to be stable, then the statistical analysis can be omitted.

For the drug substance less stable on temperature, long-term testing may be carried out at $6^{\circ}\text{C} \pm 2^{\circ}\text{C}$ for 12 months according to the above described requirements. The examination should be continued after 12 months. Shelf life of the drug stored at low temperature should be formulated based on the results of stability testing.

The condition of $25^{\circ}\text{C} \pm 2^{\circ}\text{C}/60\% \pm 10\%$ for long-term stability testing is adopted on the basis of the International climatic zone (see table).

Mean climatic conditions: calculated data and derived storage conditions¹

Climatic zone	Calculated data			Derived storage conditions (for real-time studies)	
	$^{\circ}\text{C}^2$	$^{\circ}\text{CMKT}^3$	$\% \text{RH}^4$	$^{\circ}\text{C}$	$\% \text{RH}$
I	20.0	20.0	42	21	45
II	21.6	22.0	52	25	60
III	26.4	27.9	35	30	35
IV	26.7	27.4	76	30	70

¹ Based on: Grimm W. Storage conditions for stability testing in the EC, Japan and USA; the most important market for drug products. *DN9 development and industrial pharmacy*, 1993, 19: 27952830.

² Calculated temperatures are derived from measured temperatures, but all measured temperatures of less than 19°C were set equal to 19°C .

³ MKT=mean kinetic temperature (see p. 198).

⁴ RH=relative humidity.

The United Kingdom, North Europe, Canada and Russia are in the region of temperate zone. The United States of America, Japan and West Europe (Portugal-Greece) are in the region of subtemperate zone. Iran, Iraq and Sudan are in the region of dry and hot zone. Brazil, Ghana, Indonesia, Nicaragua and Philippine are in the region of humid and hot zone. The long-term testing condition of $25^{\circ}\text{C} \pm 2^{\circ}\text{C}/60\% \pm 10\%$ RH is adopted because China is mostly in the region of subtemperate zone, which is basically consistent with that adopted by ICH.

The drug substance for accelerated testing and long-term testing should be packaged with simulated small barrel, but the material and packaging conditions should be similar with those of the big barrel.

Drug Preparation The stability studies for the drug preparation should be based on the knowledge of stability of the drug substance, especially the influence of temperature, humidity and light on the drug substance stability. During the process of formula optimization and technical designation, some necessary affecting factors testing should be carried out, and the packaging conditions should also be investigated to conduct the following testings:

1. *Accelerated stability testing* This testing is carried out

under exaggerated storage conditions. The purpose is to predict stability of the drug preparation by accelerating the chemical or physical change of drug preparation and provide the necessary data for evaluation, manufacturing, transportation and storage of the drug. Three batches of samples, with the package as same as market package, should be placed under the conditions of accelerated testing at $40^{\circ}\text{C} \pm 2^{\circ}\text{C}/75\% \pm 5\%$ RH for 6 months. The equipment must be capable of controlling temperature within a range of $\pm 2^{\circ}\text{C}$ and relative humidity of $\pm 5\%$ RH and monitoring the actual temperature and humidity during storage. The preparation should be examined respectively at the first, second, third, sixth month during the testing periods according to the specified items for stability testing. If the examined preparation does not conform to the quality standard during 6 months under above mentioned conditions, additional testing at an intermediate condition, such as $30^{\circ}\text{C} \pm 2^{\circ}\text{C}/65\% \pm 5\%$ RH, should be conducted for six months. Relative humidity is not required for Solutions, Suspensions, Creams and Injections. The equipment used is the same as those used for drug substance. For temperature sensitive or less stable drug preparation, suppose to be stored in a refrigerator ($4-8^{\circ}\text{C}$), the six months accelerated testing may be carried out at $25^{\circ}\text{C} \pm 2^{\circ}\text{C}/60\% \pm 5\%$ RH.

It is appropriate that the accelerated testing is directly carried out at $30^{\circ}\text{C} \pm 2^{\circ}\text{C}/65\% \pm 5\%$ RH for Creams, Suspensions, Ointments, Eye ointments, Suppositories, Aerosols, Effervescent tablets and Effervescent granules, other requirements are the same as those described above.

For the drug preparations in semi-permeable container, such as Solutions in plastic bag, Eye drops or Nasal drops in plastic bottle, etc., the accelerated testing should be carried out at $40^{\circ}\text{C} \pm 2^{\circ}\text{C}/20\% \pm 2\%$ RH (saturated solution of $\text{CH}_3\text{COOK} \cdot 1 \frac{1}{2} \text{H}_2\text{O}$ may be used).

2. *Long-term stability testing* Long-term stability testing is carried out under the condition close to the actual drug storage conditions. The purpose is to provide data for the drug shelf life. Three batches of drug preparation with package as same as the market package are placed for 12 months under the defined conditions long-term stability testing at $25^{\circ}\text{C} \pm 2^{\circ}\text{C}/60\% \pm 10\%$ RH. The stability testing on the specified items will be carried out at the 0, 3rd, 6th, 9th, 12th month. Thereafter the examinations at the 18th, 24th and 36th month are still required. The drug shelf life is fixed by comparing the results at different time duration with those at 0 month. Statistical analysis is generally conducted using 95% confidence limit because of the variation of the experimental data. If the variation of the statistical analytical results of the three batches is small, the average is taken as the shelf life, if the variation is significant, the shortest time duration is taken as the drug shelf life. Statistical analysis can be omitted for stable drug. For the temperature sensitive or less stable drug preparation, long-term testing may be carried out at $6^{\circ}\text{C} \pm 2^{\circ}\text{C}$ for 12 months and the preparation should be examined according to the time requirement described above. The shelf life of the drug stored at low temperature should be formulated based on the results of the stability testing.

For some drug preparation, stability should be investigated in the process of use.

Important items of drug stability testing The major items are shown in the following table. The items of the various preparation types unlisted in this table may be determined according to the requirements for the correlated preparations.

Tab. The important items of stability testing for new drug substance and preparation

Type of preparation	Emphatic items for drug stability
Drug substance	Appearance, melting point, content, related substances, hygroscopic and other items selected according to monograph
Tablets	Appearance, content, related substances, disintegration time or dissolution or drug release
Capsules	Appearance, content, related substances, disintegration time or dissolution or drug release, water content, precipitate on the content of soft capsules
Injections	Appearance, content, pH, visible particles, related substances, sterility should be inspected
Suppositories	Appearance, content, softening time and related substances
Ointments	Appearance, homogeneity, particle size and related substances
Creams	Appearance, homogeneity, particle size, related substances and demixing
Pastes	Appearance, homogeneity, particle size and related substances
Gels	Appearance, homogeneity, particle size, related substances, demixing on emulsion
Ophthalmic preparations	Appearance clarity, visible particles, content, pH, and related substances for solutions Appearance, content, pH, related substances, particles size and redispersibility for suspensions Appearance, clarity, content, pH, related substances and sterility for eye lotions Appearance, clarity, content, pH, related substances, particles size and sterility for eye pills
Pills	Appearance, content, related substances and disintegration
Syrups	Appearance, content, clarity, relative density, related substances and pH
Oral solutions	Appearance, content, clarity and related substances
Oral creams	Appearance, content, demixing and related substances
Oral suspensions	Appearance, content, ratio of settling volume, related substances and redispersibility
Powders	Appearance, Content, particle size, related substances and uniformity of appearance
Inhale aerosols	Leakage rate, dose in each bottle, related substance, number of deliveries of each bottle, dose in each delivery and particle size distribution.
Powders for Inhalation	Emptying rate, number of deliveries of each bottle, dose in each inhale, related substances and particle size distribution
Sprays	Number of deliveries in each bottle, volume in each delivery, dose in each inhale, related substances and droplet size distribution
Granules	Appearance, content, particle size, related substances
Patches (transdermal patches)	Appearance, content, related substance, release rate and adhesion
Rinsing agents, lotions, enemas	Appearance, content, related substance, demixing (emulsion type), dispersibility (suspension type), sterile for rinsing agents
Liniment, Paints	Appearance, content, related substance, demixing (emulsion type), dispersibility (suspension type) filming for film paints
Ear preparation	Appearance, content, related substances. For Ear powders, sprays and semi-solid preparations, selection of items is base on requirements of the dosage form respectively.
Nasal preparation	Appearance, pH, content, related substances. For nasal powders, sprays and semi-solid preparations, selection of items is based on the requirements of the dosage form respectively.

Note: The variation of number and quantity of related substances including decomposition products and other products produced by other factors should be stated in the item of related substances. If possible, it should be stated that which related substance is the intermediate of the drug substance or decomposition product.

XX D Guidelines for Sustained, Controlled and Delayed Release Preparations

Comparing to ordinary preparations, sustained and controlled release preparations have longer therapeutic effect, lower adverse effects and lower dosing frequency. According to the requirements of the design of the preparations, drugs in these preparations can release in vivo slowly, and drug plasma concentrations show less peak-valley fluctuation, thus they can avoid adverse effects caused by extra amount of drugs beyond the therapeutic range (therapeutic window) and maintain the effective concentration in the therapeutic

range. Sustained and controlled release preparations also include ocular, nasal, ear, vaginal, rectal, oral cavity or dental, transdermal or subdermal, intramuscular and subdermal implant preparations, which can lag the release and absorption of drugs and avoid the "first pass effect" of *portahepatic* system. Delayed release preparations are those which do not release drug rapidly after administration, such as intestinal-specific drug delivery systems or colon-specific drug delivery systems which can avoid deactivation in stomach or stimulation of drugs to stomach. Delayed release preparations also include pulsatile release systems which burst release their drugs under certain conditions. Release theories of sustained, controlled and delayed release preparations mainly include controlling dissolution, diffusion, *erosion* or a combination of dissolution and diffusion, sometimes also include osmotically controlled and ion-exchange mechanism. Releasing processes can be fitted using different equations,

such as first-order kinetic, Higuchi and zero-order kinetic equations, etc. The main difference between sustained release and controlled release is that sustained release preparations do not release their drugs at a steady rate, that is to say its release rate is not constant but declines with time; while the controlled release preparations release their drugs through zero-order kinetic pattern, of which the release rate maintains constant. Administration of these preparations results in a considerably steady plasma concentration of the drug with little peak-valley fluctuation, until almost completely absorbed. Usually the amount of drugs in sustained and controlled release preparations is larger than that in corresponding ordinary single dose preparations and they are prepared by more complex processes. In order to generate reliable therapeutic effects and reduce adverse effects caused by burst releasing, in the process of preparation design, pilot production and manufacturing, measures should be taken to avoid or reduce burst releasing. Drug release profile in vitro and performance in vivo must accord with clinical requests and be affected very little, if any, by physiological or food factors. On the other hand, in order to control the quality and ensure the safety and efficacy of the preparations, release profile testing in vitro must reflect the basic condition in vivo. While the following guidelines will focus on sustained, controlled and delayed release oral preparations, the principles may be applicable to other routes of drug administration.

Definition of sustained, controlled and delayed release preparations

1. *Sustained release preparations* They are a kind of preparations which slowly release drug or drugs at a non-steady rate in a stipulated medium, and the dosing frequency should be reduced to half of or less than that of the corresponding ordinary preparations, thus can improve the patient's compliance evidently.

2. *Controlled release preparations* They are a kind of preparations which slowly release drug or drugs at a steady or almost steady rate in a stipulated medium, and the dosing frequency should be reduced to half of or less than that of the corresponding ordinary preparations, the drug plasma concentration should be more steady than that of sustained release preparations, thus can improve the patient's compliance evidently.

3. *Delayed release preparations* They are a kind of preparations which do not release drugs rapidly after administration, including intestinal dissolution preparations, colon-specific preparations and pulsatile release preparations. Intestinal dissolution preparations are a kind of intestinal specific preparations which do not or almost do not release drugs in a certain acidic solution within a fixed duration, but can release drugs completely or almost completely in phosphate buffer solution pH 6.8. Colon-specific preparations are a kind of preparations which do not release drugs at the upper part of the gastrointestinal tract, but can release most or all of drugs in the colon. That is to say they can not or almost can not release the drugs in an acidic medium or a phosphate buffered solution of pH 6.8 within a fixed duration, but can release most or all of the drugs in a phosphate buffer solution pH 7.5-8.0. Pulsatile release preparations are a kind of preparations which do not release drugs rapidly after administration but can burst release once or several times under certain conditions (such as in body fluid for a period of time, certain pH value or the effect of some enzyme).

Drug release test in vitro

This test is conducted under the imitative condition of gastrointestinal environment in vivo (such as temperature, pH value of the medium and stirring speed, etc.) to

investigate the drug release rate of the preparations. And then finally, on the basis of the testing, to establish a rationalized release profile in vitro which can be used for supervision of the manufacturing process and quality control.

1. *Apparatus* Unless otherwise indicated, release test in vitro of sustained, controlled and delayed release preparations can be carried out with dissolution determination apparatuses.

Patches can be tested by release test methods (Appendix X D, method 3) and the results should comply with the requirements.

2. *Temperature control* The release test of sustained, controlled and delayed release preparations should be conducted at $37^{\circ}\text{C} \pm 0.5^{\circ}\text{C}$ approximating to the body temperature, but patches at $32^{\circ}\text{C} \pm 0.5^{\circ}\text{C}$ approximating to the temperature of epiderm.

3. *Release medium* Deaerative freshly prepared purified water is regarded as the preferable release medium; if substantiated by the solubility characteristic of the drug substance, the formulation or the absorption site, dilute hydrochloric acid (0.001 mol/L to 0.1 mol/L) or phosphate buffer solution pH 3 to 8 may be used; for some drugs with limited solubility use of organic solvents is not favored, but addition of a small amount of surfactants (such as sodium lauryl sulfate) is allowed.

The volume of the release medium should conform to the sink condition.

4. *Time points of sampling for release test* Except delayed release preparations, release profile test in vitro must reflect the characteristics of the variation of the release profile of the tested preparations and meet the needs of statistic analysis. The complete release time duration must not be less than the interval time of dosing frequency and the generated cumulative release rate should be more than 90%. Unless otherwise specified, usually the data of the whole releasing process are utilized to make a curve of cumulative release rate versus time, thus the rational release rates are worked out.

From the release rate curve at least three test time points are chosen to characterize the in vitro drug release profile for sustained release preparations. An early time point, usually 0.5-2 hours is chosen to show that the potential burst release is not happened. An intermediate time point is chosen to define the character in vitro release profile of the dosage form, and a final time point is chosen to convey essentially complete release of the drug. These three points can be used to convey the drug release profile in vitro as a whole.

For controlled release preparations two additional test time points should be added, these five points can be used to convey the drug release profile of controlled release preparations in vitro. The range of percentage of drug release amount should be smaller than that of sustained release preparations.

If necessary, more test time points can be added.

The test time points of delayed release preparations are chosen according to the clinical requirements.

For products containing more than a single active ingredient, every main active ingredient should be tested according to the above requirements.

5. *Test on reproducibility and uniformity of manufacturing process* Batch-to-batch reproducibility for the release profile in vitro of over three batches (6 tablets or pills each batch) should be examined. The uniformity for the release profile in vitro of the same batch product (6 tablets or pills each batch) should be examined.

6. *Model fitting for drug release* The data of drug release can be fitted using first-order equation and Higuchi equation:

$$\ln(1 - M_t/M_{\infty}) = -kt \text{ (first-order equation)}$$

$$M_t/M_{\infty} = kt^{1/2} \text{ (Higuchi equation)}$$

The data of drug release of controlled release preparations can be fitted using zero-order equation:

$$M_t/M_{\infty} = kt \text{ (zero-order equation)}$$

where M_t is the cumulative release amount at time t , M_{∞} is the cumulative release amount while time tends to ∞ , M_t/M_{∞} is the percentage of cumulative drug release amount at time t . The fitted results of the largest regression coefficient (r) and the smallest mean square error (MSE) are regarded to be the best.

Tests on sustained, controlled and delayed release preparations in vivo

In vivo pharmacodynamic and pharmacokinetic tests should be used to evaluate the safety and efficacy of sustained, controlled and delayed release preparations. First of all, the special physicochemical characters of the drugs in sustained, controlled and delayed release preparations should be studied completely, which include polymorphism, particle size and distribution, solubility, dissolution rate, stability and variables controlling the drug release under extreme conditions of physiological environment. Some physicochemical characters of drugs in preparations (such as solubility) may be affected by the prescription, so solubility of drug under related conditions should be tested. For the drugs with limited solubility, if any surfactant (such as sodium lauryl sulfate) is used in their prescription, it is necessary to understand their solubility.

For the pharmacokinetic characters of drug, the ordinary preparations of the drug (vascular or oral solution, or other approved preparation) are recommended as reference to recognize and evaluate the release and absorption of sustained, controlled and delayed release preparations. During the designing course of oral sustained, controlled and delayed release preparations, it is significant to test the drug absorption in each section of gastrointestinal tract (especially for absorption in colon section of colon-specific drug delivery system). Influence of food also should be considered.

The pharmacodynamic characters of drug should reflect the relationship in sufficiently extensive dosage range between the drug plasma concentration and clinical response (therapeutic effect or side effect). In addition, the characters of equilibrium time between drug plasma concentration and clinical response should be studied. If there is a well-defined relationship between the plasma concentration of drug or metabolite and clinical response, the clinical performance of sustained, controlled and delayed release preparations could be characterized by plasma concentration-time data, otherwise, clinical tests and pharmacokinetics-pharmacodynamics tests should be carried out.

Details of bioavailability and bioequivalence testing of sustained, controlled and delayed preparations can be seen in Appendix XIX B, under the guidelines on bioavailability in vivo and bioequivalence of preparations.

Stimulation and/or allergy at their action sites should be examined for non-oral sustained, controlled and delayed release preparations.

In vivo-in vitro correlations

Methods for establishment of in vivo-in vitro correlations

In vivo-in vitro correlations refers to the establishment of a rational quantitative relationship between a biological property produced by a dosage form, or the parameters (e.g. T_{max} , C_{max} or AUC) derived from the biological property, and the physicochemical property or characteristic (such as release profile in vitro) of the same dosage form.

For sustained, controlled and delayed release preparations,

a test on correlation between drug release in vitro and absorption in vivo should be carried out. It should reflect the relationship between the whole release curve in vivo and the whole plasma concentration-time curve which determines the correlation. Only when the correlation between release in vitro and absorption in vivo exists, the situation in vivo can be predicted by the release curve in vitro.

There are three situations involved in the in vitro-in vivo correlation: (1) Each corresponding time point on release in vitro curve and absorption in vivo curve (cumulated by drug plasma concentration data) is correlated, respectively. This is called the point-to-point correlation, showing that the two curves are coincident. (2) The correlation between the average release time in vitro and the average delay time in vivo is established by using statistical moment analysis principle. Because the average delay time of close values may be produced by many different curves in vivo, the average delay time in vivo cannot indicate the whole plasma concentration-time curve in vivo. (3) Single point correlation between a release time point ($t_{50\%}$, $t_{90\%}$ etc.) and a pharmacokinetic parameter (e.g. AUC, C_{max} or t_{max}) only indicates the partial correlation.

Methods adopted by these guidelines

These guidelines on the in vitro-in vivo correlation of sustained, controlled and delayed release preparations admit that, when each time point on the absorption curve of the absorbing phase in vivo and each corresponding time point on the release curve in vitro are regressed, if the correlation coefficient of the obtained linear regression equation meets the corresponding requirements, correlation can be concluded.

1. Establishment of in vitro-in vivo correlation

(1) Release curve in vitro of cumulative release percentage in vitro versus time If the release profile of sustained, controlled and delayed release preparations changes with external conditions, two types of samples should be made (one releases slower, the other faster than the original preparation). The external conditions affecting the release speed should be investigated first. Then, according to the optimal conditions based on the release test in vitro, the release curve in vitro of cumulative release percentage in vitro versus time can be drawn.

(2) Absorption curve in vivo of absorption percentage in vivo versus time The data of plasma concentration-time curve generated from the single dose crossover test, for the drug whose absorption in vivo fits with one-compartment model can be converted into absorption curve of absorption percentage in vivo versus time. The absorption percentage (F_a) in vivo of the drug at any time can be calculated by the following Wagner-Nelson equation:

$$F_a = (C_t + kAUC_{0-t}) / (kAUC_{0-\infty}) \times 100\%$$

where C_t is the plasma concentration at time t , k is the elimination rate constant.

The absorption percentage of each time point of drug with two-compartment model can be calculated by simplified Loo-Rigleman equation.

2. Examination of in vivo-in vitro correlation When the release of drug in vitro is the rate-determining step of the absorption process in vivo, the release percentage on the release curve in vitro and the absorption percentage of each corresponding time point on the absorption curve of the absorbing phase in vivo of the same batch samples are regressed by the method of linear least square regression principle, thus the linear regression equation can be obtained.

If the correlation coefficient of the line is larger than the critical correlation coefficient ($P < 0.001$), the in vivo-in vitro correlation is confirmed.

XX E Guidelines for Preparations of Microcapsules, Microspheres and Liposomes

Preparations of microcapsules, microspheres and liposomes are those made up of drugs and suitable excipients, which after microencapsulation, are used to produce various kinds of preparations for different uses and modes of administration to meet clinical requirements.

Transformation of drugs into microcapsules, microspheres and liposomes can cover their unpleasant smell and flavor, enhance stability, prevent them from deactivation in stomach or lessen their stimulation to stomach, facilitate transportation, application and storage by solidification of liquid drugs, reduce the incompatible changes in compound preparations and help the preparations achieve sustained, controlled and delayed release, for some of them, targeting release characteristics.

Microcapsules, microspheres and liposomes can be used as drug carriers, some of them with targeting characteristics are usually called targeted preparations. Targeted preparations can concentrate the drug in or near the targeted tissues and organs to increase the therapeutic effects and to significantly lessen their adverse drug reaction on other tissues, organs and the whole body.

The drug release mode of targeted preparations can be divided into three types: ① Targeted preparations of the first class are those which deliver the drug in the capillary vessel bed of the targeted organs; ② Targeted preparations of the second class are those which deliver the drug in specific cells (e.g. tumor cells) of the targeted area without effects on normal cells; ③ Targeted preparations of the third class are those which act on a certain area in the cell.

Types of drug carriers

1. **Microcapsules** Microcapsules are extra fine capsules produced by coating the solid or liquid drug with a thin layer of excipients. Usually their size ranges from 1 μm to 250 μm , while those whose size ranges from 0.1 μm to 1 μm are called sub-microcapsules, from 10 nm to 100 nm, called nanocapsules.

2. **Microspheres** Microspheres are extra fine spheres of solid entity in which drug is dispersed or dissolved in the excipients. Usually their size ranges from 1 μm to 250 μm , while those whose size ranges from 0.1 μm to 1 μm are called sub-microspheres, from 10 nm to 100 nm, called nanospheres.

3. **Liposomes** Liposomes are extra fine vesicles formed by entrapping drug in the molecular bilayers of lipid excipients. They are divided into unilamellar and multilamellar vesicles. Usually small unilamellar vesicles are 0.02-0.08 μm in size and large unilamellar vesicles 0.1-1 μm in size; multilamellar are 1-5 μm in size. Usually small unilamellar vesicles are called nano-liposomes.

Excipients in common use

Usually excipients can be divided into three types;

1. **Natural materials** Natural materials are bioconsistent and biodegradable, such as gelatin, protein, starch, chitosan, alginate, phospholipid and cholesterol, etc.

2. **Semisynthesized materials** They are divided into two types; biodegradable and unbiodegradable materials *in vivo*. The biodegradable materials include hydrosoybean phospholipid, polyethylene glycol distearic phospholipid,

ethanolamine, etc. Unbiodegradable materials include methylcellulose, ethylcellulose, carboxymethylcellulose salt, hydroxypropylmethyl cellulose, cellulose acetate phthalate, etc.

3. **Synthesized materials** They are divided into two types; biodegradable and unbiodegradable materials *in vivo*. The considerably widely used biodegradable materials include poly-lactic acid, poly-amino acid, poly-hydroxybuturate, poly-lactide-glycolide, etc. Unbiodegradable materials include polyamide, polyvinyl alcohol, Eudragin, and silicon rubber, etc.

In addition, wetters, emulsifiers, antioxidants or surfactants can be added for preparing microcapsules, microspheres and liposomes.

Testing items for controlling manufacturing processes and in storage periods

1. **Limit test of harmful organic solvents** When harmful solvents have been brought in the manufacturing processes, the residual solvent should be determined according to the Appendix VIII P of the Pharmacopoeia under *Determination of residual solvents*. If no limits have been stipulated, relevant ICH guidelines can be consulted, or a method for determining the solvent and the limit should be established.

2. Tests of shape, particle size and its distribution

(1) **Shape observation** Microcapsules, microspheres and liposomes can be observed under a microscope. If the particles size is less than 2 μm , scanning or transmission electron microscope should be utilized. Photos should be provided in any cases.

(2) **particle size and its distribution** The average value of particle size and the data or graphs of its distribution should be provided. There are several methods to determine the particle size, such as optical microscopy, electrical induction method, light induction method or laser scattering method, etc. A minimum of 500 particles must be measured, and a computer software or the following equation can be used to calculate the arithmetic average diameter (d_{av}):

$$d_{av} = \frac{\sum(nd)}{\sum n} = \frac{(n_1d_1 + n_2d_2 + \dots + n_nd_n)}{(n_1 + n_2 + \dots + n_n)}$$

where n_1, n_2, \dots, n_n are particle numbers with particle size of d_1, d_2, \dots, d_n respectively.

The data of particle size distribution of microcapsules, microspheres and liposomes are often expressed by the particle numbers or percentage in different particle size ranges; sometimes span is employed instead. The smaller the span, the narrower the distribution, i.e. the particles are more uniform in size.

$$Span = (D_{90} - D_{10}) / D_{50}$$

where D_{10}, D_{50}, D_{90} are diameters corresponding to the position of 10%, 50%, 90% in the accumulated distribution graph.

If graphs are necessary, the particle size of the data of the particle size distribution is plotted as abscissa against the frequency (the percentage of particle numbers in different size ranges in the total number of the particles) as the ordinate to produce the histogram of size distribution. The particle size distribution curve can be obtained by plotting the frequency of different particle size ranges against the mean values of different particle size ranges.

3. **Examination of drug content or entrapment rate** The data of drug content or entrapment rate must be provided for microcapsules, microspheres and liposomes.

Drug content is the percentage of drug by weight in the system (microcapsules, microspheres and liposomes):

$$\text{Drug content} = \frac{\text{drug wt. in the system}}{\text{total wt. of the system}} \times 100\%$$

where wt. is weight.

If microcapsules, microspheres and liposomes are dispersed in the liquid medium, determination should be performed after using proper separation methods (such as gel column chromatography, centrifugation or dialysis), then the following equation is used to calculate the entrapment rate:

$$\text{Entrapment rate} = \frac{\text{trapped drug wt. in the system}}{\text{total drug wt. in the system}} \times 100\%$$

$$= \frac{\text{total drug wt. in the system} - \text{untrapped drug wt. in the liquid medium}}{\text{total drug wt. in the system}} \times 100\%$$

Entrapment rate should not be less than 80%.

4. *Examination of burst effect or leakage rate* The conditions of drug trapped in microcapsules, microspheres, liposomes are commonly divided into adsorbed, entrapped or implanted. The drug adsorbed on the surface of microcapsules, microspheres and liposomes releases rapidly when tested in vitro, which is called burst effect. Released amount should be less than 40% in the first 0.5 h.

If the product of microcapsules, microspheres and liposomes are dispersed and stored in the liquid medium, the leakage rate should be calculated according to the following equation:

Leakage rate

$$= \frac{\text{drug amount leaked into the medium after a period of storage}}{\text{trapped drug amount before storage}} \times 100\%$$

5. *Examination of oxidation degree of liposomes* Phosphatide in liposomes may easily be oxidized, which is an important problem in liposomes. There are three stages for the oxidation of phosphatide in the lipid mixed with unsaturated fatty acid: the coupling of single double bond, the formation of oxidation products, and the formation of aldehyde and the rupture of bond. The oxidation degree is difficult to be evaluated by just one test, because the products formed in each stage are different. The oxidation index is used as indication in the Guidelines.

Determination of the oxidation index The phosphatide after oxidative coupling exhibits a maximum absorbance at about 230 nm, which is different from those inoxidables. When the lecithoid liposomes is examined, the oxidation index should be less than 0.2. The procedure is: dissolve the phosphatide in anhydrous ethanol to produce a clear solution with a certain concentration, measure the absorbances of the solution at 233 nm and 215 nm respectively. The oxidation index is calculated by the following equation:

$$\text{Oxidation index} = \frac{A_{233 \text{ nm}}}{A_{215 \text{ nm}}}$$

6. *Preparations of microcapsules, microspheres and liposomes should conform to the general requirements for the corresponding preparations* Besides the requirements of these guidelines, preparations of microcapsules, microspheres and liposomes should also conform to the stipulation of the general requirements for the corresponding preparations (such as tablets, capsules, injections, ophthalmic preparations, nasal preparations, patches, aerosols, etc). Sustained, controlled and delayed release preparations made from microcapsules, microspheres and liposomes should conform to the guidelines of sustained, controlled and delayed release preparations.

7. *Evaluation of targeted drug delivery systems* Targeting data should be provided for targeted drug delivery systems, such as drug distribution data *in vivo* and pharmacokinetic parameters of distribution *in vivo*.

XX F Guidelines for the Analysis of Impurities in Drugs

This appendix is the guideline on the analysis of impurities for the quality specifications of chemically synthesized or semi-synthesized organic drug substances and their preparations, and can be used for the drug research, production, and drafting or revising of quality specifications as reference.

Any substance that affects the purity of a drug is considered as an impurity. Impurities included in a drug specification may be introduced from production process, starting materials or excipients of the drug produced with specified process and materials officially approved by the competent drug regulatory authority. The impurities may be the degradation products arising in the storage period, which could be validated by stability testing. The new impurities caused by change of production process or materials, or from foreign substances adulterated or contaminated are not included in the impurities of the drug specification. Application for changing in production process or materials, and requesting for revision of the drug specification due to new impurities caused by the changing shall be submitted to the competent authority for approval according to law. Drugs shall not be adulterated or contaminated by foreign substances. Non-official methods may be adopted to monitor the counterfeit drugs on the basis of individual case when necessary.

The classification of impurities and their testing item titles in the drug specification

Impurities could be classified as organic impurities, inorganic impurities and organic volatile impurities according to their chemical category and characteristics. Impurities could be classified as related substances (including degradation products), other impurities, foreign substances, and so on according to their source. Impurities could be classified as other steroids, other alkaloids, geometric isomers, optical isomers, etc based upon the structural relationship. Impurities could be classified as toxic and ordinary impurities according to their toxicity. The ordinary impurities have no significant biological activity when limited amount of the impurities exists in drug. However, toxic impurities have significant undesirable biological activity. There are different ways for classifying impurities. The item title for an impurity test in a drug specification shall be normalized based on the requirements of the *Manual for Revising to National Drug Standards* published by the Commission of the Chinese Pharmacopoeia. The item title for organic impurity may be selected according to the following principles:

(1) Where the impurity is a known substance, the chemical name of the impurity can be used as the item title, such as "Morphine" in the monograph of Codeine Phosphate, "*p*-Chlorophenol" in the monograph of Clofibrate, "Piperidylpropionophenone" in the monograph of Benzhexol Hydrochloride, "Lincomycin B" in the monograph of Lincomycin Hydrochloride, and "Chymotrypsin" in the monograph of Trypsin. Where the chemical name of the impurity is too long to describe, and has no corresponding adopted abbreviation, such principle for the selection of item title may be used as "Mercapto compounds" in the monograph of Spironolactone, "Phenones" in the monograph of Adrenaline, and "Alkene" in the monograph of Difenidol Hydrochloride. The impurities with confirmed structure should be provided in the description of the draft of the

quality specification.

(2) Where the category of the impurity is known, but the impurity can not be justified to be a single substance, the item title of such impurity may be "other steroids", "other alkaloids", "other amino acids", "reducing sugars", "fatty acids", "primary aromatic amines", "chlorinated compounds", "residual solvents", or "related substance", and so on.

(3) For some unknown impurities, the selection of item title may be based upon the testing method, such as "light absorption of impurity", "oxidizable substances", "carbonisable substances", "non-volatile substances", "volatile impurities", and so on.

Selection of impurity testing items for quality specification

Study on impurities in new drug substances and new preparations shall be conducted in accord with the relevant requirements for registration application of new drugs in China. The study could also be performed by referring to the ICH guidelines Q3A or Q3B. The safety evaluation for impurities and degradation products should be made. Effective analytical method of separation shall be adopted by the new drug research institutions for determining actually present and potential impurities arising from synthesis, purification and storage. Characterization or structure confirmation shall be carried out for the impurity that its apparent level is 0.1% or above 0.1%, and for the toxic impurity or impurity with significant biological action that its apparent level is even less than 0.1%. The degradation products found in the stability testing (accelerate and long term testing) shall be studied according to the above requirements. Impurity testing items in the new drug specification should include the impurities and degradation products detected in the quality study and stability testing, and appeared in the batches produced in an industrial scale. The corresponding acceptance criteria shall be provided. Impurities controlled in the drug substance specification will generally not be controlled in its preparation specification except degradation products and toxic impurities. Inorganic impurity testing items for drug substances and preparations shall be selected according to the manufacturing process and starting materials. Testing items for toxic inorganic impurities shall be established for the drug specification.

Where the impurity profile found in the study or production of a generic drug is different from that of the innovated one or from the existing official standard, the new impurities shall be studied according to the above requirements, and an application for revising to the original specification or establishing a new specification shall be submitted to the relevant drug regulatory authority for review and approval.

The concomitant isomers and the antibiotics multi-components are generally not the testing items of impurities. For concomitants, their proportion may be specified in the specification to ensure the consistency of drug substances used for production and those for registration application. The toxic concomitants will be considered as impurities instead of concomitants. Where the drug is a single enantiomer, other co-existent enantiomers shall be impurities. Where there is an official standard for a single enantiomer drug, the testing item of optical rotation should be set for the specification of the corresponding racemic drug.

Testing items for organic volatile impurities may be established according to the organic solvents used in the production process and the residual amount. The pharmacopoeia requirement for testing organic volatile impurities or the ICH document Q3C may be used as reference. The testing items for the residual toxic solvents shall be established.

Analytical methods for impurity testing and acceptance criteria of impurity

The analytical methods for impurity testing should be specific

and sensitive. Modern analytical methods for separation should be used for impurity testing. The substance to be examined should be well resolved with impurities and degradation products. The limit of detection should meet the requirement for the limit tests. For the impurities to be quantified, the limit of quantification should meet the corresponding requirement.

The analytical methods for impurity testing should be validated according to the requirements of the Chinese Pharmacopoeia. Several different methods or conditions for separation and determination may be adopted in the research stage, results obtained should be compared to select a suitable method as the compendium method. The suitability of an established method should be considered, equipments and materials selected should be available. The special materials used for the testing should be specified in the specification when necessary. In the research stage for the analysis of impurity, testing solutions can be prepared for chromatographic determination using the possible impurities and products from forced degradation, or by adding such impurities into the substance to be examined. Suitability requirements should be established by necessary adjustment of chromatographic parameters to ensure the method to be specific and sensitive.

Impurities and degradation products of a new drug developed, and new impurities or new degradation products found in the generic drugs should be prepared by isolation and purification, or by synthesis for the safety evaluation and quality study. When the impurities or degradation products could not be obtained, reason should be provided in the application dossier submitted, and in the description of the draft of the quality specification by the research institution.

Where modern chromatographic method is used for the separation of impurities, the known impurities and toxic impurities may be identified using impurity reference substances. Relative retention values can be used for the identification when the reference substances are not available. Impurities can be studied with different wavelengths using multi-wavelength detector, relative response factors of known and/or toxic impurities at a fixed wavelength to the substance to be examined should be calculated. Where the relative response factor is in the range of 0.9-1.1, content of impurity can be calculated using the response factor of the reference standard of the substance to be examined. Where the relative response factor exceeds the range of 0.9-1.1, it is suitable to use impurity reference standard to calculate the content, or the result be calculated by correction with a validated relative response factor. The unknown impurities could be quantified by comparison with the reference standard of the substance to be tested. The method of quantitative calculation for impurities should clearly be described in the drug specification. In general, The acceptance criteria of each single impurity and total impurities should be specified in the quality specification.

Where the thin-layer chromatography is used for impurity analysis, semi-quantitative estimation for impurity spots may be conducted by comparison with multi-level reference solutions of the impurity reference substance or the substance to be examined. The number and acceptance criteria for impurities should be specified in the quality specification.

The result of impurity limit test obtained by using chromatography may be influenced by the chromatographic parameters, relevant operation precautions should be provided in the description of the draft of the specification. For critical parameters the adjustments should be defined clearly in the specification to ensure the system suitability when necessary.

Several factors should be considered for establishing the acceptance criteria of impurities, such as the toxicology study of the impurity or the substance containing limited

quantity of the impurity, the route of administration, daily dose, patient population, possible pharmacology research on the impurity, the acceptability of the cost for the manufacturers to produce safe and high quality drugs and acceptability of the drug price for the consumers. Strict limits for toxic impurities or toxic residual organic solvents should be specified in the drug quality specification. The limit of residual solvent may be established according to the requirements of relevant Appendix of the Pharmacopoeia or relevant ICH documents.

XX G Guidance for the Quality Control of Positron Emission Tomographic Radiopharmaceutical Preparation

Positron emission tomographic (PET) radiopharmaceutical preparations refer to radiopharmaceuticals containing positron-emitting radionuclides. They are generally prepared at the time of clinical use by medical institutions or radiopharmaceutical manufacturers. There are two main sources of positron-emitting radionuclides: cyclotron produced and generator produced. The guidance is only suitable for the quality control of the PET radiopharmaceutical preparations produced through cyclotron. The quality control of PET radiopharmaceutical preparations produced through generator should refer to Guidance for the Quality Control of Technetium [^{99m}Tc] Radiopharmaceutical Preparations.

In order to assure the safety and efficacy of PET radiopharmaceutical preparation administration, quality control tests must be carried out according to the corresponding national standard for each batch of PET radiopharmaceutical preparation produced. If there is no national standard for a PET radiopharmaceutical preparation, the acceptance criteria should be established by the manufacturer, but such an acceptance criteria must be validated by the National Institute for the Control of Pharmaceuticals and Biological Products before its practical use.

The characteristics of preparation and quality control of PET radiopharmaceutical preparations:

1. Because of a very short physical half-life of the positron-emitting radionuclide, the preparation of PET radiopharmaceutical preparations must be rapid. Automated radiochemical synthesis devices are usually used to protect personnel involved from excessive radiation exposure.

2. PET radiopharmaceutical preparations are generally prepared locally, typically at sites located within, or affiliated with, medical institutions at the time of use. With a relatively longer half-life of fluorine [^{18}F], fluorine [^{18}F] PET radiopharmaceuticals can be prepared and supplied by other qualified medical institutions or radiopharmaceutical manufacturers nearby.

3. With the exception of fluorine [^{18}F] PET radiopharmaceutical preparations, each batch of PET radiopharmaceutical preparation generally leads to only a single or several doses administration.

4. Quality control tests must be rapid and practical.

Being subject to the characteristics of preparation and quality control of PET radiopharmaceutical preparations described above, it is impossible to carry out all quality control tests for every batch of PET radiopharmaceutical preparation before administration. According to the Drug Administration Law and the Regulations for the Administration of Radiopharmaceutical Preparation, this guidance is drawn up to guarantee the quality of PET radiopharmaceutical preparations, assure the safety and the efficacy of PET radiopharmaceutical preparation administration, and standardize the quality control for

PET radiopharmaceutical preparations.

1. For PET radiopharmaceutical preparations labelled with a nuclide having a physical half-life longer than 20.0 minutes (such as fluorine [^{18}F] PET radiopharmaceutical preparations), the following quality control tests should be performed on each batch prior to release or administration:

- (1) Description
- (2) pH value
- (3) Radiochemical purity
- (4) Radioactivity or radioactive concentration

Other quality control tests can be performed retrospectively after release or administration (retrospective quality control tests).

2. For PET radiopharmaceutical preparations labelled with a nuclide of a physical half-life equal to or shorter than 20.0 minutes (such as carbon [^{11}C], nitrogen [^{13}N] and oxygen [^{15}O] PET radiopharmaceutical preparations), a batch is defined as all related preparations (i.e., sub-batches) of the PET radiopharmaceutical preparation prepared under the same condition during a given day. The following quality control tests should be performed on an initial sub-batch from such PET radiopharmaceutical preparations prior to preparation of subsequent sub-batches:

- (1) Description
- (2) pH value
- (3) Radiochemical purity
- (4) Radioactivity or radioactive concentration

Other quality control tests can be performed retrospectively.

3. Retrospective quality control tests

If all the quality control test results of the PET radiopharmaceutical preparations prepared under the same compounding procedure (at least 6 consecutive batches) consistently conform to the established minimal acceptance criteria, the retrospective quality control tests can be performed at a defined periodic interval, but all quality control tests must be performed on a batch of PET radiopharmaceutical preparation at a minimum of once a month.

4. Quality control tests results

Accept or reject the individual batch of the PET pharmaceutical based on the conformity of quality control test results with established minimal acceptance criteria. If a batch of PET radiopharmaceutical preparation does not meet the established minimal acceptance criteria, its release or administration must be stopped immediately, and the subsequent preparation must be stopped too. The preparation of PET radiopharmaceutical preparations for human use can begin again only after having investigated what resulted in the unacceptable quality control test results, having solved the problem, and three consecutive validation studies that meet minimum acceptance criteria having been performed. If the unacceptable PET radiopharmaceutical preparation had been used clinically, it is necessary to observe the related patients carefully and follow them periodically, and take appropriate measures if necessarily. The manufacturer or medical institution that prepared the unacceptable PET radiopharmaceutical preparation should submit a report immediately to the local drug administration bureau and health bureau in case serious adverse reaction has occurred.

5. Quality assurance

(1) A PET radiopharmaceutical manufacturer or medical institution should have adequate facilities, instruments and equipment adaptable to the scale of PET radiopharmaceutical preparation and quality control. The instruments and equipment should be calibrated periodically to ensure the correct performance. Written operation and calibration procedures for the instruments and equipment should be established. Each use, calibration and maintenance should be documented.

(2) A PET radiopharmaceutical manufacturer or medical

institution should have an adequate number of corresponding technical personnel with the appropriate education and training. Each person performing an activity or a function in the quality control of PET radiopharmaceutical preparations should be trained in quality control of radiopharmaceutical preparations by the National Institute for the Control of Pharmaceuticals and Biological Products or other institutions authorized by State Food and Drug Administration.

(3) The standard operation procedures for preparation and quality control of PET radiopharmaceutical preparations should be established and performed strictly. The preparation and quality control of PET radiopharmaceutical preparations should be documented, and the documents should be maintained at least one year.

(4) Drug substances, materials and reagents used for the preparation and quality control of PET radiopharmaceutical preparations must be in compliance with established written specifications. Regulation procedures for the order, storage, testing and use of these materials should be established.

(5) To ensure the stability of the preparation process of PET radiopharmaceutical preparations, the computer and related automated equipment for preparation of PET radiopharmaceutical preparations must be controlled appropriately to ensure that changes in compounding software are instituted only by authorized personnel, that such changes are documented and verified.

(6) The standard operation procedures and computer software program that control the preparation process should be validated periodically, at a minimum of once a year. Whenever there is a change in the compounding procedures or computer software program that has the potential to alter the identity, quality, or purity of the PET radiopharmaceutical preparation, revalidation must be performed. Verification studies on a minimum of three consecutive batches, which show that the final product meets the acceptance criteria, are to be performed prior to the approval, for human use, of the revised standard operation procedures or computer software program for a given PET radiopharmaceutical preparation.

(7) The cleaning room or the aseptic workstation should be validated periodically to ensure proper performance.

(8) Each PET radiopharmaceutical preparation prepared by a medical institution can not be used clinically until the quality control testing of three consecutive batches of PET radiopharmaceutical preparations have been performed by the National Institute for the Pharmaceuticals and Biologic Products or other institutions authorized by State Food and Drug Administration, and the quality control tests results meet the acceptance criteria.

XX H Guidance for the Quality Control of Technetium [^{99m}Tc] Radiopharmaceutical Preparations

Technetium [^{99m}Tc] radiopharmaceutical preparations refer to radiopharmaceuticals containing technetium [^{99m}Tc] radionuclide for clinical diagnostic use, which include Sodium Pertechnetate [^{99m}Tc] Injection eluted from ^{99}Mo - ^{99m}Tc generators and other radiopharmaceutical preparations prepared with Sodium Pertechnetate [^{99m}Tc] Injection and corresponding freeze-dried cold kits.

Technetium [^{99m}Tc] radiopharmaceutical preparations are generally prepared through reconstituting ready-to-use freeze-dried cold kits with Sodium Pertechnetate [^{99m}Tc] Injection under aseptic condition by instant-labeling radiopharmaceutical manufacturers (radiopharmacy) or medical institutions that have the third or higher class license for Radiopharmaceutical Use.

As the preparation of technetium [^{99m}Tc] radiopharmaceutical preparations involves complicated chemical reactions between technetium-99m and non-radioactive compound, quality control tests for final products must be performed in addition that Sodium Pertechnetate [^{99m}Tc] Injection and the ready-to-use freeze-dried cold kits must meet corresponding acceptance criteria. Because the half-life of technetium [^{99m}Tc] is only 6.02 hour, technetium [^{99m}Tc] radiopharmaceutical preparations must be administered within minutes to several hours after preparation. It is impossible for a technetium [^{99m}Tc] radiopharmaceutical preparation to have completed all quality control tests before its release or administration. Technetium [^{99m}Tc] radiopharmaceutical preparations can be released and administered while quality control tests are being performed pursuant to article 16 of the Regulations for the Administration of Radiopharmaceutical Preparation. As one batch of technetium [^{99m}Tc] radiopharmaceutical preparation generally leads to only a single or several doses administration, the volume of which is usually only several milliliters, it is impracticable to perform all quality control tests for each batch of technetium [^{99m}Tc] radiopharmaceutical preparation.

Considering the above mentioned specialty of technetium [^{99m}Tc] radiopharmaceutical preparations, according to the Drug Administration Law and the Regulations for the Administration of Radiopharmaceutical Preparation, this guidance is drawn up to guarantee the quality of technetium [^{99m}Tc] radiopharmaceutical preparations and to assure the safety and the efficacy of technetium [^{99m}Tc] radiopharmaceutical preparation administration. The guidance is suitable for quality control of technetium [^{99m}Tc] radiopharmaceutical preparations prepared by instant-labeling radiopharmaceutical manufacturers (radiopharmacy) or medical institutions that have the third or higher class license for Radiopharmaceutical Use.

1. The obligatory quality control tests performed prior to release or administration

(1) Description

Visually examined through lead glass, physical appearance of a technetium [^{99m}Tc] radiopharmaceutical preparation should not significantly differ from the description described in the monograph. As for a clear colourless solution technetium [^{99m}Tc] radiopharmaceutical preparation, if particles, appearance of turbidity or a change in colour are observed, it must not be released or administered.

(2) pH value

The pH value of a technetium [^{99m}Tc] radiopharmaceutical preparation can be determined with a calibrated precise pH test paper, and must be in the defined range as described in the monograph.

(3) Radiochemical purity

Radiochemical purity should be determined according to the method described in the corresponding official monographs or other acceptance criteria. In case it takes long time to carry out the methods described in the official monographs, instant-labeling radiopharmaceutical manufacturers (radiopharmacy) or medical institutions can establish their own instant methods validated. The validation must be performed on at least three batches of technetium [^{99m}Tc] radiopharmaceutical preparations at three different periods (at time immediately after preparation, middle, and at the point of expiration time). The requirement described in the method established by instant-labeling radiopharmaceutical manufacturers (radiopharmacy) or medical institutions can't be lower than that described in the official monograph. For routine use, the method should be revalidated periodically, at a minimum of once a year, to ensure its applicability.

(4) Radioactivity

Radioactivity should be measured according to the Test of Radiopharmaceutical Preparations (Appendix XIII).

(5) Particle Size

For a technetium [^{99m}Tc] radiopharmaceutical preparation, particle size distribution is described in the monograph it should be tested according to Test for particle size distribution under the Test of Radiopharmaceutical Preparations (Appendix XIII) prior to release or administration and complied with the requirements

2. The quality control tests that can be performed while or after release or administration

(1) Bacterial endotoxin

Carry out the bacterial endotoxins test of a technetium [^{99m}Tc] radiopharmaceutical preparation as described under the corresponding monograph or the Test for Bacterial Endotoxin (Appendix XI E), the result should meet the minimal acceptance criteria.

(2) Sterility

Complies with the Test for Sterility (Appendix XI H).

(3) Biodistribution

For a technetium [^{99m}Tc] radiopharmaceutical preparation, test for biodistribution is described in the monograph, the test for biodistribution should be performed as described under corresponding monograph. The experiment animals should meet relevant regulations.

(4) If the result of any quality control tests described above does not meet the minimal acceptance criteria, its release, administration and related preparation should be stopped immediately, and make investigation to find the reasons. If the unacceptable technetium [^{99m}Tc] radiopharmaceutical preparation has been used clinically, it is necessary to observe the related patients carefully and visit them periodically, and take appropriate measures if necessarily. The manufacturer or medical institution that prepared the unacceptable technetium [^{99m}Tc] radiopharmaceutical preparation should submit a report immediately to the local drug administration bureau and health bureau.

(5) If all results of the quality control tests described above for technetium [^{99m}Tc] radiopharmaceutical preparations prepared under the same compounding procedure (at least 6 consecutive batches) consistently conform to the established minimal acceptance criteria, the test for bacterial endotoxins, sterility and biodistribution can be performed at a defined periodic interval, which depends on the quality control testing results.

3. Corresponding quality assurance

(1) A technetium [^{99m}Tc] radiopharmaceutical manufacturer (radiopharmacy) or medical institution should have adequate facilities, instruments and equipment adaptable to the scale of technetium [^{99m}Tc] radiopharmaceutical preparation and quality control. The instruments and equipment should be calibrated periodically to ensure the proper performance. Written operation and calibration procedures for the instruments and equipment should be established. Each use, calibration and maintenance should be documented.

(2) A technetium [^{99m}Tc] radiopharmaceutical manufacturer (radiopharmacy) or medical institution should have an adequate number of corresponding technical personnel with the appropriate education and training. Each person performing an activity or a function in the quality control of technetium [^{99m}Tc] radiopharmaceutical preparations should be trained in quality control of radiopharmaceuticals by the National Institute for the Control of Pharmaceuticals and Biological Products or other institutions authorized by State Food and Drug Administration.

(3) The standard operation procedures for preparation and quality control of technetium [^{99m}Tc] radiopharmaceutical preparations should be established and performed strictly. The preparation and quality control of technetium [^{99m}Tc] radiopharmaceutical preparations should be documented, and the documents should be maintained at least one year.

(4) Drug substances, materials and reagents used for the

preparation and quality control of technetium [^{99m}Tc] radiopharmaceutical preparations must be in compliance with established written specifications. Regulation procedures for the order, storage, testing and use of these materials should be established.

(5) The cleaning room or the aseptic workstation should be validated periodically to ensure its proper performance.

(6) For a technetium [^{99m}Tc] radiopharmaceutical manufacturer (radiopharmacy), all quality control tests for the first batch of Sodium Pertechnetate [^{99m}Tc] Injection eluted from newly purchased ^{99}Mo - ^{99m}Tc generators should be carried out before subsequent batches of Sodium Pertechnetate [^{99m}Tc] Injection eluted from the ^{99}Mo - ^{99m}Tc generators to prepare other technetium [^{99m}Tc] radiopharmaceutical preparations (measurement of molybdenum [^{99}Mo] content is only required for radionuclidic purity test). If all bacterial endotoxin and sterility tests of Sodium Pertechnetate [^{99m}Tc] Injections eluted from many batches of ^{99}Mo - ^{99m}Tc generator (at least 6 consecutive batches produced by the same manufacturer) meet the minimal acceptance criteria, tests for bacterial endotoxin and sterility of Sodium Pertechnetate [^{99m}Tc] Injections eluted from ^{99}Mo - ^{99m}Tc generators produced by the manufacturer can be performed periodically. But complete quality control tests for Sodium Pertechnetate [^{99m}Tc] Injection must be carried out at least once a month. Complete quality control tests for the first batch of technetium [^{99m}Tc] radiopharmaceutical preparation should be carried out when the batch of ready-to-use freeze-dried cold kit changes.

XX J Guidelines for Hygroscopicity

Hygroscopicity characterize the capability of drugs absorbing moisture at certain temperature and humidity. It is underlined that this method has been accepted as only an indication of hygroscopicity, and should be carried out on material which complies with the test for loss on drying or water content of the monograph of the Chinese pharmacopoeia. This method can also be used as a reference for choosing suitable package and store conditions of the drugs.

Determine as follow:

1. Use a glass weighing vessel 50 mm in external diameter and 15 mm high. Weigh the vessel and stopper (m_1). Place the amount of substance prescribed for the test for loss on drying or water in the vessel and weigh (m_2).
2. Place the unstoppered vessel in a desiccator at 25°C containing a saturated solution of ammonium chloride or ammonium sulphate or place it in a climatic cabinet set at 25±1°C and 80±2% relative humidity.
3. Allow to stand for 24 hours.
4. Stopper the weighing vessel and weigh (m_3).

Calculate the percentage increase in mass using the expression:

$$\frac{m_3 - m_2}{m_2 - m_1} \times 100\%$$

5. The result is interpreted as follows:

very hygroscopic: increase in mass is equal to or greater than 15%

hygroscopic: increase in mass is less than 15% and equal to or greater than 2%

slightly hygroscopic: increase in mass is less than 2% and equal to or greater than 0.2%

deliquescent: sufficient water is absorbed to form a liquid

XX K Guideline for Near-infrared(NIR) Spectrophotometry

Near-infrared (NIR) spectrophotometry is an analysis technique used in qualitative and quantitative analysis in which the specified spectrum of the substance being examined is measured among Near-infrared region (from about 780 nm to about 2500 nm or from about 12800 cm^{-1} to about 4000 cm^{-1}) and the correlation information is extracted by suitable chemometric algorithms. NIR spectra are dominated by C-H, N-H, O-H and S-H overtone resonances and combinations of fundamental vibrational modes. NIR bands are much weaker than the fundamental mid-IR vibrations from which they originate. NIR bands are always overlapping. Direct comparison of the spectrum obtained with the substance being examined with a reference spectrum of a chemical reference substance, as used in infrared absorption spectrophotometry, is not appropriate. Suitable validated mathematical treatment of the data is required.

Application range

Near-infrared spectrophotometry is advantageous because quick and accurate measurement can be often made without destroying the sample. Near-infrared spectrophotometry is a method that can test both off-line sample and on-line process sample. NIR spectrophotometry has a wide variety of applications for both chemical and physical analysis of pharmaceutical.

1. Chemical analysis

(1) Qualitative analysis

Identification of active substances, excipients, dosage forms, manufacturing intermediates, chemical raw materials and packaging materials.

(2) Quantitative analysis

Quantification of active substances and excipients, determination of chemical values such as hydroxyl value, iodine value, acid value, determination of water content, determination of degree of hydroxylation, control of solvent content.

(3) Process control.

2. Physical analysis

(1) Crystalline form and crystallinity, polymorphism, pseudopolymorphism, particle size.

(2) Examination of film properties.

(3) Process control, for example monitoring of blending and granulation.

Apparatus and control of instrument performance

1. Apparatus

NIR spectrophotometers are used for recording spectra in the region of about 780 nm to about 2500 nm (about 12800 cm^{-1} to about 4000 cm^{-1}). All NIR measurements are based on passing light through or into a sample and measuring the attenuation of the emerging beam. Spectrophotometers for measurement in the NIR region consist of a suitable light source, sampling device, a monochromator or interferometer, detector and suitable data processing and evaluation system. High intensity light sources such as tungsten lamp with shell of quartz or similar are used usually. The tungsten lamp light source can be highly stabilized. Silicon, lead sulphide, indium arsenide, indium gallium arsenide, mercury cadmium telluride (MCT) and deuterated triglycine sulphate are commonly used detector materials. Conventional cuvette sample holders, fibre-optic probes, transmission dip cells and spinning or traversing sample holders are a few common

sampling devices. The selection of detector and sampling device are based on the intended application, paying particular attention to the suitability of the sampling system for the type of sample to be analysed.

2. Control of instrument performance

(1) Verification of the wavelength scale

Verify the wavelength scale employed, generally in the region between about 780 nm to about 2500 nm (about 12800 cm^{-1} to about 4000 cm^{-1}) or in the intended spectral range using one or more suitable wavelength standards which have characteristic maxima or minima within the range of wavelengths to be used, for example, a mixture of rare-earth oxides such as dysprosium, holmium and erbium oxides. Measure the position of at least 3 peaks distributed over the range used. Acceptable tolerances are ± 1 nm at 1200 nm, ± 1 nm at 1600 nm and ± 1.5 nm at 2000 nm (± 8 cm^{-1} at 8300 cm^{-1} , ± 4 cm^{-1} at 6250 cm^{-1} and ± 4 cm^{-1} at 5000 cm^{-1}).

(2) Verification of photometric linearity

Verification of photometric linearity is demonstrated with a set of transmission or reflection standards with known values of transmittance or reflectance in percentage. Stability of the instrument is demonstrated with standards.

(3) Verification of photometric noise.

Determine the photometric noise using a suitable reflectance standard and/or two transmittance standards that one with high absorbance property is used at high-light flux to evaluate the instrument noise and the other one with low absorbance property is used at low-light flux to evaluate the instrument noise. When suitable standard can not be getting, the noise can be measured using 100 per cent of absorbance line. Scan the reflection standard over a suitable wavelength/wavenumber range in accordance with the manufacturer's recommendation and calculate the photometric noise as peak-to-peak noise. The photometric noise is consistent with the specification of the spectrophotometer.

Measurement methods

1. Transmission mode Transmittance (T) is a measure of the decrease in radiation intensity at given wavelengths when radiation is passed through the sample. The sample is placed in the optical beam between the source and detector. This method is suitable for liquid sample usually. Suitable sampling device is necessary for solid sample by this method. Another Transmission mode is transreflection mode. The detector and light source are on the same side of the sample. In the measurement of transreflection a mirror or a diffuse reflectance surface is used to reflect the radiation transmitted through the sample a second time. The result can be presented directly in terms of transmittance (T) or/and absorbance (A) in both cases.

$$T = I/I_0$$

$$A = -\lg T = \lg (1/T) = \lg (I_0/I)$$

Where, I_0 = intensity of incident radiation,
 I = intensity of transmitted radiation.

2. Diffuse reflection mode The diffuse reflection mode gives a measure of reflectance (R), the ratio of intensity of light reflected from the sample (I) to that reflected from a background or reference reflective surface (I_r). This method is suitable for solid sample usually. The sample is placed in a suitable sampling device. NIR radiation can penetrate a substantial distance into the sample, where it can be absorbed by vibrational combinations and overtone resonances of the analyte species present in the sample. Non-absorbed radiation is reflected back from the sample to the detector. A typical NIR reflectance spectra are obtained by calculating and plotting $\lg (1/R)$ versus the wavelength or wavenumbers.

$$R = I/I_r$$

$$A_R = \lg (1/R) = \lg (I_r/I)$$

Where, I = intensity of light diffusively reflected from the sample,

I_r = intensity of light reflected from the background or reference reflective surface.

Factors affect NIR spectral response

The main factors affect the NIR spectral response are sample temperature, moisture and solvent residues, sample thickness, sample optical properties, polymorphism and age of samples.

Basic requirement of qualitative analysis and quantitative analysis by Near-infrared (NIR) spectrophotometry

1. Qualitative analysis

Establish a spectral reference library first. Then pre-treat data and evaluate data. Validate the specificity and robustness of the database finally.

(1) Establishment of a spectral reference library.

Record the spectra of a suitable number of batches of the substance which have been fully tested according to established specifications and which exhibit the variation typical for the substance to be analysed (for example, manufacturer, physical form, particle size). The set of spectra represents the information for identification and characterization that defines the similarity border for that substance and is the entry for that substance in the spectral library used to identify the substance.

(2) Pre-treatment of data.

In many cases, some form of mathematical pretreatment of the spectrum must be performed prior to the development of a classification or calibration model. Typical methods are multiplicative scatter correction (MSC), the Kubelka-Munk transforms, spectral compression techniques that may include windowing and noise reduction and the numerical calculation of the first- or second-order derivative of the spectrum. In some cases spectra may also be normalized. Caution must be exercised when performing any mathematical transformation, as artefacts can be introduced or essential information can be lost. In all cases the rationale for the use of transform must be documented.

(3) Data evaluation.

Direct comparison of the spectrum of the substance being examined is made with the individual or mean reference spectra in the database on the basis of their mathematical correlation or other suitable algorithms. There are several different algorithms based on principal component analysis (PCA) combined with cluster analysis, SIMCA (soft independent modeling by class analogy), and others used in the software of NIR instruments.

(4) Validation of the database

a. Specificity

The validation of specificity involves of the classification using database spectra for positive identification of a given material and adequate discrimination against other materials in the database is to be established during the validation procedure. Potential challenges must be addressed to the spectral database. These can be materials received on site that are similar to database members in chemical structure. This challenge must fail identification. Independent samples of materials represented in the database, but not used to create it (i.e. different batches, blends) must give positive identification when analysed.

b. Robustness

The robustness of the qualitative procedure must also be

challenged to test the effect of minor changes to normal operating conditions on the analysis. There must be no changes to pre-processing and calibration algorithm parameters. Typical challenges are:

① Effect of differences across operators on variations in environmental conditions (for example, temperature and humidity in the laboratory).

② Effect of sample temperature, sample positioning on the optical window, probe depth and compression/packing of material.

③ Replacement of instrument parts or sampling presentation devices.

2. Quantitative analysis

Establish a spectral reference library for a calibration model first. Then pre-treat data. Validate the analytical procedures finally.

(1) Establishment of a spectral reference library for a calibration model.

Record spectra of a suitable number of samples with known values of the content throughout the range to be measured. Establish the calibration model to relate the response from an instrument to the properties of the samples. Any calibration algorithm that can be clearly defined in an exact mathematical expression and gives suitable results can be used. Multiple linear regression (MLR), partial least squares (PLS) and principal component regression (PCR) are commonly used.

(2) Pre-treatment of data.

Data pre-treatment can be defined as the mathematical transformation of the NIR spectral data to enhance spectral features and/or remove or reduce unwanted sources of variation prior to the development of the calibration model. The selection of suitable algorithms and pre-treatment calibration is based on the suitability for the intended use.

(3) Validation parameters.

Analytical performance characteristics to be considered for demonstrating the validation of NIR methods are similar to those required for any analytical procedure. Specific acceptance criteria for each validation parameter must be consistent with the intended use of the method. The validation parameters include specificity, linearity, range, accuracy, precision, robustness and outliers.

Ongoing model evaluation

Revalidation of a qualitative model will be necessary when changes in the physical properties of the material occur and when changes in the source of supply take place. Revalidation of a quantitative model is required on account of changes in the composition of the finished product, in the manufacturing process and in sources/grades of raw materials.

Transfer of databases

When databases are transferred to another instrument, type of the instrument, format of the data, spectral range, number of data points, spectral resolution and other parameters have to be taken into consideration. For example, when to establish a model on one instrument by representative samples the number of which is decided by the model, measure the spectra of these samples on another instrument. The spectra on both instruments are analysed by the model established on the first instrument. Two results must be tested statistically to demonstrate that the model is valid on the second instrument or not, otherwise model must be rebuilt on the second instrument.

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